Universidade do Estado do Rio de Janeiro
Centro Biomédico
Instituto de Medicina Social Hesio Cordeiro

Alessandra Raymundo Bomfim

O tratamento da lesão de cárie dentária não cavitada é efetivo? Uma revisão sistemática

Rio de Janeiro
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Tese apresentada, como requisito parcial para obtenção do título de Doutora, ao Programa de Pós-Graduação em Saúde Coletiva, da Universidade do Estado do Rio de Janeiro. Área de concentração: Epidemiologia.

Orientador: Prof. Dr. Paulo Nadanovsky

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2022

DEDICATÓRIA

Para o meu avô Onofre (*in memoriam*).

Para a Luiza, Dudu, Lucas, Maria Antonia, Manu, Henrique e Noah,

e todos os sobrinhos do coração, crianças, e ex-crianças, livres de cárie.

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Aos meus pais Chrisanto (in memoriam) e Sonia, por me fazerem acreditar que só crescemos com conhecimento e fé. Cresci ouvindo o meu pai dizer que a herança que me deixaria seria o estudo e que isto me possibilitaria conquistar o que quisesse. Ainda hoje, ouço a minha mãe dizer que, com calma e fé, eu posso alcançar meus objetivos.

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Sem vocês, eu não teria conseguido!

PARA SER GRANDE, sê inteiro: nada
Teu exagera ou exclui.
Sê todo em cada coisa. Põe quanto és
No mínimo que fazes.
Assim em cada lago a lua toda
Brilha, porque alta vive.

Ricardo Reis (Fernando Pessoa)
14.2.1933

RESUMO

BOMFIM, Alessandra Raymundo. O tratamento da lesão de cárie dentária não cavitada é efetivo? Uma revisão sistemática. 2022. 278 f. Tese (Doutorado em Saúde Coletiva) – Instituto de Medicina Social Hesio Cordeiro, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 2022.

Os métodos contemporâneos de diagnóstico e tratamento de cárie preconizam uma distinção entre lesões cavitadas e não cavitadas, ativas e inativas e, quando possível, intervenções minimamente invasivas. A pergunta de pesquisa desta revisão sistemática foi: O tratamento de lesões não cavitadas de cárie é efetivo em impedir o aparecimento de cavidade dentária, restauração, dor de dente ou perda de dente, em indivíduos com dentes decíduos ou permanentes?. Foi feita uma busca bibliográfica nas principais bases de dados até o ano de 2020. Duas revisoras selecionaram os estudos e extraíram os dados independentemente. Nos casos em que houve discordância, uma terceira revisora foi consultada e a disputa foi resolvida por consenso. A análise de risco de viés foi executada utilizando-se a ferramenta RoB2 e avaliação de certeza da evidência utilizando o sistema GRADE. Foram obtidos 4.108 títulos, e após a remoção dos títulos duplicados e da aplicação dos critérios de exclusão, selecionou-se 19 estudos. Nenhum estudo apresentou o risco para o indivíduo de desenvolver pelo menos um evento relacionado aos desfechos de interesse, por isso não foi possível realizar metanálise de risco. Dez estudos apresentaram os resultados em número médio de lesões cavitadas em dentina ou restauradas por indivíduo, permitindo que fossem feitas metanálises de diferenças nas médias. Várias combinações foram feitas, uma vez que alguns estudos apresentavam mais de uma intervenção a ser comparada com placebo ou higiene bucal. Os resultados das metanálises foram semelhantes, com a estimativa pontual da diferença na média variando entre -0,22 e -0,27 nas diversas metanálises executadas. Ou seja, em média, por indivíduo, houve entre menos 0,22 e menos 0,27 dente com cavidade de cárie em dentina (ou com restauração) no grupo que recebeu tratamento em comparação com o grupo que recebeu o placebo ou nenhum tratamento. O Índice de Higgins (I^2) nos diz a proporção da variabilidade nas estimativas de efeito que pode ser atribuída à heterogeneidade entre os estudos e não ao acaso. Com base neste índice, a heterogeneidade foi substancial em todas as metanálises, variando entre 69% e 76%. Conclusão: nenhum estudo avaliou a efetividade do tratamento não invasivo de lesões não cavitadas (mancha branca) em evitar dor ou perda de dente. Poucos estudos avaliaram a efetividade do tratamento em evitar cavidades ou restaurações. Dentre esses poucos estudos, o tratamento teve um efeito relativamente modesto. O risco de viés nos estudos incluídos foi, de uma forma geral, alto ou moderado e a certeza da evidência foi baixa. Pesquisas sobre cárie dentária devem incluir desfechos verdadeiros para que seja possível conhecer a efetividade das diferentes intervenções precoces em evitar cavidades em dentina, restaurações, dor e perda de dentes.

Palavras-chave: Cárie dentária. Tratamento. Prevenção. Revisão Sistemática.

ABSTRACT

BOMFIM, Alessandra Raymundo. *Is the treatment of non-cavitated dental caries lesion effective? A systematic review.* 2022. 278 f. Tese (Doutorado em Saúde Coletiva) – Instituto de Medicina Social Hesio Cordeiro, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 2022.

Contemporary methods of diagnosing and treating caries advocate a distinction between cavitated and non-cavitated, active and inactive lesions and, when possible, minimally invasive interventions. The research question of this systematic review was: Is the treatment of non-cavitated caries lesions effective in preventing the appearance of dental cavity, restoration, toothache or tooth loss, in individuals with deciduous or permanent teeth?. A bibliographic search was carried out in the main databases until the year 2020. Two reviewers independently selected the studies and extracted the data. In cases where there was disagreement, a third reviewer was consulted and the dispute was resolved by consensus. Bias risk analysis was performed using the RoB2 tool and evidence certainty assessment using the GRADE system. A total of 4,108 titles were obtained, which after removing duplicate titles and applying the exclusion criteria, 19 studies were selected. No study presented the risk for the individual of developing at least one event related to the outcomes of interest, so it was not possible to perform a risk meta-analysis. Ten studies presented the results in terms of the average number of cavitated or restored dentin lesions per individual, allowing meta-analyses of differences in averages to be performed. Various combinations were made, as some studies had more than one intervention to be compared with placebo or oral hygiene. The results of the meta-analyses were similar, with the point estimate of the difference in the mean varying between -0.22 and -0.27 in the various meta-analyses performed. That is, on average, per individual, there were between 0.22 and 0.27 fewer teeth with dentin (or filled) carious cavity in the group that received treatment compared to the group that received the placebo or no treatment. The Higgins Index (I2) tells us the proportion of variability in effect estimates that can be attributed to heterogeneity across studies rather than chance. Based on this index, heterogeneity was substantial in all meta-analyses, ranging from 69% to 76%. Conclusion: no study has evaluated the effectiveness of non-invasive treatment of non-cavitated lesions (white spot) in preventing pain or tooth loss. Few studies have evaluated the effectiveness of the treatment in preventing cavities or restorations. Among these few studies, treatment had a relatively modest effect. The risk of bias in the included studies was generally high or moderate and the certainty of evidence was low. Research on dental caries must include true outcomes so that it is possible to know the effectiveness of different early interventions in preventing dentin cavities, restorations, pain and tooth loss.

Palavras-chave: Dental Caries. Treatment. Prevention and control. Systematic Review.

LISTA DE ABREVIATURAS E SIGLAS

Ceo	Número de dentes decíduos cariados, com extração indicada ou obturados
CPOD	Número de dentes permanentes cariados, perdidos ou obturados
CPOS	Número de superfícies cariadas perdidas ou obturadas (dentes permanentes)
FAO	Food and Agriculture Organization (Organização das Nações Unidas para a Alimentação e a Agricultura)
FDA	Food and Drug Administration (Agência Federal de Controle Alimentar e de Medicamentos dos Estados Unidos)
HIV	Human Immunodeficiency Virus (Vírus da Imunodeficiência Humana)
ICDAS	International Caries Detection and Assessment System (Sistema Internacional de Avaliação e Detecção de Cáries)
ILSI	International Life Sciences Institute (Instituto Internacional de Ciências da Vida)
OMS	Organização Mundial de Saúde
PPM	Partes por milhão
PROSPERO	International prospective register of systematic reviews

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INTRODUÇÃO

O trabalho realizado por mim durante o período do doutorado foi dividido em duas partes. Na primeira parte, durante os anos 2015 e 2019, eu fui uma das pesquisadoras que colaboraram para a execução de um estudo de viabilidade para um ensaio controlado randomizado sobre a suplementação de cálcio e vitamina D e o tratamento da periodontite em mulheres grávidas (*The IMPROVE trial*). Os detalhes sobre essa parte do doutorado, assim como o artigo publicado com os resultados do estudo, estão no apêndice 5.

Na segunda parte do doutorado, durante os anos 2018 e 2021, elaborei uma revisão sistemática para investigar se o tratamento da lesão de cárie dentária não cavitada (mancha branca) é efetivo. O corpo desta tese, que será a base para o artigo principal, é constituído pelo relato detalhado dos antecedentes, justificativa e revisão sistemática realizada sobre a efetividade do tratamento de cárie não cavitada.

1 REVISÃO DE LITERATURA

1.1 A importância da cárie dentária

De acordo com a Organização Mundial de Saúde (OMS), a saúde bucal é essencial para a saúde geral do indivíduo, sendo um fator determinante para a qualidade de vida. A cárie dentária causa dor e ansiedade, e restringe as atividades escolares, domésticas ou laborais, contribuindo para a diminuição do bem-estar da pessoa, com impacto psicossocial (PETERSEN, 2003; PERES, 2019). Desta forma, esta doença interfere negativamente na vida de adultos (BUKHARI, 2019; PERES, 2019), crianças e suas famílias (CHAFFEE et al., 2017; RAMOS-JORGE et al., 2014).

A cárie dentária é a doença mais prevalente no mundo, afetando mais de 3.5 bilhões de pessoas (WATT, 2019), com elevada prevalência em países industrializados, bem como asiáticos e latino-americanos. É menos comum e grave na África, entretanto, com a mudança nas condições de vida e, consequentemente, nos padrões alimentares da população, espera-se um aumento da sua incidência nos países em desenvolvimento africanos, como resultado do aumento no consumo de açúcar (PETERSEN, 2003; WHO, 2020). Em muitos países de renda baixa e média, a cárie dentária vem aumentando em razão do maior consumo de alimentos ricos em açúcar, estimulado pela indústria. O desenvolvimento econômico que vem tirando milhões de indivíduos da pobreza tem resultado em transições demográficas e nutricionais, muitas vezes adversas à saúde (PERES, 2019).

A cárie dentária é uma condição acumulativa. As contagens médias de lesões em uma população aumentam com a idade, indicando que novas lesões continuam a se formar ao longo da vida. Os números costumam ser mais altos em mulheres do que em homens. As diferenças muitas vezes encontradas com relação à raça, dizem mais respeito à condição social, econômica e educacional (BAELUM, 2017).

A Odontologia, claramente, tem falhado no combate à doença. A alteração afeta de forma desproporcional os mais pobres e marginalizados. Desta forma, esta condição tem sido considerada um marcador sensível de desvantagem social. O problema está na forma como a cárie dentária vem sendo atacada. Tradicionalmente, tratar cáries consiste em remover o tecido comprometido e

restaurar o dente, independentemente do tamanho ou profundidade da cavidade. Desta forma, os serviços odontológicos são centrados no atendimento individualizado e em profissionais especializados, que privilegiam o modelo cirúrgico-restaurador, e são considerados dispendiosos pelos governos. Assim, sempre que há necessidade de cortes no orçamento relacionado à saúde, estes são os primeiros a sofrer (PERES, 2019; WATT, 2019). Este é um equívoco comum e que demonstra que não há, entre os gestores de saúde pública, a consciência de que a saúde bucal é componente indissociável da saúde geral.

No que se refere aos determinantes socioeconômicos, a Pesquisa Nacional de Saúde do Ministério da Saúde em 2019 correlaciona os hábitos de saúde bucal com nível de instrução, grupo etário e renda. Embora o documento relate que 93,6% dos brasileiros acima de 18 anos de idade escovavam os dentes pelo menos duas vezes ao dia, verificou-se também que esta proporção é maior entre os habitantes das áreas urbanas, bem como mulheres, jovens e indivíduos com maior nível de instrução. No que se refere ao consumo de açúcar, o documento aponta um consumo de regular de refrigerantes por 9,2% da população, sendo mais frequente entre homens, jovens e na área urbana. O consumo de sucos de caixa e refresco em pó apresentou números ainda mais elevados. No que se refere ao consumo de alimentos doces, os números são ainda mais elevados, alcançando 23,8% entre os jovens de 18 a 24 anos. Infelizmente, o documento nada traz a respeito da cárie dentária, que decorre notadamente do consumo de açúcar e do hábito de higiene bucal (BRASIL, 2019).

Segundo a Pesquisa Nacional de Saúde Bucal de 2010, aos cinco anos de idade, uma criança brasileira possui, em média, 2,4 dentes com experiência de cárie. Crianças brasileiras de 12 anos de idade e adolescentes de 15 a 19 anos apresentam, respectivamente, em média, 2,1 e 4,3 dentes com experiência de cárie dentária. Para os adultos, o índice de Dentes Cariados, Perdidos e Obturados (CPOD) médio encontrado foi de 16,8 entre os 35 e 44 anos de idade e 27,4 na faixa etária entre 65 e 74 anos. Em todas as faixas etárias, a experiência de cárie é menor no sudeste do país (BRASIL, 2012).

As doenças bucais ocupam o 4º lugar entre as que possuem tratamento mais dispendioso nos países industrializados. Esta estimativa, contudo, leva em conta apenas os custos diretos para o seu tratamento. Existem custos indiretos, que incluem perda de produtividade e absenteísmo no trabalho ou escola, que devem

ser levados em consideração. Estima-se que o custo econômico global com as doenças dentárias atingiu US$ 442 bilhões em 2010, sendo US$ 298 bilhões relativos ao custo direto e outros US$ 144 bilhões relacionados aos custos indiretos (LISTL *et al.,* 2015).

Parte deste custo está associado a interesses econômicos por parte das instituições de ensino privadas, que abrem novos cursos e formam cada vez mais profissionais, especialmente nos países de baixa e média renda; dos profissionais, que, apesar do entendimento acerca da patogênese, epidemiologia e etiologia da doença indicarem a importância de uma abordagem conservadora, ainda têm a sua remuneração baseada nos procedimentos executados; e da indústria, a quem não interessa a redução do consumo do açúcar, e que colabora para a manutenção de um modelo de atenção centrado no atendimento de necessidades individuais. Urge que o modelo de atenção seja modificado, para que o tratamento da cárie dentária se torne mais efetivo e economicamente viável (FEJERSKOV, 2013; WATT, 2019).

1.2 A formação da lesão de cárie dentária

A cárie dentária é definida como uma destruição localizada dos tecidos dentários duros decorrente da ação direta de ácidos formados pela ação de bactérias bucais metabolizando o açúcar da dieta (SELWITZ, 2007).

A parte visível do processo de cárie é a desmineralização dos tecidos dentários (SELWITZ, 2007). Esta desmineralização é consequência direta da dissolução química do tecido mineral do dente, que ocorre em superfícies de esmalte, dentina ou cemento, em presença de biofilme, rico em microrganismos (FEJERSKOV, 2017). A microbiota oral é composta por mais de 750 microrganismos reconhecidos, entre vírus, protozoários, fungos e bactérias. Parte desta microbiota compõe o biofilme, um ecossistema extremamente ativo e complicado, alimentado por açúcares e produtos presentes na saliva, cuja composição varia em função da sua localização, tempo de desenvolvimento e estado de maturação. *Bifidobacterium dentium, Bifidobacterium, adolescentis, Streptococcus mutans, Scardovia wiggsiae, Bifidobacterium longum, Selenomounas spp., Prevotella spp., Atopobium, Propionibacterium, Veillonella, Rothia, Leptotrichia* e *Lactobacillus spp* são bactérias relacionadas com a cárie dentária (MOSADDAD *et al.*, 2019). Cada tipo de lesão, bem como cada indivíduo, conta com a presença de

uma combinação diversa de bactérias. Além disso, diferentes colônias bacterianas estão associadas aos diferentes estágios de desenvolvimento da alteração (SIMON-SORO; MIRA, 2015). Ademais, a virulência das diferentes combinações de bactérias é modulada pela presença dos demais microrganismos da microbiota (MOSADDAD *et al.*, 2019). Diante das características da microbiota responsável pela cárie dentária, o controle da doença através do uso de antimicrobianos, antibióticos ou vacinas não se mostra eficiente.

Em nível microbiológico, alternativas com a intenção de interferir no desenvolvimento do biofilme vem sendo tentadas (SIMON-SORO; MIRA, 2015). Tentativas de uso de antibióticos e antimicrobianos no controle da cárie dentária surgiram a partir de dos anos 1940. Vários fatores, tais como efeitos colaterais, resistência bacteriana e o fato de a microbiota causadora da cárie ser diversa e hospedeira natural da cavidade bucal, são empecilhos para o seu sucesso (QIU, 2020; NIU, 2021). Ademais, Walsh et al. (2015) concluíram, em uma revisão sistemática *Cochranne*, haver pouca evidência de que o digluconato de clorexidina, um antimicrobiano muito utilizado em Odontologia, é eficaz na redução dos níveis de *Streptococcus mutans* ou na prevenção da cárie dentária, em comparação com placebo ou nenhum tratamento. No que se refere a vacinas, poucas pesquisas têm sido feitas em humanos, sendo a maioria centrada nos *Streptococcus mutans* e com resultados que demonstram apenas proteção de curto prazo (PATEL, 2020). Além dos resultados ruins oferecidos por estes poucos estudos, os *Streptococcus mutans*, frequentemente presentes em indivíduos livres de cárie, compreendem menos de 1% do total da comunidade bacteriana isolada em lesões de cárie (TWETMAN, 2018).

A atividade microbiana no biofilme leva à queda do pH e a um desequilíbrio na saturação mineral. Este desequilíbrio é compensado por minerais perdidos pelo tecido dentário, que se encontra em íntima relação com o biofilme, levando à sua desmineralização. Quando o biofilme fica saturado, “devolve” os minerais perdidos pelo tecido dentário, em um processo de remineralização. A cárie dentária acontece quando uma intensa atividade microbiana, modulada pela presença de carboidratos, notadamente o açúcar, faz com que o processo de desmineralização do dente seja mais intenso que o de remineralização; ou seja, quando há uma situação de desequilíbrio fisiológico (VAN LOVEREN, 2017). Desta forma, além de biofilme dependente, a cárie dentária é, principalmente, açúcar dependente, visto que o

açúcar é o principal responsável pelo desequilíbrio relatado, uma vez que aumenta a atividade microbiana.

1.3 O papel do açúcar na cárie dentária

A relação entre o consumo de açúcar e cárie dentária ficou claramente estabelecida no clássico estudo experimental de Vipeholm na Suécia (GUSTAFSSON,1950). Subsequentemente foi observado que, em diversos países e períodos históricos a restrição no consumo de açúcar levou a marcantes reduções na incidência de cárie dentária.

Jamel (2004) demonstrou que as sanções econômicas impostas pelas Nações Unidas após a Guerra do Iraque levaram a uma redução do consumo de açúcar de 50kg/pessoa/ano entre 1984 e 1990 para 12 kg/pessoa/ano após 1990, acarretando uma redução expressiva nos índices de ceo e CPOD em crianças e adolescentes. Eriksen (1991) relata a mesma situação de declínio na prevalência de cáries em decorrência da diminuição de consumo de açúcar, em razão da 2ª Grande Guerra, em países como Noruega, Dinamarca, Finlândia, Inglaterra e Japão. Segundo o mesmo autor, a Suécia, que permaneceu neutra no conflito, apresentou menores variações.

Os estudos sobre a associação entre cárie dentária e dieta sofrem uma considerável variabilidade no que se refere a desfecho, indicadores, idade populacional, duração, terminologia empregada, ou mesmo, intervenção (MOYNIHAN; KELLY, 2014). Embora Moynihan & Kelly (2014) tenham concluído que as evidências são de qualidade moderada, ainda assim, é possível identificar ligação consistente entre o consumo de açúcar e uma maior prevalência de cárie dentária, mesmo quando há exposição ao flúor.

1.4 Indicadores de cárie dentária

São vários os indicadores para medir cárie dentária. O índice mais utilizado é o CPOD (PERES *et al.,* 2019). Este índice vem sendo utilizado desde a primeira metade do século XX e tem o aval da OMS (WHO, 2013). O CPOD propõe-se a

medir a gravidade da cárie, através da contagem do número de dentes Cariados, Perdidos ou Obturados no indivíduo ou em um grupo de indivíduos. Para dentes decíduos, existe um equivalente, chamado índice de dentes cariados, com extração indicada e obturados (ceo), que segue a mesma lógica, substituindo-se apenas a contagem de dentes perdidos pela contagem de dentes com extração indicada.

Uma vantagem do CPOD é que este índice mede a gravidade da cárie dentária. Ele engloba toda a experiência passada de cárie, mas ainda assim discriminando o dente cariado, o dente restaurado e o dente perdido devido à cárie. É fácil de usar, internacionalmente utilizado e permite avaliação de tendências temporais de longo prazo – ele resiste ao teste do tempo como poucos indicadores de saúde (NADANOVSKY, 2008; PERES, 2019).

Entre dentistas, discute-se quando um dente deve ser considerado cariado. As condições em que o exame é executado, tais como iluminação, posição do paciente e os diferentes tipos de instrumentos que podem ser utilizados, influenciam no diagnóstico. De acordo com o CPOD, um dente cariado é aquele com uma lesão de cárie claramente visualizada, sem margem de dúvida, ou seja, o dente com cavidade ou aquele com esmalte intacto, mas claramente com cavidade por baixo. (NADANOVSKY, 2008).

O índice CPOD, como qualquer outro, apresenta problemas. A ocorrência de novas lesões cárie em superfícies já restauradas não altera o escore do índice. Este problema, entretanto, pode ser resolvido fazendo-se a contagem de superfícies com cárie presente. Outra limitação do índice é que não há pesos diferentes para os três componentes do índice. Uma restauração pequena vale o mesmo que um dente extraído. Uma alternativa para se obter um resultado mais sensível é utilizar o Índice de Superfícies Cariadas Perdidas e Obturadas (CPOS), cuja unidade de análise é a superfície dentária, e não o dente. Esta alternativa é útil nos registros de estudos de incidência, uma vez que é mais sensível a mudanças ocorridas em pequenos espaços de tempo. Por outro lado, tem a desvantagem de possuir uma gama mais ampla de valores possíveis, e, consequentemente, desvio e erro-padrão mais amplos, sendo menos confiável que o CPOD (NADANOVSKY, 2008).

A cavitação ainda é o critério mais comum para detecção de cárie na maioria dos estudos epidemiológicos (PERES, 2019), embora outros indicadores que diagnosticam lesões em estágios pré-cavidade venham sendo cada vez mais utilizados (MOYNIHAN; KELLY, 2014), refletindo as críticas que existem ao CPOD.

Uma dessas críticas é que ele não está coerente com os conhecimentos mais atuais da cariologia, isto é, com os conhecimentos modernos sobre os mecanismos da cárie dentária. A cárie dentária passou a ser entendida pela cariologia não como uma cavidade no dente, mas sim como um processo que eventualmente pode levar a uma cavidade no dente. A cavidade seria o estágio final da cárie dentária. Nessa visão mais recente, todo o processo de atividade do biofilme dentário produzindo ácido, de des-remineralização, com a formação da mancha branca na superfície do esmalte dentário, mesmo na ausência de uma cavidade, é entendido como doença.

Aqui reside o âmago desta tese: será que esta visão mais moderna, que define a presença da doença com base no conceito de atividade em um processo que pode ou não levar a uma cavidade no futuro é correta? Será que esta definição da doença é melhor para a saúde das pessoas do que a definição antiga de cárie dentária como cavidade no dente? Um conceito chave da medicina moderna é que nem sempre o diagnóstico mais cedo é melhor - "*Earlier is not necessarily better*" (ARONSON *et al.*, 2019).

O CPOD mede a cárie dentária somente quando há cavidade. Na visão moderna, o CPOD detecta a cárie dentária tarde demais. Além disso, o CPOD não avalia se a lesão de cárie está ativa ou não. Definir se a lesão está ativa ou não, é importante na visão moderna da cariologia, mas o CPOD não avalia este aspecto da lesão de cárie. O que precisa ser respondido é se, mesmo que seja possível se medir de forma confiável se uma lesão de cárie está ativa ou não, esta mensuração terá implicação relevante para a saúde da pessoa.

Antes de entrar nesta discussão, vamos descrever a seguir um índice que tem sido adotado como uma alternativa ao CPOD para diagnosticar a presença de cárie. Este índice é coerente com os conceitos modernos de definição da doença, diagnosticando a presença de desmineralização do esmalte dentário mesmo quando não há cavidade e a definição se a superfície com sinal de desmineralização representa uma lesão "ativa" ou "inativa".

Este índice mais recente, que vem sendo cada vez mais utilizado, é o Sistema Internacional de Avaliação e Detecção de Cáries (ICDAS). O índice ICDAS foi desenvolvido entre 2002 e 2004. Seu desenvolvimento baseou-se nos argumentos de que a confiabilidade dos sistemas de detecção/diagnóstico de cárie disponíveis, inclusive com critérios táteis e visual-táteis não é boa e de que existem muitos sistemas de detecção incompatíveis entre si. O objetivo foi desenvolver um índice

que fosse simples, lógico, baseado em evidência para a classificação e detecção de cárie, de modo a permitir o correto diagnóstico, prognóstico e acompanhamento clínico da cárie dentária em nível individual e coletivo (EKSTRAND *et al.*, 2018).

Este índice se propõe a detectar cárie o mais precocemente possível. Avaliando a validade preditiva e de constructo do índice através de um estudo de coorte, observou-se que lesões oclusais ativas não cavitadas tem maior chance de progredirem do que as lesões inativas. Uma característica do ICDAS é que ele permite aos profissionais identificar que tipo de lesão de cárie tem maior probabilidade de progredir, concentrando assim os seus esforços em impedir sua progressão (GUEDES *et al.*, 2014). Desde o início, o índice foi pensado e desenhado não só para pesquisadores, mas também para uso na prática clínica, com o objetivo de possibilitar um plano de tratamento personalizado, de acordo com as necessidades do paciente (PITTS, 2009).

O índice possui uma escala que varia de 0 (zero) a 6 (seis), onde 0 (zero) corresponde a dente hígido, 1 (um), cárie inicial, identificada como a presença de mancha branca após secagem; 2 (dois), alteração visível no esmalte dentário, identificada como a presença de mancha branca mesmo sem secagem; 3 (três), cavidade inicial em esmalte; 4 (quatro), sombreamento da dentina, com o aparecimento de imagem escurecida; 5 (cinco), cavidade perceptível alcançando dentina visualmente; e 6 (seis), cavidade extensa com comprometimento da dentina (ICDAS, 2019; PITTS, 2009).

A vantagem relatada deste índice é a possibilidade de se registrar cárie em estágio inicial, permitindo que se identifique o próprio processo histopatológico da lesão. Entretanto, existem desvantagens, tais como a imperatividade de que o exame seja feito com boa iluminação, em dente limpo, livre de biofilme e com possibilidade de secagem, o que nem sempre é possível em estudos epidemiológicos. Além dessas questões relacionadas ao ambiente adequado para o exame, a padronização do exame também é difícil, uma vez que o diagnóstico das fases iniciais de cárie é mais difícil e sujeito a erro (ICDAS; BRAGA, 2012). Ekstrand *et al.* (2018), em uma revisão sistemática que avalia a reprodutibilidade do índice, verificaram que a maioria dos estudos encontrados eram laboratoriais (77%) e desenvolvidos em dentes permanentes (60%). A maioria desses estudos (75%), ainda, avaliou face oclusal. Os autores indicaram que os estudos que buscam aproximar os resultados da realidade da atividade clínica são limitados quando a

precisão do método de detecção de cárie é testada, por causa de problemas relacionados aos métodos de referência utilizados para a validação. Com isso, os estudos clínicos pesquisados mostraram uma ligeira redução na performance dos examinadores que utilizaram o ICDAS, provavelmente causado pelo fato dos exames terem sido executados sob condições naturais. O treinamento de examinadores para o ICDAS é bastante oneroso e os profissionais menos experientes tendem a ser menos precisos na detecção de cárie através de inspeção visual. Entretanto, o ICDAS é considerado um sistema de detecção de cárie sólido na maioria das condições testadas (EKSTRAND *et al.*, 2018).

Além dos índices CPOD, CPOS, ceod, ceos e ICDAS, diversos outros índices foram propostos ao longo do tempo para medir cárie dentária. São índices menos utilizados, tais como o Índice simplificado de Viegas (VIEGAS, 1969), Índice de dentes funcionais, Índice de equivalência a dentes saudáveis (MERCENES; AUBREY, 1993), e o Índice de Nyvad 1999 (NYVAD; MACHIULSKIENE; BAELUM, 1999). Existem ainda índices para medir cárie radicular e lesões secundárias.

1.5 O diagnóstico da cárie dentária

Baelum *et al.* (2006) pontuam que a cárie deve ser definida pelos seus sinais e sintomas. Os métodos contemporâneos de diagnóstico de cárie devem permitir, portanto, uma distinção entre lesões cavitadas e não cavitadas, ativas e inativas.

Além das radiografias interproximais como auxiliar de diagnóstico, Gomez (2015) indica que métodos adicionais de detecção de cárie, tais como a fluorescência induzida pela luz, a transiluminação por fibra ótica e a condução elétrica, podem ser usados como técnicas adjuntas para a decisão clínica no diagnóstico de cárie. A transiluminação por fibra ótica parece ser bem confiável para a detecção de cárie em superfícies proximais, enquanto os equipamentos de fluorescência são questionados no que se refere à detecção de lesões de cárie oclusais ou em presença de hipomineralização de esmalte de origem outra que não a cárie dentária (FRENCKEN, 2012). Nyvad (2017) afirma que a melhor alternativa para o diagnóstico das lesões de cárie ainda é o exame clínico visual-tátil, que permite identificar as lesões cavitadas ativas e inativas.

As lesões de cárie, passíveis de identificação, em seu processo de evolução, vão desde uma lesão mal discernível em nível de esmalte até cavidades francas e

evidentes. Esse fato, segundo Nyvad (2017), “levanta uma questão sobre qual limiar (inferior) deve ser utilizado para diferenciar acárie da não cárie”.

Fejerskov (2017) e Nyvad (2017) pontuam várias razões pelas quais deve-se questionar a filosofia de que quanto antes uma lesão é identificada, melhores são as possibilidades de uma intervenção não operatória ser bem-sucedida. Para os autores, reduzir o limiar diagnóstico não resulta somente na detecção de um número maior de lesões iniciais, mas também em um maior número de diagnósticos falso-positivos, o que levaria a um número maior de intervenções não-operatórias desnecessárias. Baelum *et al.* (2006) concorda e indica que as consequências de diagnósticos falso-positivos devem ser avaliadas. O autor pontua, ainda, que os diagnósticos falso-positivos são mais comuns que os falso-negativos. Lembra, ainda, que “muitas lesões subclínicas apresentarão supressão ou regressão sem intervenção profissional ativa como resultado dos processos fisiológicos naturais do biofilme”.

Não existe um conjunto de critérios diagnósticos que seja considerado um “padrão ouro”, indicado para todas as situações. Cabe ao profissional escolher os critérios que melhor se adaptem às suas necessidades. Entretanto, atualmente, é preconizado que tanto as lesões cavitadas como as não cavitadas sejam identificadas (NYVAD, 2017). Isto leva ao questionamento sobre como proceder com essas lesões não cavitadas identificadas precocemente. Devem sofrer alguma intervenção especial e direcionada a elas? Ou devem, simplesmente ser monitoradas, mantendo-se ou intensificando os métodos preventivos destinados a todos os dentes e faces? Essas lesões têm condições de se tornarem inativas somente com a exposição ordinária ao fluoreto presente na pasta de dente? Autores como Nyvad *et al.* (2003) pensam que, em muitos casos, sim.

A última palavra fica com Fejerskov (2017), que é um dos cariologistas mais influentes na atualidade: “...*It thus* ***remains to be demonstrated that lowering the diagnostic threshold by means of more refined caries diagnostic methods can bring about a health benefit to the patients that outweighs the additional costs that will be incurred due to unnecessary treatments*** (grifo nosso). *Until such evidence has been presented, we cannot recommend lowering of the diagnostic threshold below that which can be obtained by visual-tactile examination for practical clinical purposes. However, this does not preclude the use of more advanced methods for research purposes”* (NYVAD, 2008). A lesão de cárie não cavitada

(mancha branca) é identificável pelo exame táctil-visual assim como a definição se ela está ativa ou inativa. Fejerskov (2017), portanto, questiona a identificação de lesões ainda mais imperceptíveis do que a mancha branca. Esta tese utiliza exatamente os argumentos de Fejerskov (2017) para questionar a identificação da mancha branca e sua definição como cárie (Quadro 1).

QUADRO 1: limiares de identificação da cárie com escores do ICDAS e proponentes de cada limiar. Em destaque o limiar que é o foco da pesquisa desta tese.

limiares de identificação da cárie com escores do ICDAS	Proponente
Superfície sem sinal sub clínico de desmineralização = ICDAS 0.	Fejerskov: cárie ausente Esta tese: cárie ausente
Superfície com sinal sub clínico de desmineralização (Detectável com métodos avançados mais sensíveis) = ICDAS 0.	Fejerskov: para pesquisa, cárie presente; para clínica cárie ausente Esta tese: idem
Superfície com sinal clínico de desmineralização – mancha branca (Detectável ao exame clínico táctil-visual) = ICDAS 2 e 3.	**Fejerskov: cárie presente** **Esta tese: para pesquisa, cárie presente; para clínica, cárie ausente**
Superfície com cavidade (Detectável ao exame clínico táctil-visual) = ICDAS 4, 5 e 6.	Fejerskov: cárie presente Esta tese: idem

A contribuição do profissional de Odontologia para a redução dos níveis de cárie dentária parece estar mais relacionada a mudanças nos critérios e decisões de tratamento do que na execução do mesmo (NADANOVSKY e SHEIHAM, 1995; FEJERSKOV, 2013). Refletir e avaliar o que fizemos e estamos fazendo ao longo dos anos é um elemento essencial para o exercício de uma odontologia voltada para a saúde da população. As intervenções que executamos tradicionalmente nos

consultórios alterou muito pouco o declínio da cárie dentária que ocorreu a partir da segunda metade do século XX (NADANOVSKY e SHEIHAM, 1995). De um modo geral, fica a impressão de que intervimos no processo de cárie, mas será que o estamos solucionando? A intervenção é sempre necessária?

1.6 Tratamento da lesão de cárie dentária não cavitada (mancha branca)

A higiene bucal com dentifrício fluoretado é considerada a principal razão para o declínio de cárie observado em muitas populações a partir da década de 1970 (NADANOVSKY e SHEIHAM, 1995). Quando disponível na cavidade bucal, mesmo em pequenas quantidades, o fluoreto tem um efeito importante sobre a estabilidade do processo de des-remineralização do dente, uma vez que é um potente agente na precipitação de minerais. Desta forma, o fluoreto reduz a desmineralização do tecido dentário e ativa a remineralização. Sendo assim, o efeito do fluoreto é tópico. O efeito preventivo do flúor é causado por sua capacidade de controlar a dinâmica da lesão de cárie. Mesmo uma atividade pequena de flúor irá reduzir a perda de cálcio e fosfato dos tecidos duros do dente e aumentar a presença do fluoreto na superfície da lesão. A pasta de dente ou qualquer outro veículo que venha a agir localmente, aumenta a concentração de fluoreto no meio bucal (FEJERSKOV; TENUTA; MARINHO, 2017). Há forte evidência de que dentifrícios contendo entre 1000 e 1250 partes por milhão (ppm) são os mais efetivos na prevenção de cárie dentária (WALSH *et al.*, 2019). Achados *in situ* sugerem, ainda, que a frequência de utilização de dentifrício fluoretado com 1000 ppm é importante para reduzir o desenvolvimento de novas lesões de cárie (NOBREGA *et al.*, 2016). Ou seja, quanto maior a frequência com que o fluoreto se faz disponível na cavidade bucal, maior será a sua disponibilidade para atuar no processo de des-remineralização do esmalte dentário. Segundo Nyvad *et al.* (2003), esse mecanismo nos leva a formular a predição de que as lesões ativas de cárie expostas ao flúor têm uma maior chance de se tornarem inativas ou saudáveis que as não expostas. O flúor só faz efeito quando ocorre um processo ativo de cárie.

A ingestão de água fluoretada também tem um papel importante na prevenção da cárie dentária, sendo capaz de reduzir a sua incidência em 35% (IHEOZOR-EJIOFOR *et al.*, 2015). A fluoretação da água de abastecimento

antecedeu todos os produtos fluoretados desenvolvidos. Embora inicialmente se pensasse que a sua ação era sistêmica, sabe-se, atualmente, que a principal forma de atuação do fluoreto é local, mesmo para a água potável. A partir da sua introdução, surgiram não só as pastas de dente fluoretadas, mas também os enxaguantes, géis e vernizes, todos produtos de atuação tópica, com comprovada eficácia no controle da cárie dentária (MARINHO *et al.*, 2003).

Géis ou espumas de fluoreto de aplicação profissional são indicados para indivíduos com risco moderado a alto de cárie, embora o seu custo-efetividade venha sofrendo questionamentos. Estes géis de alta concentração (em torno de 12.300 ppm de flúor) podem ser de pH acidulado ou neutro, sendo os acidulados mais efetivos, e são tipicamente aplicados entre uma e várias vezes ao ano (MARINHO *et al.,* 2015). O seu mecanismo de ação baseia-se na formação de reservatórios de fluoreto na superfície dentária, que interferem no processo de des-remineralização O seu uso não é recomendado em crianças abaixo dos seis anos de idade, por causa do risco de intoxicação. Estudos sugerem que a utilização desses géis pode levar a uma redução média de 28% das lesões de cárie em ambas as dentições (MARINHO *et al.,* 2015), embora autores como van Rijkom *et al.* (2004) sugiram que a redução não é clinicamente relevante. Marinho *et al.* (2015) e Twetman & Keller (2016) concordam que a qualidade da evidência dos estudos, entretanto, varia entre moderada e baixa. Ademais, a execução de profilaxia prévia a aplicação do gel parece não trazer benefícios adicionais (WEYANT, 2013), embora seja comumente executada.

O verniz fluoretado é uma substância com alta concentração de fluoreto utilizada para o controle de cárie. A utilização do verniz fluoretado é amplamente indicada para crianças e adolescentes com alto risco de cárie, como forma complementar à utilização de água e dentifrício fluoretados. Comparando-se revisões sistemáticas sobre pasta de dente, enxaguatórios, géis e verniz fluoretados, este último apresenta maior fração prevenida de DMFS médio (FEJERSKOV et al., 2017). Apesar disso, Sousa *et al.* (2019), em uma revisão sistemática sobre a utilização de verniz fluoretado em pré-escolares, encontraram que, no nível de superfície, os resultados encontrados foram favoráveis à utilização do verniz fluoretado, mas o tamanho do efeito foi pequeno e, portanto, com pouca relevância clínica, e quando a avaliação se deu a nível de dente, não foi encontrada diferença estatisticamente significativa entre as crianças tratadas com verniz fluoretado e as

que não receberam o produto. Estes autores apontaram, ainda, que estudos mais recentes não mostraram resultados favoráveis ao verniz. Entretanto, Timms e Deery (2020), comentando esta informação acreditam que este dado ainda não é suficiente para que se elimine a indicação de utilização do verniz fluoretado em crianças do Reino Unido com alto risco de cárie.

O diamino fluoreto de prata é um composto formado pelo nitrato de prata somado ao flúor, que vem sendo utilizado em países como Japão, China e Nova Zelândia há várias décadas, em diferentes concentrações. Em 2014, a *Food and Drug Administration* (FDA) autorizou a utilização da substância nos Estados Unidos para o tratamento de hipersensibilidade dentinária, levando muitos profissionais a fazer uso do produto *off-label* para o tratamento de lesões de cárie, o que fez aumentar muito o número de estudos (RAJENDRA *et al.,* 2017). De baixo custo, possui a capacidade de paralisar o processo de cárie, sendo conhecido como cariostático. O produto reduz o crescimento de bactérias cariogênicas, dificulta a degradação de colágeno da dentina e inibe a desmineralização, promovendo a remineralização dos tecidos dentários. De fácil utilização, dispensa o uso de instrumentos rotatórios. Por esta razão, é indicado para uso em crianças com alto risco de cárie e dificuldade de manejo comportamental, bem como naquelas de pouca idade, com cárie de acometimento precoce, uma vez que não é necessária a remoção de tecido cariado (CRYSTAL; NIEDERMAN, 2017). Sua grande desvantagem está relacionada a questões estéticas. O produto escurece a lesão paralisada, que fica com um aspecto enegrecido. Entretanto, tem sido demonstrado que esta questão costuma afetar muito mais os dentistas que os pais e responsáveis pelas crianças. (CHU *et al.*, 2010; OLIVEIRA *et al.*, 2019).

Géis e vernizes a base de clorexidina são agentes antibacterianos que vêm sendo testados para avaliar sua capacidade de intervir no metabolismo do biofilme, reduzindo a presença de microrganismos cariogênicos. Zhang et al. (2006) sugerem que a frequência de aplicação parece ser importante para a eficácia dos vernizes a base de clorexidina. Entretanto, poucas evidências têm sido encontradas de que são eficazes na prevenção da cárie dentária ou na redução nos níveis de *Streptococcus mutans* (WALSH *et al.*, 2015).

Agentes não fluoretados de aplicação tópica contendo caseína, cálcio e/ou fosfato tem sido investigados como alternativa ou combinados aos fluoretos, para melhorar a remineralização dos tecidos dentários (PARNELL *et al*, 2012). O CPP-

ACP (caseína fosfato de cálcio amorfo) está disponível em formulações do tipo mousses, cremes, pastas, pastilhas, gomas de mascar, leite ou enxaguatórios (BIJLE *et al*, 2017). Alguns autores têm relatado que formulações contendo CPP-ACP possuem efeitos semelhantes aos de dentifrícios e soluções para bochecho fluoretadas em estudos *in vitro*, *in situ* ou clínicos randomizados (COCHRANE; REYNOLDS, 2012; ABDULLAH; JOHN, 2016; LI *et al*., 2014). Aykut-Yetkiner *et al.* (2014), entretanto, encontraram um efeito leve de remineralização após 3 meses de uso da pasta contendo esta substância. O objetivo principal da introdução do CPP-ACP seria aumentar as concentrações de íons cálcio e fosfato nas lesões incipientes de cárie para promover a remineralização pela inibição da adesão bacteriana ao dente, prevenindo a formação do biofilme dental ou a produção de amônia (COCHRANE *et al.,* 2010). Entretanto, em pH neutro, o biofilme já está supersaturado, o que suscita dúvidas quanto a sua atuação (FONTANA, 2016). Cabe ressaltar ainda, que tal substância não deve ser utilizada em indivíduos que relatam alergia à proteína do leite.

Superfícies dentais oclusais são de difícil higienização, em razão da sua anatomia, que favorece a retenção de alimentos e estagnação do biofilme dental. As oclusais dos molares permanentes são as faces mais atacadas por cárie, especialmente durante o processo de erupção dentária (CARVALHO, 2014). O desenvolvimento dos conceitos e técnicas de adesão, na década de 1950, possibilitou o surgimento dos selantes. Os selantes foram originalmente desenvolvidos para serem aplicados na superfície oclusal com o objetivo de criar uma barreira física que previne o crescimento do biofilme nas fóssulas e fissuras (AHOVUO-SALORANTA *et al*., 2017). Embora os selantes tenham surgido com propósito preventivo, atualmente, estes materiais também têm sido usados para o controle e monitoramento das lesões iniciais de cárie dentária. Os selantes resinosos e ionoméricos são os mais comuns. Evidências mostram que o selamento de lesões de cárie, em esmalte ou mesmo em dentina, reduz a probabilidade da sua progressão, alcançando uma fração preventiva de mais de 70% e demonstrando a sua efetividade no controle de cárie (GRIFFIN *et al.,* 2008; BORGES *et al.,* 2012).

O ionômero de vidro tem como característica a liberação de flúor no ambiente bucal, sua mais celebrada vantagem. Outra vantagem é a menor vulnerabilidade à umidade, o que favorece a sua indicação para dentes não completamente erupcionados, quando o controle de umidade é mais difícil. O selante ionomérico foi

introduzido como um material alternativo ao selante resinoso para selar fóssulas e fissuras. Entretanto, ao contrário dos selantes resinosos, não são capazes de realizar micro retenção no esmalte dentário. Desta forma, possui adesão mais frágil ao esmalte (MICKENAUTSCH; YENGOPAL, 2013; COLOMBO, 2018).

Existem muitos ionômeros disponíveis no mercado. Eles podem ser quimicamente ativados, fotoativados ou modificados com resina. Os ionômeros quimicamente ativados podem, ainda, ser divididos de acordo com a sua viscosidade, que pode ser alta ou baixa. Os ionômeros de alta viscosidade parecem ter melhores propriedades de retenção que os de baixa viscosidade, particularmente quando utilizados na técnica de pressão digital do tratamento restaurador atraumático (AHOVUO-SALORANTA *et al.*, 2016).

O selante resinoso vem sendo utilizado desde a década de 1960, sendo largamente difundido. Seu sucesso depende da sua retenção, que depende de um bom isolamento do campo operatório. O selante ionomérico, por sua vez, tem a possibilidade de ser aplicado em condições mais adversas de trabalho, como locais sem equipamento odontológico (LIU *et al.*, 2014).

A atuação do selante resinoso se dá, essencialmente, pela formação de uma barreira física que bloqueia e impede o crescimento do biofilme na região. A maior vantagem dos selantes resinosos é a sua maior durabilidade, influenciada pela boa penetração do material nos diferentes tipos de fissuras e pela adesão ao esmalte dentário (CVIKL, 2018)

Embora o uso dos selantes esteja consagrado na literatura e indicado em *guidelines* de Odontopediatria e Promoção de Saúde (WRIGHT, 2016), há evidência moderada de que a presença de selantes resinosos é capaz de prevenir lesões de cárie na face oclusal entre 11% e 55% quando comparada à ausência de selantes. Não há evidência suficiente para avaliar a efetividade dos selantes ionoméricos (AHOVUO-SALORANTA*, et al.*, 2017).

Diante do sucesso do selante resinoso para a prevenção de cáries oclusais, alguns autores resolveram testá-lo em lesões incipientes de faces proximais, relatando sucesso (URIBE, 1999). Abuchaim *et al.* (2010) também encontraram bons resultados no selamento dessas lesões com sistemas adesivos.

Uma alternativa mais recente, para utilização em superfícies lisas, dentro da filosofia da Odontologia minimamente invasiva, são os infiltrantes. Os infiltrantes foram desenvolvidos com o objetivo de paralisar lesões iniciais de cárie em

superfícies proximais. Anauate-Netto *et al.* (2017) obtiveram sucesso na aplicação deste material em 23 voluntários após 3 anos de estudos. Paris *et al.* (2020) relata sucesso após 7 anos acompanhamento em 22 adultos jovens. Outros autores também indicam que o selamento de lesões proximais de cárie, em dentes permanentes e decíduos parece ser efetivo no controle de lesões iniciais de cárie (AMMARI *et al.*, 2014). Todos os estudos, entretanto, referem-se a um único produto, não havendo ainda diversidade de fabricantes no mercado.

Além da utilização no diagnóstico, diferentes tipos de lasers têm sido pesquisados para a prevenção de cárie dentária. Ainda são poucos os estudos feitos em humanos; entretanto, alguns desses estudos têm se mostrado promissores, especialmente quando estes aparecem associados aos fluoretos, seja de forma alternativa ou sinérgica. O efeito do laser se dá alterando a estrutura do esmalte, de modo a torná-lo menos susceptível à ação desmineralizante dos ácidos produzidos pelos microrganismos cariogênicos (AL-MALIKY, 2020).

Abanto et al. (2015) sugerem que as consultas periódicas odontológicas são de grande valia para a prevenção de lesões iniciais de cárie, sugerindo que estas devem ter seu intervalo determinado de acordo com o risco de cárie do paciente. Lee et al. (2020) ponderam, entretanto, que, em seu estudo, embora o aumento de consultas tenha melhorado o acesso a medidas preventivas e uma diminuição na procura por serviços de emergência, também foi verificado um aumento dos reembolsos associados à sedação.

1.7 O prognóstico da lesão de cárie dentária não cavitada (mancha branca)

A cárie dentária é uma doença crônica não transmissível, que se manifesta através de lesões nos dentes que só causam desconforto, dor ou pode trazer algum comprometimento ao indivíduo quando uma cavidade em dentina se estabelece. Pode-se traçar um paralelo com a diabetes. Quando um médico trata um indivíduo com diabetes, este tem plena consciência de que as lesões causadas pela doença são resultado da doença e não a doença em si. O tratamento deve visar ao equilíbrio do indivíduo doente e a lesão deve sofrer intervenção na medida em que esta traz comprometimento ao indivíduo. É importante saber a proporção de lesões iniciais de cárie (mancha branca) que evoluem para cavidades, ou seja, quais sequelas da doença trazem comprometimento ao paciente, para que se planeje como intervir.

Este dado está relacionado ao risco de progressão da doença, que pode ser alto, moderado ou baixo, e ao seu prognóstico.

A progressão das lesões para cavidade varia de acordo com o tipo de superfície dentária, a severidade da lesão e o seu status de atividade. Ferreira Zandona *et al.* (2012), em um estudo sobre a história natural da cárie, encontraram que em 4 anos, em apenas 3% das superfícies hígidas acompanhadas houve diagnóstico de lesão de cárie. Nos dentes não erupcionados no início do estudo, apenas 1% das superfícies tornaram-se cavitadas. Aproximadamente 20% das lesões classificadas como ICDAS 1, 32% das classificadas como ICDAS 2 e 68% das classificadas como ICDAS 3 no início do estudo, evoluíram para cavidade em dentina ao final de quatro anos.

Os molares são mais susceptíveis à cárie, seguidos dos pré-molares e dentes anteriores (BATCHELOR; SHEIHAM, 2004). Com relação as superfícies, as oclusais são as mais susceptíveis. Lesões em crianças progridem mais rapidamente, provavelmente devido a imaturidade do esmalte dentário recém erupcionado (FERREIRA ZANDONA *et al.*, 2012).

Lesões não cavitadas ativas em superfícies oclusais têm chances 60% maiores de se tornarem cavitadas. Considerando todas as superfícies de um dente, por volta de 10% de lesões ativas não cavitadas e 50% de lesões cavitadas somente em esmalte se tornaram francamente cavitadas, restauradas ou perdidas no desfecho. Entre as lesões inativas, 6,2% das lesões não cavitadas e 34,3% das lesões cavitadas em esmalte ou microcavitadas tornam-se francamente cavitadas, restauradas ou perdidas. Considerando todas as superfícies, lesões ativas não cavitadas tem maior chance de progredirem para cavidade do que as lesões inativas (NYVAD *et al.*, 2003; GUEDES *et al.*, 2014). Segundo Nyvad *et al.* (2003), ainda, lesões ativas não cavitadas têm um maior risco de progressão para cavidade do que lesões não ativas. Lesões ativas não cavitadas, assim como lesões inativas, têm, ainda, um risco consideravelmente maior de progredir para cavidade do que as superfícies hígidas.

A proporção de lesões oclusais não cavitadas pode atingir mais de dois terços de todas as lesões oclusais identificadas. A diferença é ainda maior nas populações com baixa prevalência de cárie, onde a maioria das lesões não cavitadas vão continuar neste mesmo estágio de desenvolvimento. Existe uma tendência a se superestimar a presença e a profundidade das lesões de cárie, bem como de tratar

de forma invasiva lesões em esmalte (CARVALHO *et al.*, 2016). Pode estar havendo tratamento desnecessário. Ainda não estão claros os limiares clinicamente relevantes para a detecção da cárie dentária. Segundo Nyvad (2017), devemos compreender que "o processo chamado 'diagnóstico' ou 'detecção' da cárie, na realidade, é o diagnóstico ou a detecção das 'lesões que precisam ser tratadas', e não da doença".

Hummel *et al.* (2019) consideram que as lesões em esmalte levam um período relativamente longo para desenvolver lesões em dentina. Desta forma, considera-se que 3 anos é o período mínimo para se observar a progressão de cárie. O autor alerta, entretanto, que este tempo talvez não seja necessário para a dentição decídua, uma vez que as lesões em dentes decíduos geralmente progridem mais rapidamente que nos dentes permanentes. Mejàre et al. (1998) acompanharam radiograficamente o desenvolvimento de cárie de adolescentes dos 11 aos 22 anos e verificaram que a porcentagem de lesões proximais que atingiram a metade interna da dentina antes de serem restauradas variou de 0 a 1% ao logo dos anos do estudo. Em geral, a progressão da lesão em esmalte é lenta, sendo que a sua velocidade aumenta consideravelmente quando a lesão atinge a dentina (MEJARE *et al*., 2004). Desta forma, levando-se em consideração essa lentidão na progressão da cárie dentária na maioria dos indivíduos, o tempo de acompanhamento deve ser consideravelmente extenso para que se detecte a progressão na metade interna da dentina.

A regressão de lesões não cavitadas de cárie é comum em estudos longitudinais. A chance desta transição ocorrer é marcadamente influenciada pela presença de flúor. Lesões ativas expostas ao flúor têm maior chance de se tornarem saudáveis e menor risco de se tornarem cavitadas do que as não expostas ao flúor (NYVAD *et al.*, 2003), especialmente quando o processo de des-remineralização está equilibrado.

A presença do flúor no meio bucal inibe a progressão para os estágios de cárie ativa ou cavitada em todos os estágios de formação de lesão, embora este efeito apareça mais pronunciado para superfícies recém erupcionadas ou com lesão ativa. O flúor também melhora a regressão da mancha branca ativa. Muitas superfícies hígidas e superfícies com mancha branca inativa podem experimentar um processo ativo de cárie em algum momento. A presença do flúor interfere neste

processo (NYVAD *et al.*, 2003). Desta forma, expor todos os dentes ao flúor parece ser uma medida custo-efetiva.

1.8 Desfechos verdadeiros versus desfechos substitutos – a lesão de cárie não cavitada (mancha branca) pode ser considerada um desfecho verdadeiro?

Vários pesquisadores têm optado por continuar utilizando o índice CPOD, mas fazendo modificações no C de cariado, para incluir mancha branca. Alguns autores optam por incluir dentes com mancha branca no grupo de dentes hígidos, enquanto outros optam pela sua colocação no grupo de cariados (AXELSSON *et al.*, 1987; ALANEN *et al.*, 2000; AUTIO-GOLD; COURTS, 2001). Por outro lado, ainda é significativo o número de autores que medem CPOD no seu formato original, sem incluir mancha branca (BAGRAMIAN, 1982; BACA *et al.*, 2004; CHANDRASHEKAR *et al.*, 2014). Fica claro, então, que existe uma dúvida na comunidade científica sobre como lidar com a mancha branca e uma questão importante quando se planeja um estudo clínico é definir o desfecho que se deseja estudar. Deve ser considerada cárie? Se a mancha branca for considerada cárie, ela deve ser tratada. Por outro lado, a mancha branca pode ser entendida como um sinal do estado dinâmico do processo des-remineralização que pode remineralizar e desaparecer, estabilizar ou transformar-se em uma cavidade. Caso uma proporção grande de dentes com manchas brancas não se tornem cariados ou caso o tratamento da mancha branca reduza relativamente pouco o risco de cárie (cavidade), mancha branca não deve ser considerada um desfecho (ou estado) relevante que deva ser diagnosticado, detectado ou tratado.

Esta questão pode ser mais esclarecida no contexto da discussão sobre a utilização dos desfechos verdadeiros e desfechos substitutos. O desfecho pode ser definido como um resultado, condição ou evento que está associado a um tratamento ou objeto de estudo.

A mais importante característica para a seleção do desfecho primário em ensaios clínicos é que os efeitos sobre o desfecho devem fornecer evidência confiável sobre se a intervenção é capaz de prover benefícios clínicos significativos. Desta forma, o desfecho verdadeiro deve ser um evento clínico relevante para o paciente, ou, o desfecho deve medir diretamente o que o paciente sente, suas

funções ou sobrevivência, onde as funções referem-se à habilidade do paciente em executar atividades do seu cotidiano (FLEMING; POWERS, 2012).

Sendo assim, o desfecho verdadeiro deve trazer benefício tangível, que pode ser sentido ou verificado pelo paciente. Ou seja, o paciente deve conseguir perceber que a intervenção testada é capaz de beneficiá-lo de alguma forma, impactando em sua vida (FLEMING; POWERS, 2012).

O desfecho verdadeiro, em uma alteração crônica, normalmente, é raro ou distante no tempo, o que, por vezes, inviabiliza a pesquisa. Desfechos substitutos, que são preditores dos verdadeiros são, então, utilizados em seu lugar. Desfechos substitutos não constituem evidência inequívoca de que o tratamento pesquisado produz benefícios tangíveis para o paciente (HUJOEL; DEROUEN, 1995).

A FDA regulamenta o uso de desfechos substitutos nos Estados Unidos em estudos clínicos quando os dados são utilizados para sustentar novas aplicações de medicamentos ou expandir as indicações em bulas de medicamentos já aprovados. Para novos medicamentos, os desfechos dos estudos clínicos devem ser verdadeiros com benefícios diretos para os pacientes (HOLLOWAY; DICK, 2002).

Um desfecho substituto é uma medida de resultado utilizada como um substituto para um desfecho verdadeiro, clinicamente significativo. Espera-se que as alterações induzidas por uma terapia em um desfecho substituto reflitam as mudanças ocorridas em um desfecho verdadeiro. Um desfecho substituto válido é aquele que tem o seu significado clínico semelhante ao do desfecho verdadeiro (HOLLOWAY; DICK, 2002). Muitas medidas de resultados usadas na pesquisa clínica não são desfechos clinicamente significativos, mas são medidas indiretas que são usadas como desfechos substitutos (FLEMING; POWERS, 2012). A existência de correlação entre o desfecho verdadeiro e o substituto é necessária, mas não é suficiente. O desfecho substituto deve, também, capturar o efeito do tratamento sobre o desfecho verdadeiro (GRIMES, 2005).

A principal motivação para a utilização de desfechos substitutos é a possibilidade de se utilizar uma amostra reduzida ou uma duração de tempo menor em um ensaio clínico. A opção pelo desfecho verdadeiro pode ser mais invasiva, desconfortável ou dispendiosa (PRENTICE, 1989).

A validação de um desfecho substituto requer o fornecimento de uma evidência

justificada, geralmente baseada em ensaios clínicos controlados e randomizados, de que a obtenção de efeitos substanciais no desfecho substituto prediz de forma confiável o alcance de efeitos importantes no desfecho verdadeiro (FLEMING; POWERS, 2012). Para isso, seria importante que estudos fossem conduzidos analisando-se ambos os desfechos, para validar os desfechos substitutos. Entretanto, no caso de se desenvolver um estudo utilizando-se um desfecho verdadeiro, entende-se que a utilização de um desfecho substituto perde a sua razão de ser, e isso termina não ocorrendo. Ainda assim, esta medida traria benefícios a futuros estudos, que poderiam se valer das vantagens do desfecho substituto, com a segurança de se alcançar o objetivo adequado (GRIMES, 2005). Deve-se reconhecer, entretanto, que nenhum desfecho substituto consegue substituir completamente o desfecho verdadeiro (HOLLOWAY; DICK, 2002).

A utilização de desfechos substitutos é comum nos estudos relacionados a cárie dentária. A completa retenção do selante resinoso tem sido utilizada como um desfecho substituto para avaliar se esta intervenção evita a cárie dentária. Para isso, é desejável que exista associação direta entre presença ou ausência de cárie em dentes selados e independência da proporção entre retenção e cárie com o tipo de material selante utilizado. Mickenautsch and Yengopal (2013), em uma revisão sistemática, concluíram que a retenção dos selantes não pode ser considerada um desfecho substituto válido, uma vez que a eficácia de diferentes materiais não pode ser deduzida da sua capacidade de retenção.

Embora o efeito de uma intervenção em um biomarcador forneça evidência direta sobre a atividade biológica, tais evidências podem não ser confiáveis quanto aos benefícios do tratamento, ainda que o biomarcador esteja fortemente correlacionado com o tratamento realizado (FLEMING; POWERS, 2012).

Biomarcadores fortemente correlacionados com medidas clínicas de eficácia nas observações da história natural de uma doença, ainda que não estejam no caminho causal do processo da doença, provavelmente fornecerão informações enganosas sobre a eficácia clínica. Um exemplo disso é que, embora o risco de mulheres grávidas infectadas pelo HIV transmitirem a infecção a seus bebês esteja fortemente correlacionado com a contagem materna de CD4, uma intervenção como a interleucina-2 no final da gravidez, para aumentar a contagem materna de CD4 não afetaria esse risco de transmissão. Essa correlação entre CD4 materna e risco de transmissão de mãe para filho do HIV existe porque ambas as medidas são

influenciadas pela carga viral materna. Informações mais confiáveis sobre possíveis efeitos sobre a transmissão do HIV de mãe para filho seriam obtidos ao avaliar se uma intervenção antirretroviral fornece grandes reduções nas taxas da carga viral materna, onde essas reduções são sustentadas durante a gravidez, trabalho de parto e amamentação. Obviamente, a abordagem preferida seria avaliar o efeito da intervenção direta no resultado da proporção de bebês infectados pelo HIV (FLEMING; POWERS, 2012).

Questões relacionadas à contagem de linfócitos CD4 como biomarcadores fizeram com que a OMS alterasse a sua recomendação para o início da terapia antirretroviral em indivíduos HIV positivos. Há alguns anos, a indicação para a terapia se dava apenas para indivíduos infectados com baixa contagem de linfócitos CD4, ou seja, já imunossuprimidos. Atualmente, a OMS recomenda fortemente, baseada em evidência moderada, que se inicie a terapia antirretroviral para pacientes acima de 19 anos de idade HIV positivos, independente da contagem de CD4. Esta recomendação baseia-se na observação de que o início precoce da terapia reduz o risco de progressão para a AIDS e/ou morte, tuberculose e doenças relacionadas a AIDS não definidas e aumenta a probabilidade de recuperação imunológica, além de reduzir o risco de transmissão sexual do vírus. Se antes de 2013, a OMS recomendava que o monitoramento fosse feito através da contagem de CD4, atualmente, a recomendação é que se monitore a carga viral como resposta preferida a terapia antirretroviral. Uma baixa contagem de CD4 faz supor que a carga viral do paciente está aumentada. A contagem de CD4 é um indicador que substituiria o indicador que realmente interessa, que é a carga viral. Não faz sentido monitorar o CD4, que pode ter seu número impactado por outras situações, ao invés de monitorar a carga viral, que é o que realmente importa. A OMS corrigiu esta distorção (WHO, 2015).

Duas revisões sistemáticas apresentam conclusões diferentes sobre a validade de biomarcadores salivares. Hegde *et al.* (2019) concordam com a existência de associação entre componentes da saliva e a cárie dentária e Martins *et al.* (2012) afirmam não haver evidência suficiente para se estabelecer que proteínas salivares possam ser vistas como biomarcadores confiáveis.

Kelly *et al.* (2021) sugerem a existência de biomarcadores genômicos extraídos da saliva para cárie dentária. Alguns fenótipos poderiam exercer um papel protetivo aumentando a chance de indivíduos se manterem livres de cárie ao longo

da vida. Desta forma, a presença destes fenótipos poderia ser útil para determinar a susceptibilidade de um indivíduo à cárie. Ressalte-se, entretanto, que a cárie dentária é uma condição multifatorial, que sofre forte influência dos cuidados pessoais individuais, bem como alimentação e medidas de prevenção, além de determinantes sociais e econômicos. É difícil determinar qual a capacidade de tais fenótipos de impactar na saúde bucal do indivíduo em diferentes condições de vida.

Tainio *et al.* (2018), em uma revisão sistemática, estudou a neoplasia intraepitelial cervical de grau 2 não tratada e verificou que metade das lesões não tratadas regrediu espontaneamente. Apenas uma lesão em cinco evoluiu progressivamente. As demais permaneceram estáveis. O tratamento das neoplasias intraepiteliais de grau 2 e 3 envolve excisão local no cervix e frequentemente é bem-sucedido. Entretanto, esta intervenção aumenta o risco de partos prematuros e perda do feto no primeiro trimestre de gestação em mulheres que engravidam após o tratamento. Levando-se em consideração a alta taxa de regressão espontânea da patologia e os riscos envolvidos na intervenção para mulheres jovens, em fase reprodutiva, têm aumentado o questionamento se deve-se intervir na neoplasia grau 2. Desta forma, uma abordagem conservadora dos casos de grau 2, com uma vigilância ativa, em lugar do procedimento invasivo, foi sugerido, especialmente para mulheres jovens.

O rastreamento do câncer de mama também é um exemplo de que excessos podem trazer danos aos indivíduos. A detecção e o tratamento precoces são considerados os meios mais efetivos de se reduzir a sua mortalidade. A recomendação do Ministério da Saúde é de que o rastreamento não seja realizado em mulheres com menos de 50 anos de idade, pois as probabilidades de danos são bem maiores do que benefícios para mulheres com menos de 50 anos. O dano mais comum é o resultado falso-positivo, cuja probabilidade cumulativa de ocorrência é de 61% quando o exame é executado com periodicidade anual. O resultado falso-positivo leva a paciente a um estresse desnecessário, podendo ter, ainda, consequências mais graves, que são o sobrediagnóstico e o tratamento desnecessário (MIGOWSKI *et al.*, 2018).

Ainda na oncologia, marcadores tumorais como o antígeno prostático específico (APE/PSA) e o antígeno carcinoembrionário (ACE/CEA) estão correlacionados nas observações da história natural da doença com medidas de eficácia clínica, como sintomas de câncer e morte. Essas correlações são suficientes

para permitir que se considere essas medidas úteis para avaliar o prognóstico em pacientes recebendo tratamento para a doença, ou para diagnóstico da doença. No entanto, os efeitos no CEA e PSA fornecem informações não confiáveis, uma vez que é o processo de carga tumoral, mais que os níveis de CEA ou PSA, o verdadeiro mecanismo causal para o risco de sintomas e mortalidade induzidos pelo câncer (FLEMING; POWERS, 2012).

A validade do uso da pressão arterial como desfecho substituto em doenças cardiovasculares em estudos clínicos de hipertensão arterial muitas vezes é discutida. A validade das medidas de pressão arterial como desfecho substituto depende fortemente da definição das medidas de eficácia clínica. As medidas de pressão arterial são muito preditivas de efeitos no acidente vascular cerebral, entretanto, são menos preditivas de efeitos no infarto do miocárdio, morte cardiovascular e morte em geral e pouco preditivas de efeitos na insuficiência cardíaca. Isso reforça o argumento de que, quando se utiliza um biomarcador como desfecho substituto, é preciso ter clareza sobre qual desfecho verdadeiro se deseja substituir (FLEMING; POWERS, 2012).

Desta forma, desfechos verdadeiros devem ser preferidos, uma vez que desfechos substitutos têm levado a conclusões enganosas para várias doenças crônicas (HUJOEL; DEROUEN, 1995).

Pode-se perceber, então, que a discussão acerca de benefícios da detecção precoce, riscos de diagnóstico equivocado, sobrediagnóstico e sobretratamento não estão restritas à cárie dentária.

2 JUSTIFICATIVA

Não se sabe quão cedo uma lesão de cárie deve ser detectada. Existe uma crença de que quanto mais cedo melhor. Porém, nem sempre o diagnóstico precoce é melhor. A detecção precoce de cárie dentária pode levar a tratamento desnecessário de pacientes que nunca seriam prejudicados pela doença.

Tradicionalmente a cárie é detectada quando há uma cavidade que já destruiu parte do esmalte e dentina. Recentemente tem havido uma tendência a detectar a cárie quando há apenas sinais de desmineralização do esmalte dentário sem a presença de cavidade. A desmineralização do esmalte não causa transtorno ao indivíduo, enquanto a cavidade frequentemente causa desconforto, dor, perda de dente e dificuldade para mastigar os alimentos, sorrir e interagir socialmente. A desmineralização do esmalte (mancha branca), portanto, somente deve ser detectada caso aumente significativamente o risco de progredir para cavidade. Além disso, a mancha branca somente deve ser tratada caso o tratamento diminua significativamente o risco de cavidade (isto é, mancha branca tratada deve ter risco menor de progredir para cavidade do que mancha branca não tratada).

Estudos anteriores investigaram a efetividade do tratamento da mancha branca. Entretanto, esses estudos não foram agregados nem criticamente discutidos dentro deste contexto da pertinência da detecção da mancha branca. A agregação de todos esses estudos de forma sistemática pode ajudar a definir se há evidência suficiente que justifique a detecção de mancha branca e sua definição como cárie dentária.

3 OBJETIVO

Investigar a efetividade do tratamento de lesões de cárie não cavitadas em dentes decíduos e permanentes, tendo como desfecho cavidade, restauração, perda ou dor de dente.

OBJETIVO ESPECÍFICO:

Investigar a efetividade de diferentes tipos de tratamento de lesões de cárie não cavitadas, incluindo fluoretos (pasta de dente, gel, verniz, bochecho, etc), selante de fóssulas e fissuras, infiltrante, instrução de higiene bucal, controle da dieta, limpeza profissional ou qualquer outro tipo de tratamento, em comparação com nenhum tratamento ou com placebo.

4 MÉTODO

Desenho de estudo

Foi realizada uma revisão sistemática da literatura, cujo protocolo foi registrado prospectivamente na base *International prospective register of systematic reviews* (PROSPERO) (ANEXO 1).

Busca bibliográfica

As buscas foram feitas nas seguintes bases de dados: The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE através do PubMed, EMBASE, WEB OF SCIENCE, SCOPUS, LILACS, Biblioteca Brasileira de Odontologia (BBO), EUA Clinical Trials Register (ClinicalTrials.gov). Resumos dos encontros da International Association of Dental Research (IADR) entre 2001 e 2019 e da European Organisation for Caries Research (ORCA) entre 1998 e 2020 também foram visitados. As referências dos estudos elegíveis e revisões sistemáticas e narrativas sobre o assunto estudado foram analisadas para verificar a presença de estudos potencialmente elegíveis.

As estratégias de busca completas para as diferentes bases de dados estão detalhadas no apêndice 1. A busca foi elaborada com a colaboração de uma bibliotecária especializada em revisões sistemáticas.

Todas as estratégias utilizaram-se obrigatoriamente dos termos: "Dental Caries", “dental decay”, “Caries”, “carious”, “tooth decay”, "Tooth Demineralization", “Tooth demineralization”, “Tooth demineralisation”, “initial caries”, “enamel caries”, “early caries”, “early tooth decay”, “non-cavitated”, “noncavitated”, “white spot lesion”, “White Spots”, “White Spot”, “white lesion”, “white lesions”, “initial caries”, “enamel caries”, “early caries”, “early tooth decay”, “caries reversal”, “approximal caries”, “demineralized lesions”, “demineralised lesions”, “enamel demineralisation”, “enamel demineralization” e “enamel white spot lesions”.

Pergunta PICO

A pergunta de pesquisa utilizada nesta revisão foi: “O tratamento de lesões não cavitadas de cárie é efetivo em impedir o aparecimento de cavidade dentária, restauração, dor de dente ou perda de dente, em indivíduos com dentes decíduos ou permanentes?”. Desmembrando a pergunta através da utilização do formato PICO (acrônimo de *Population, Intervention, Comparation, Outcome*) temos:

População – Adultos e crianças, incluindo dentes permanentes e decíduos, com lesão inicial, não cavitada de cárie.

Intervenção - Todo e qualquer tratamento não operativo (não invasivo) de cárie apresentado na literatura encontrada, incluindo o tratamento com substâncias infiltrantes, fluoretos em suas diferentes apresentações, diamino fluoreto de prata, caseína fosfato de cálcio fosfopeptídeo amorfo (CPP-ACP), probióticos, polióis, xilitol, polifenóis, controle de dieta, higiene bucal, selantes resinosos e ionoméricos, substâncias a base de clorexidina, agentes cariostáticos e profilaxia profissional.

Comparação - Placebo ou nenhuma intervenção.

Desfecho – Lesão de cárie cavitada no nível de dentina, imagens radiográficas de lesões em dentina a partir do seu terço médio (situação em que grande parte dos autores indica restauração), restaurações, perda do dente e dor decorrente de cárie.

Tipos de estudos incluídos e contexto dos estudos

Ensaios controlados randomizados, conduzidos em escolas e comunidades, bem como em ambiente clínico (hospitais, clínicas, consultórios, isto é, quaisquer unidades públicas ou privadas de saúde), em nível individual ou em grupos, em todas as faixas etárias, em adultos e crianças, onde os diferentes tipos de intervenção para lesões de cárie não cavitada são comparados entre si, com placebo ou com nenhuma intervenção. Estudos em pacientes com qualquer tipo de deficiência foram excluídos.

Seleção dos estudos

Duas pesquisadoras leram inicialmente todos os títulos levantados na busca bibliográfica, eliminando os que não estavam adequados a pergunta norteadora da pesquisa. Em seguida, foram lidos os resumos dos estudos que permaneceram e feita nova depuração dos que não se encaixavam nesta pesquisa. Os estudos remanescentes foram lidos em sua totalidade e novamente os inadequados foram excluídos.

Extração dos dados

Duas revisoras extraíram os dados independentemente usando formulários de extração de dados criados no programa Excel®. Nos casos em que houve discordância sobre quais estudos deveriam participar da pesquisa, uma terceira revisora foi consultada e a disputa foi resolvida por consenso. Os autores dos estudos incluídos foram consultados pela primeira revisora em caso de dados relevantes encontrarem-se incompletos ou ausentes. Os motivos da exclusão de estudos nesta fase foram documentados.

Avaliação do risco de viés

O risco potencial de viés nos estudos incluídos foi avaliado usando a ferramenta *"Cochrane Risk of Bias Tool for Randomized Trials"* (RoB2) para avaliar o risco de viés. A avaliação envolveu cinco domínios referentes a possíveis vieses: risco de viés decorrente do processo de randomização; risco de viés devido a desvios das intervenções pretendidas; dados de resultados ausentes; risco de viés na medição do resultado e risco de viés na seleção do resultado relatado. Outras fontes potenciais de viés também foram avaliadas, como a comparabilidade entre os grupos na linha de base e a confiabilidade do diagnóstico do desfecho. Cada item foi classificado como tendo risco de viés baixo, alto ou com alguma preocupação. O baixo risco de viés é definido como um viés que dificilmente altera seriamente os resultados. O alto risco de viés é definido como um viés que pode alterar seriamente os resultados. O risco com alguma preocupação de viés é considerado como um viés que levanta dúvidas sobre os resultados.

Estratégia para a síntese dos dados

Foram realizadas várias metanálises (forest-plots) incluindo dez estudos selecionados. Não foi possível incluir mais estudos nas metanálises, em razão dos dados apresentados não permitirem. Uma situação comum foram estudos que apresentaram os desfechos (cavidade ou restauração) no nível dos dentes ou de superfícies, mas não no nível do indivíduo. Por isso, não foi possível realizar metanálises de risco. Os estudos incluídos nas metanálises permitiram apenas comparações de médias, quando os estudos apresentaram dados de médias de dentes ou de superfícies, por indivíduo. Diferentes tipos de tratamentos foram comparados dentro de um mesmo estudo e entre estudos, o que permitiria a realização de uma meta-análise em rede ou de comparações indiretas (network meta-analysis). Entretanto, optamos por realizar análises de sensibilidade através de várias metanálises de comparações diretas, pois o objetivo principal não foi comparar a efetividade de diferentes tipos de intervenção, mas qualquer tipo de intervenção versus nenhuma intervenção ou placebo.

Avaliação da certeza da evidência

A certeza da evidência foi avaliada em relação ao desfecho “lesão cavitada em dentina (incluindo restauração)”, utilizando o sistema GRADE. Este sistema tem como objetivo classificar a certeza da evidência em revisões sistemáticas e diretrizes clínicas (GUYATT *et al.*, 2011; BALSHEM *et al*., 2011; SCHÜNEMANN *et al.,* 2013).

A certeza da evidência é classificada como alta, moderada, baixa ou muito baixa.

As comparações foram feitas separadamente de acordo com as intervenções testadas nos diferentes estudos.

5 RESULTADOS

Foram obtidos 4.108 títulos, que após a remoção dos títulos duplicados, chegou a 2344 títulos, os quais foram sendo avaliados e descartados seguindo os nossos critérios de exclusão até que se obtivesse o número final de 19 estudos. Foram excluídos, desta forma, 2.242 títulos, sendo o principal motivo o desenho do estudo, seguido de estudos que utilizaram desfechos diferentes do objetivo deste estudo; vários estudos foram excluídos porque relataram progressão de cárie, mas não no nível de cavidade (APÊNDICE 2).

Características dos estudos incluídos

Os estudos selecionados foram publicados entre 1999 e 2020, sendo 1 em português (tese de doutorado; a publicação em periódico não foi identificada) e os demais em inglês, publicados em onze diferentes revistas científicas, sendo a *Caries Research* a com maior número de publicações incluídas. Os estudos foram realizados em onze diferentes países, sendo quatro estudos na Suécia, quatro no Brasil, dois na Tailândia, dois no Irã e um nos demais (Grécia, Turquia, Hungria, Alemanha, Austrália, Estados Unidos da América e Holanda). Houve estudos realizados em dentes decíduos e permanentes. Entre os que informaram a faixa etária dos participantes, existem pesquisas feitas em crianças, desde a 1ª infância, adolescentes e adultos, cobrindo uma ampla faixa etária.

As intervenções propostas nos estudos incluídos foram diversas: dois estudos avaliaram diferentes formas de educação em saúde (MEMARPOUR et al., 2015; MOHEBBI et al., 2009), dois investigaram dentifrício fluoretado (MADLÉNA et al., 2002; DETSOMBOONRAT et al., 2016), três avaliaram verniz fluoretado (BERGSTRÖM et al., 2014; MEMARPOUR et al., 2015; SKÖLD et al., 2016), gel fluoretado (TRUIN et al., 2005; GISSELSSON et al., 1999; ACHILLEOS et al., 2019) e preparações a base de CPP-ACP (SITTHISETTAPONG et al., 2012; MORGAN et al., 2008; MEMARPOUR et al., 2015) e um estudo avaliou selante (BORGES et al., 2012), enxaguante bucal fluoretado (SKÖLD et al., 2005), diamino fluoreto de prata (MATTOS-SILVEIRA, 2016) e diferentes protocolos de acordo com o risco de cárie (ACHILLEOS et al., 2019). O infiltrante resinoso esteve presente no maior número de estudos: seis no total (ARSLAN et al., 2020; ARTHUR et al., 2018; JORGE et al.,

2019; MATTOS-SILVEIRA, 2016; PARIS et al., 2020; PETERS et al., 2019). As intervenções foram comparadas a higiene bucal costumaz, dentifrícios com xilitol, placebo e nenhuma intervenção (Tabela 1).

Tabela 1: Características dos estudos incluídos.

Primeiro autor (país)	Ano	Intervenção	Controle	Tempo de estudo	Dentição
ACHILLEOS (Grécia)	2019	Instrução de higiene bucal + dentifrício 5000 ppm F + Aconselhamento dietético + Fluor gel NaF 1,23% ou CPP-ACP, 1 vez/3 meses + selantes + revisão a cada 3 meses.	Instrução de higiene bucal + creme dental 1450 ppm F	12 meses	permanente
		Instrução de higiene bucal + dentifrício 5000 ppm F + Aconselhamento dietético + Fluor gel NaF 1,23% , 1 vez/6 meses + selantes (opcional) + revisão a cada 6 meses.			
		Instrução de higiene bucal + Aconselhamento dietético + Fluor gel NaF 1,23% , 1 vez/12 meses + revisão a cada 12 meses.			
ARSLAN (Turquia)	2020	Infiltrante Resinoso (ICON)	Higiene bucal com dentifrício fluoretado + fio dental + Aconselhamento dietético	12 meses	permanente
ARTHUR (Brasil)	2018	Infiltrante Resinoso (ICON) + Instrução de higiene bucal + Dentifrício fluoretado + Aconselhamento dietético	Instrução de higiene bucal + Dentifrício fluoretado + Aconselhamento dietético	36 meses	permanente
BERGSTRÖM (Suécia)	2014	Verniz fluoretado + sessões de higiene bucal supervisionada.	Sessões de higiene bucal supervisionada.	42 meses	permanente
BORGES (Brasil)	2012	Selante de fossas e fissuras + Instrução de higiene bucal	Educação em saúde	36 meses	permanente
DETSOMBOONRAT (Tailândia)	2016	Dentifrício contendo Flúorfostato de sódio	Dentifrício sem F, contendo xilitol	12 meses	decídua
GISSELSSON (Suécia)	1999	Gel fluoretado a 1%	Placebo	36 meses	permanente
JORGE (Brasil)	2019	Infiltrante Resinoso (ICON) + Fio dental	Fio dental	24 meses	decídua
MADLÉNA (Hungria)	2002	Dentifrício fluoretado + gel fluoretado	Hábitos de higiene bucal usuais	24 meses	permanente
MATTOS-SILVEIRA (Brasil)	2016	Diamino Fluoreto de Prata a 30%	Instruções de higiene bucal	24 meses	decídua
		Infiltrante resinoso (ICON)			
MEMARPOUR (Irã)	2015	Higiene bucal + Aconselhamento de dieta	Nenhuma intervenção	12 meses	decídua
		Verniz fluoretado			

		CPP-ACP			
PARIS (Alemanha)	2020	Infiltrante resinoso (ICON)	Placebo	84 meses	permanente
SKÖLD (Suécia)	2005	6 utilizações de enxaguante bucal fluoretado a cada ano.	Nenhuma intervenção	36 meses	permanente
		27 utilizações de enxaguante bucal fluoretado a cada ano.			
		Todos as possibilidades de utilização de enxaguante bucal			
SKÖLD (Suécia)	2016	Verniz Fluoretado	Nenhuma intervenção	36 meses	permanente
MOHEBBI (Irã)	2009	panfleto + lembrete	Nenhuma intervenção	6 meses	decídua
		panfleto			
MORGAN	2008	CPP-ACP	Placebo	24 meses	permanente
PETERS (EUA)	2018	Infiltrante resinoso (ICON)	Placebo	24 meses	permanente
SITTHISETTAPONG (Tailândia)	2012	mousse CPP-ACP 10%	Placebo	12 meses	decídua
TRUIN (Países Baixos)	2005	Gel fluoretado a 1%	Placebo	48 meses	decídua

Em oito estudos selecionados para esta revisão sistemática, a intervenção recebida pelo grupo controle foi higiene bucal. Se somarmos a estes estudos, os que consideraram como controle nenhuma intervenção, uma vez que a higiene bucal atualmente faz parte da rotina de higiene diária da maioria das pessoas, ou o uso de fio dental, que também é uma forma de higiene bucal, este número sobe para 15. Os seis estudos restantes utilizaram placebos como comparativo.

O tempo de duração da maioria dos estudos (sete) foi de 36 meses. Pesquisas com 12 e 24 meses de seguimento responderam por cinco e três estudos incluídos, respectivamente. O menor tempo de seguimento incluído foi de 6 meses (MOHEBBI et al., 2009), e o maior, 84 meses (PARIS et a., 2020).

Doze estudos foram realizados em dentes permanentes, seis em dentes decíduos e apenas um admitiu ambas as dentições. Dos 19 estudos incluídos, 15 utilizaram unidade de randomização individual, sendo que três utilizaram-se de modelo de estudo do tipo *"split-mouth".* Quatro estudos utilizaram-se de *clusters*. As unidades de randomização foram vilarejos, salas de aula, centros de saúde e superfícies dentárias. As unidades de análise foram cuidador-criança ou indivíduo.

Nos estudos de Detsomboonrat et al. (2016) e Mohebbi et al. (2009) os autores levaram o agrupamento em consideração na análise dos dados. O efeito do desenho não foi levado em consideração nos demais estudos que utilizaram *clusters.* Os 19 estudos inseridos na revisão somaram um total de 6241 indivíduos participantes; em alguns estudos (ARSLAN et al., 2019; ARTHUR et al., 2018; BORGES et al., 2012; JORGE et al., 2019; PARIS et al., 2020; MORGAN et al., 2008; PETERS et al., 2019; DETSOMBOONRAT et al., 2016; ACHILLEOS et al., 2018; MATTOS-SILVEIRA, 2016; SKOLD et al., 2005), os dados analisados foram relatados em números de lesões de cárie por intervenção, não permitindo saber o risco no nível do indivíduo. Todos os estudos utilizaram a estratégia de análise por protocolo. Nesta estratégia são incluídos na análise somente os indivíduos que concluíram o estudo, ou seja, somente uma parcela dos participantes que foram inicialmente selecionados. Apesar do índice ICDAS ser mais moderno e permitir a avaliação das lesões incipientes, 5 estudos utilizaram o índice CPOS/CPOD ou uma variação deste. Somente 3 estudos utilizaram o índice ICDAS. Os demais optaram por utilizar índices de avaliação radiográficos.

Em cinco estudos, os autores concluíram que a intervenção pesquisada para o tratamento de lesões não cavitadas foi efetiva, quando comparado com higiene bucal; em cinco estudos, os autores concluíram a favor da intervenção quando comparado ao placebo e em quatro estudos, os autores concluíram que a intervenção apresentou resultado mais favorável que nenhuma intervenção. Quatro estudos apresentaram conclusões neutras, avaliando não haver diferença entre tratamento e os controles, a saber: higiene bucal e placebo. Em um estudo, as diferentes intervenções estudadas apresentaram resultados conflitantes, ora favorável a intervenção, ora neutro. Nenhum estudo relatou que o controle se mostrou mais efetivo do que a intervenção.

Em cinco estudos, a pesquisa envolveu mais de uma intervenção. Nestes casos, optamos por tratar cada uma das intervenções em separado, sempre comparando-a com o grupo controle, que variou entre nenhuma intervenção (três estudos) e higiene bucal (dois estudos). Em um estudo, os autores compararam somente grupos de intervenção, não apresentando nenhum grupo controle.

Também houve diferenças na apresentação dos resultados, que foram divididos em dois grupos: os que apresentaram os resultados em forma de média e os que apresentaram os resultados em forma de progressão das lesões. Em dez

estudos os resultados foram apresentados em médias dos grupos controle e teste e em onze estudos os resultados foram apresentados mostrando o número de lesões que progrediram e as que não progrediram. Skold et al. (2005) e Detsomboonrat et al. (2016) apresentaram os resultados em ambas as versões. (Tabelas 2 e 3).

No grupo de estudos que apresentou os resultados avaliando a progressão das lesões, 15 comparações foram avaliadas, uma vez que três dos estudos apresentavam mais de um grupo de intervenção e oito, avaliaram apenas um grupo de intervenção em comparação com o grupo controle. Entre os estudos avaliados neste grupo, quatro das quinze intervenções testadas não apresentaram nenhum caso de progressão no grupo teste e o mesmo fato ocorreu em dois estudos no grupo controle, sendo que em um deles a comparação era higiene bucal e no outro controle de paciente de baixo risco de cárie. Neste grupo de estudos a unidade de randomização foi cruzada em três comparações, cluster em duas e individual nas dez demais comparações. O tempo de acompanhamento variou entre 12 e 84 meses. Onze comparações foram feitas em dentes permanentes e as quatro demais na dentição decídua (Tabela 2).

Em três das 15 comparações deste grupo, os dentes do grupo teste sofreram mais progressões que os do grupo controle. Em duas situações, os resultados empataram e nas demais 10 comparações, a progressão foi em maior número no grupo controle. O maior percentual de progressão encontrada foi no grupo controle do estudo de Borges *et al.* (2012), onde, em 36 meses, 25 das 26 lesões do grupo controle, submetidas a higiene bucal, progrediram para lesão em dentina, enquanto o mesmo ocorreu com apenas três dos dentes submetidos a intervenção com selante (Tabela 2).

Morgan et al. (2008) apresentaram os seus resultados em número de faces de dentes onde houve progressão de cárie pelo total de faces, ao invés de usar dentes como unidade de pesquisa. Onze em 231 faces com lesão na metade externa do esmalte (R1) progrediram para a metade externa da dentina (R3) e outras 3/231 lesões progrediram para a metade interna da dentina (R4), no grupo controle. No grupo do CPP-ACP foram 18/222 progressões de R1 para R3 e 1/222 progrediu de R1 para R4.

Os estudos presentes na tabela 2 (ARSLAN, 2019; ARTHUR, 2018; BORGES, 2012; JORGE, 2019; PARIS, 2020; MORGAN, 2008; PETERS, 2019; DETSOMBOORAT, 2016; ACHILLEOS, 2018; MATTOS-SILVEIRA, 2016; MOBERG

SKÖLD, 2005) não foram submetidos a metanálise, desta forma, não é possível verificar o peso dos resultados de cada estudo no grupo.

Tabela 2 – Dados das comparações/estudos que forneceram o resultado em número de dentes ou faces (Morgan et al., 2008) não puderam ser submetidos a metanálise.

Estudo	Progressão Teste	Sem Progressão Teste	Progressão Controle	Sem Progressão Controle	Comparação	Unidade de randomização	Tempo de acompanhamento	Dentição
arslan 2019	0	45	4	41	infiltrante resinoso + higiene bucal vs higiene bucal	cruzada	12 meses	permanente
arthur 2018	1	26	0	27	infiltrante resinoso + higiene bucal vs higiene bucal	cruzada	36 meses	permanente
borges 2012	3	23	25	1	selante + higiene bucal vs higiene bucal	individual	36 meses	permanente
jorge 2019	4	25	9	20	infiltrante resinoso + fio dental vs fio dental	cruzada	24 meses	decídua
paris 2020	1	21	2	20	infiltrante resinoso vs tratamento simulado	individual	84 meses	permanente
morgan 2008	77	14589	97	14017	goma de mascar CPP-ACP vs goma de mascar controle	cluster	24 meses	permanente
peters 2019	3	26	2	27	infiltrante resinoso vs tratamento simulado	individual	36 meses	permanente
detsomboonrat 2016	20	64	16	31	dentifrício fluoretado vs dentifrício xilitol	cluster	12 meses	decídua
achilleos 2018	0	118	6	93	intervenção alto risco de cárie vs controle alto risco de cárie	individual	12 meses	permanente
achilleos 2018	0	105	3	84	intervenção risco moderado de cárie vs controle risco moderado de cárie	individual	12 meses	permanente
achilleos 2018	0	51	0	53	intervenção baixo risco de cárie vs controle baixo risco de cárie	individual	12 meses	permanente
mattos-silveira 2016	3	91	5	77	diamino fluoreto de prata 30% vs higiene bucal	individual	24 meses	decídua
mattos-silveira 2016	6	66	5	77	infiltrante resinoso vs higiene bucal	individual	24 meses	decídua
moberg skold 2005	10	117	15	79	6 bochechos/ano vs nenhuma intervenção	individual	36 meses	permanente
moberg skold 2005	15	139	15	139	27 bochechos/ano vs nenhuma intervenção	individual	36 meses	permanente

Os dez estudos que apresentaram os resultados em número médio de lesões cavitadas em dentina ou restauradas por indivíduo, permitiram que fossem feitas metanálises de diferenças nas médias. Várias combinações foram feitas, uma vez que alguns estudos apresentavam mais de uma intervenção a ser comparada com placebo ou higiene bucal. A tabela 3 mostra todos os estudos e dados incluídos nas diferentes metanálises executadas, cujos gráficos (forest plots) que não estão incluídos no texto, estão no apêndice 3.

Tabela 3: Dados dos estudos utilizados nas metanálises

Estudo	n teste	média teste	Desvio padrão teste	n controle	média controle	Desvio padrão controle	Comparação	Unidade de randomização	Tempo de acompanhamento	Índice	Dentição
gisselsson 1999	182	0.44	1.00	98	0.50	1.19	gel fluoretado vs placebo	individual	36 meses	CPOS	permanente
sitthisettapong 2012	117	4.23	5.14	112	4.13	5.08	pasta CPP-ACP vs placebo	individual	12 meses	ICDAS	decídua
truin 2005	340	1.64	2.58	336	2.08	3.12	gel fluoretado vs placebo	individual	48 meses	CPOS	mista
skold 2016	301	0.34	1.00	105	0.70	1.13	verniz fluoretado vs nenhuma intervenção	individual	36 meses	CPOS	permanente
bergstron 2014	864	0.08	0.44	279	0.09	0.60	verniz fluoretado vs higiene bucal supervisionada	individual	42 meses	CPOS	permanente
detsomboonrat 2016	84	3.45	8.55	47	3.68	7.27	dentifrício fluoretado vs dentifrício com xilitol	cluster	12 meses	ceos	decídua
moberg skold 2005	528	0.32	0.70	94	0.43	0.76	todos os grupos de bochecho vs nenhuma intervenção	individual	36 meses	CPOS	permanente
madlena 2002	155	1.2	2.8	137	1.9	2.5	dentifrício com fluoreto de amina + gel com fluoreto de amina vs hábitos orais usuais	cluster	24 meses	CPOD	permanente
madlena 2002	118	1.2	2.7	137	1.9	2.5	dentifrício com fluoreto de amina + gel placebo vs hábitos orais usuais	cluster	24 meses	CPOD	permanente
memarpour 2015	29	0.3	0.90	32	2	2	verniz fluoretado vs nenhuma intervenção	individual	12 meses	CPOD	decídua
memarpour 2015	30	0.17	0.53	32	2	2	CPP-ACP vs nenhuma intervenção	individual	12 meses	CPOD	decídua
memarpour 2015	31	0.42	0.99	32	2	2	higiene bucal + aconselhamento de dieta vs nenhuma intervenção	individual	12 meses	CPOD	decídua
mohebbi 2009	55	0.1	0.6	63	0.2	0.7	panfleto + lembrete vs nenhuma intervenção	cluster	6 meses	ceod	decídua
mohebbi 2009	59	0.1	0.1	63	0.2	0.7	panfleto vs nenhuma intervenção	cluster	6 meses	ceod	decídua

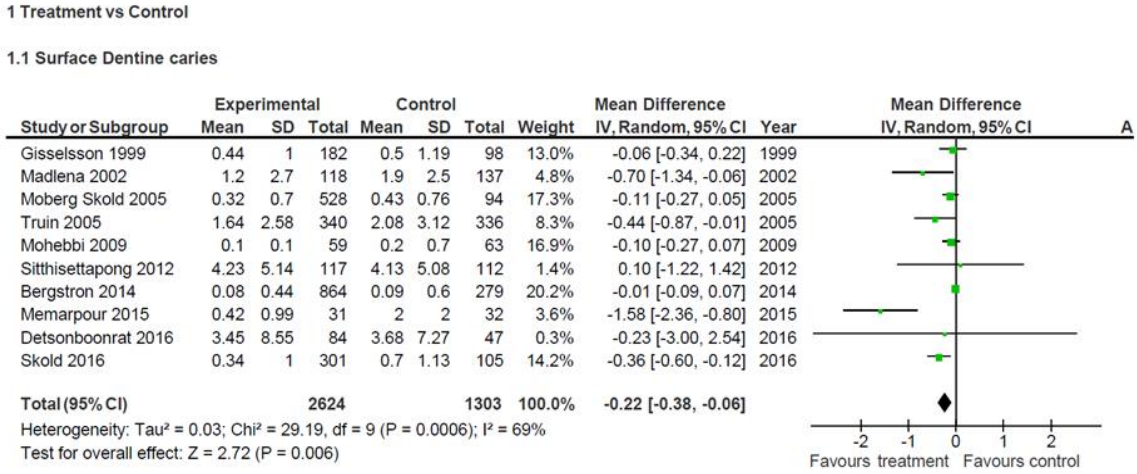
Nota: n = número de pacientes.

As medidas combinadas das metanálises foram semelhantes, com a estimativa pontual variando entre -0,22 e -0,27 nas diversas metanálises executadas. Ou seja, em média, por indivíduo, houve entre menos 0,22 e menos 0,27 dente com cavidade de cárie em dentina no grupo que recebeu tratamento em comparação com o grupo que recebeu o placebo ou nenhum tratamento. A heterogeneidade, medida pelo Índice de Higgins (I^2) nos diz a proporção da variabilidade nas estimativas de efeito que pode ser atribuída à heterogeneidade entre os estudos e não ao acaso (HIGGINS, et al., 2022). Com base neste índice, a

heterogeneidade foi substancial, variando entre 69% e 76%. (Figuras 1 e 2 abaixo e 3 a 12 no apêndice 3)

A metanálise com menor tamanho do efeito (-0,22 IC 95% -0,38 a -0,06) incluiu dez comparações que confrontaram gel fluoretado, pasta contendo CPP-ACP, verniz fluoretado, dentifrício fluoretado, enxaguante fluoretado, higiene bucal orientada associada a educação para a dieta ou educação em saúde através de panfletos, comparados a placebo, nenhum tratamento ou hábitos usuais de higiene. Entre os estudos, o de maior peso (BERGSTRON *et al.,* 2014), apresentou uma diferença de médias de -0,01 (IC: -0,09; 0,07), o que significa que as duas intervenções comparadas tiveram efeitos similares. Nesta metanálise, em seis estudos os intervalos de confiança cruzaram a linha da hipótese nula. Apesar dos dados bastante heterogêneos, com estimativas positivas e negativas, esta metanálise apresentou o menor I^2 entre as 12 metanálises executadas: 69% (Figura 1).

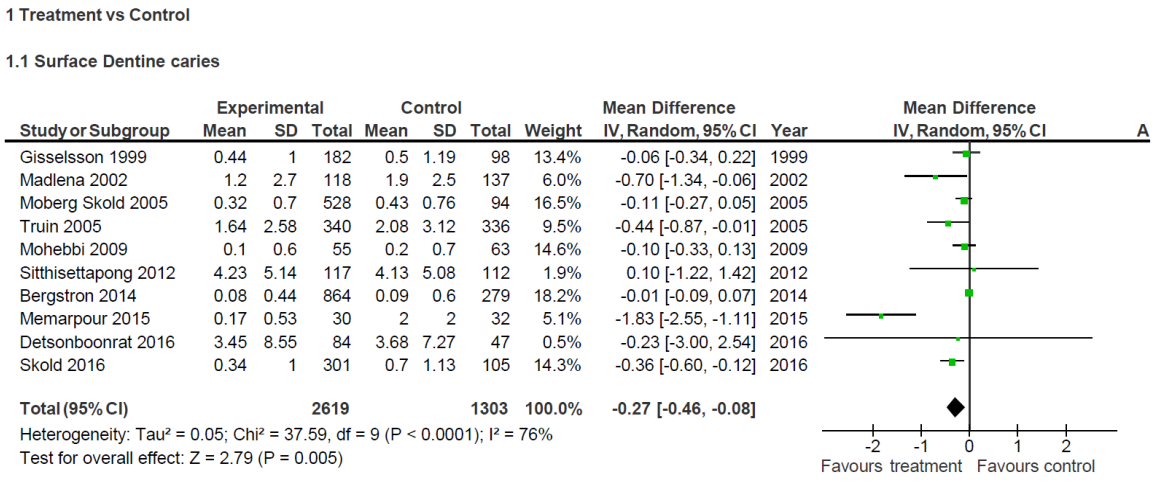
FIGURA 1: Metanálise dos estudos com somente uma intervenção acrescidos dos estudos de Madlena et al. (dentifrício com fluoreto de amina + gel placebo vs hábitos orais usuais), Memarpour et al. (higiene bucal + aconselhamento de dieta vs nenhuma intervenção) e Mohebbi et al. (panfleto vs nenhuma intervenção).



O maior efeito encontrado entre as 12 metanálises executadas (-0,27 IC 95% -0,46 a -0,08) foi a que incluiu estudos que compararam o gel, verniz, dentifrício e

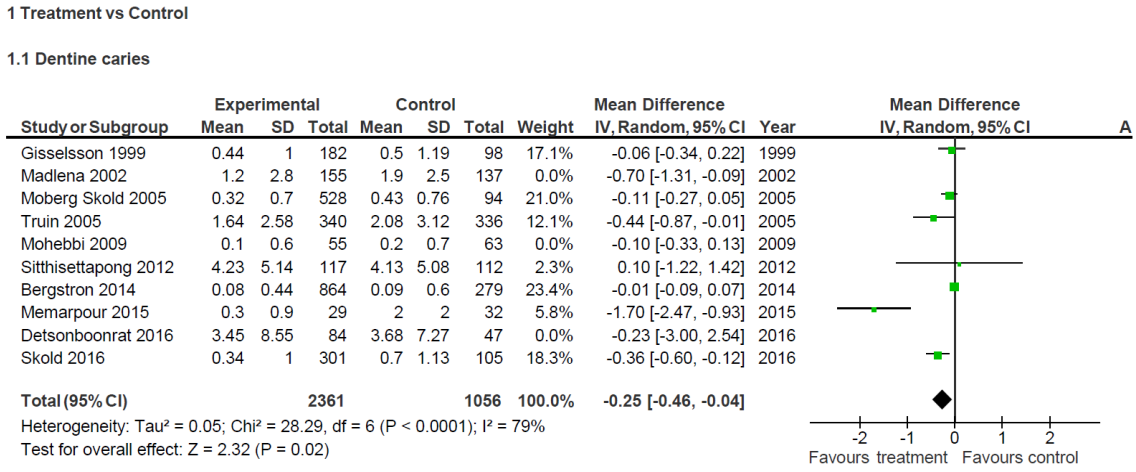
enxaguante fluoretado, a pasta CPP-ACP e educação em saúde através de panfletos com placebo, nada ou hábitos usuais de higiene. O estudo de maior peso, como na análise anterior, foi o de Bergstron *et al.* (2014), embora com um peso menor (18,2%). Mesmo fato se sucedeu em relação ao estudo de menor peso, Detsonboonrat et al. (2016), que aqui apresentou peso um pouco maior (0,5%). Esta metanálise apresentou I^2 de 76%, a mais alta heterogeneidade entre as metanálises realizadas (Figura 2).

FIGURA 2: Metanálise dos estudos com somente uma intervenção acrescidos dos estudos de Madlena et al. (dentifrício com fluoreto de amina + gel placebo vs hábitos orais usuais), Memarpour et al. (CPP-ACP vs nenhuma intervenção) e Mohebbi et al. (panfleto + lembrete vs nenhuma intervenção).



Quando os estudos do tipo cluster foram excluídos (DETSOMBOONRAT et al., 2016; MADLENA et al., 2002; MOHEBBI et al., 2009), houve pouca alteração nos resultados: diferença na média de -0,25 (IC 95% -0,04 e -0,46) e I^2 de 79% (Figura 3).

FIGURA 3: Metanálise excluindo os estudos cuja randomização foi do tipo conglomerado (*cluster*).



As maiores médias de progressão de cárie até cavidade em dentina encontradas, seja para o grupo teste ou grupo controle, foram as do estudo de Sitthisettapong *et al.* (2012): 4,23 e 4,13, respectivamente, onde a pasta com CPP-ACP foi comparada com um placebo. As menores médias, identificadas no estudo de Bergstron *et al.* (2014), foram 0,08 para a intervenção com verniz fluoretado e 0,09 para o grupo controle, que utilizou higiene bucal supervisionada. No total, 2893 indivíduos foram submetidos as intervenções propostas pelos diferentes pesquisadores e 1303 participaram dos grupos controle (Figura 3).

Quando analisamos os resultados levando em consideração a intervenção executada, percebe-se a ausência de estudos sobre o infiltrante resinoso que apresentem seus resultados em médias por indivíduo, o que impediu que eles participassem da metanálise. O único estudo da tabela 2 que avaliou enxaguantes bucais não mostrou diferença estatisticamente significante entre os dois grupos, sendo a diferença das médias igual a -0,11 (IC -0,27; 0,05). Os dois estudos que

investigaram o poder do gel fluoretado se mostraram inconclusivos. Gisselsson *et al.* (1999) apresentaram uma diferença de médias de -0,06 (IC -0,34; 0,22) ao passo que Truin; Van't Hof (2005) mostraram uma diferença de médias de -0,44 (IC -0,87; -0,01), este com uma amostra maior (676 contra 280) e um resultado que permite verificar uma leve vantagem do grupo que sofreu a intervenção. Quando comparados os estudos que avaliaram o desempenho do verniz fluoretado na progressão de cárie, os resultados também variaram, entretanto, favorecendo levemente o uso da substância. Bergstron *et al.* (2014) não encontraram diferença estatisticamente significante entre os dois grupos (Diferença de médias = -0,01; IC -0,09; 0,07). O resultado apresentado por Memarpour *et al.* (2015), entretanto, foi amplamente favorável ao uso do verniz fluoretado, com uma diferença de médias de -1,70 (IC -2,47; -0,93). Skold (2016) por sua vez, demonstrou um resultado favorável ao uso do verniz, embora com números intermediários entre os dois outros autores. Sua diferença de médias ficou em 0,36 (IC -0,60; -0,12). Ressalte-se que a maior amostra foi a do estudo de Bergstron *et al.* (2014), seguida por Skold (2016): 1143 e 406, respectivamente, enquanto a amostra do estudo de Memarpour *et al.* (2015) foi bem menor (61). Os dentífricios fluoretados foram avaliados em dois estudos, sendo que em um deles, Madlena et al. (2002), além de avaliar o uso do dentifrício sozinho, também avaliou o seu uso associado a autoaplicação de gel fluoretado, em comparação com um grupo controle, não encontrando diferenças entre as duas comparações. Ambas as comparações apresentaram diferença de médias igual: -0,70, com pequena variação no intervalo de confiança (-1,31; -0,09 e -1,34; -0,06). No outro estudo, com menor amostra, Detsonboonrat et al (2016) encontrou um resultado não significativo (IC -3,00; 2,54) para uma diferença de médias de -0,23 (Figuras 1 a 12).

Dois estudos avaliaram o CPP-ACP e os resultados apresentados para este tratamento mostraram-se divergentes. Enquanto Sitthisettapong *et al.* (2012), com uma amostra de 229 indivíduos, mostrou não haver diferença estatisticamente significativa entre os grupos estudados, Memarpour *et al.* (2015), com uma diferença de médias de -1,83 (IC -2,55; -1,11), porém com uma amostra menor de participantes (62), mostrou um resultado claramente a favor do uso do CPP-ACP no que se refere a progressão de cáries. Mohebbi et al. (2009) avaliaram se a utilização de panfletos e lembretes poderiam influenciar na progressão das lesões

de cárie. Em ambos os casos os resultados encontrados não foram estatisticamente significantes. Destaque-se, neste caso, o curto espaço de acompanhamento: seis meses. Por fim, Memarpour et al. (2015) avaliaram o efeito da orientação de higiene bucal somada ao aconselhamento de dieta e encontraram um resultado estatisticamente significante, com diferença de médias de -1,58 (IC -2,36; -0,80), embora a amostra fosse pequena (63 indivíduos) (Figuras 1 a 12).

Entre os estudos que compararam médias, o tempo de estudo variou entre 6 e 48 meses. Os estudos com duração de 6 e 12 meses apresentaram resultados estatisticamente insignificantes. É difícil avaliar se o tempo de duração destes estudos pode ter influenciado no seu resultado. O tipo de dentição, permanente, mista ou decídua parece não ter influenciado no resultado (Tabela 3 e FIGURAS 1 a 12).

Análise do risco de viés

A análise do risco de viés foi executada utilizando-se a ferramenta RoB2. As figuras relativas a esta análise encontram-se no apêndice 3.

Apenas seis dos 19 estudos não tiveram nenhum domínio avaliado como sendo de alto risco. Destes, apenas dois foram classificados na avaliação final como sendo de baixo risco de viés.

A maioria dos estudos apresentou algum problema relacionado à randomização da amostra. Somente seis em 19 dos estudos apresentaram baixo risco de viés na avaliação deste quesito. Além disso, sete estudos apresentaram alto risco de viés e os seis demais, alguma preocupação. Sete em 19 estudos apresentaram alto risco de viés para o domínio “risco de viés devido a desvios das intervenções pretendidas”. No que se refere aos dados de resultados ausentes, 12 em 19 estudos apresentaram baixo risco de viés. A maioria dos estudos (13/19) apresentou baixo risco de viés na medição do resultado. Por fim, o risco de viés na seleção do resultado relatado apresentou alguma preocupação em 14 dos 19 estudos, em razão da ausência do registro do projeto de pesquisa.

Avaliação da certeza da evidência

A avaliação da certeza de evidência foi feita a partir da ferramenta desenvolvida pelo grupo GRADE para revisões sistemáticas e *guidelines*.

O GRADE classifica a certeza da evidência encontrada como sendo alta, moderada, baixa ou muito baixa. A certeza da evidência diminui se há preocupação com o risco de viés (erros sistemáticos), com a inconsistência, com a imprecisão (erros aleatórios), com a evidência indireta e com o viés de publicação (provável ou muito provável) for considerada grave ou muito grave.

A avaliação da certeza de evidência foi feita para o desfecho único, levando-se em conta todos os estudos selecionados para a revisão. Os dados relativos a número de pacientes e feito foram inseridos no quadro 2 levando em consideração apenas os estudos que sofreram metanálise.

Por óbvio, os problemas encontrados na análise de viés, que foram significativos, influenciaram neste resultado. Registre-se, entretanto, que todas as outras dimensões examinadas, i.e., inconsistência, evidência indireta e imprecisão, também apresentaram muitos problemas, sendo que nenhuma dimensão foi considerada “não grave”. O viés de publicação foi considerado altamente suspeito uma vez que resultados que não favoreçam o tratamento precoce colocam em dúvida a prática comumente adotada pelos dentistas na clínica diária, já sendo considerado um padrão mesmo na ausência de evidência sólida. Por outro lado, há que se ressaltar que uma busca bibliográfica exaustiva foi realizada, inclusive com a presença de uma bibliotecária especializada em revisões sistemáticas, que colaborou tanto na elaboração da estratégia de busca quanto na própria busca em diferentes bases de dados e literatura cinzenta, o que ajuda a controlar o risco da ocorrência deste viés. Os estudos de algumas intervenções, como o infiltrante resinoso, o CPP-ACP e o dentifrício fluoretado não receberiam isoladamente nenhum conceito “não grave” em sua avaliação. Além disso, a maioria dos experimentos, especialmente os que fizeram a avaliação usando dentes e não indivíduos como unidade de análise, apresentaram amostras muito pequenas, o que reduziu a certeza da evidência.

A inconsistência, considerada grave, reduziu a certeza da evidência em um nível. Isto se deu porque, embora os intervalos de confiança estivessem

sobrepostos na maioria dos casos, a heterogeneidade estatística observada na metanálise foi alta. Além disso, a variação nos tempos de acompanhamento dos estudos, nas faixas etárias dos participantes e nos métodos utilizados, também foi grande.

O fato de várias intervenções apresentarem somente um estudo, indubitavelmente, empobreceu a análise como um todo, que ficava restrita a este relato narrativo individualmente, sem conseguir avaliar se os problemas encontrados eram decorrentes da metodologia empregada ou se parte do problema poderia ser creditado a intervenção pesquisada. Além disso, faltaram estudos testando algumas possíveis intervenções. Com relação ao comparador, nem todos os estudos foram adequados, uma vez que algumas intervenções utilizadas no grupo controle poderiam também ser utilizadas no grupo teste. Adicionalmente, nenhum estudo utilizou especificamente o desfecho considerado adequado. Desta forma, a evidência indireta foi considerada muito grave, sendo a certeza de evidência penalizada em dois níveis.

A imprecisão foi avaliada como grave e levou a uma penalização, em razão de alguns estudos apresentarem um intervalo de confiança muito amplo. Além disso, o efeito foi analisado como pequeno e chegou a ser descrito como não relevante e em alguns estudos.

Quadro 2: Avaliação da certeza da evidência (GRADE)

Pergunta: Intervenção comparado a higiene bucal / placebo / nenhuma intervenção para progressão de lesão incipiente de cárie até cavidade em dentina

Certainty assessment							№ de pacientes		Efeito		Certainty	Importância
№ dos estudos	Delineamento do estudo	Risco de viés	Inconsistência	Evidência indireta	Imprecisão	Outras considerações	intervenção	higiene bucal / placebo / nenhuma intervenção	Relativo (95% CI)	Absoluto (95% CI)		
cavidade em dentina/dor de dente/perda do dente (seguimento: variação 6 meses para 84 meses; avaliado com: média / novas lesões)												
19	ensaios clínicos randomizados	grave[a]	grave[b]	muito grave[c]	grave[d]	Viés de publicação altamente suspeito[e]	4460	4460	-	mean **0.27 menor** (0.46 menor para 0.08 menor)	⊕◯◯◯ Muito baixa	CRÍTICO

CI: Confidence interval

Explicações:

a. Doze dos estudos inseridos na análise tiveram como de alto risco de viés na classificação final da avaliação feita no RoB2.

b. A variação nos tempos de estudo foi muito grande. A faixa etária incluída nos diferentes estudos também foi grande. Os estudos variam bastante na sua metodologia. Nenhum estudo apresenta como desfecho cavidade em dentina, especificamente. A heterogeneidade dos estudos submetidos a metanálise foi grande. Entre os estudos avaliados por metanálise, os de maior peso apresentaram resultados inconclusivos.

c. Apesar da população ter variado adequadamente, as intervenções não foram suficientemente diversas. Faltaram estudos de algumas possíveis intervenções e em outras, o número de estudos foi pequeno. Com relação ao comparador, nem todos os estudos foram adequados, uma vez que algumas intervenções utilizadas no grupo controle poderiam também ser utilizadas no grupo teste. Por fim, nenhum estudo utilizou especificamente o desfecho adequado.

d. Entre os estudos submetidos a metanálise, alguns apresentaram intervalos de confiança grandes. Além disso, na maioria dos estudos, o efeito da intervenção foi pequeno, sendo não significante em alguns estudos.

e. Apesar da busca exaustiva que foi feita, e da intervenção pesquisada ser bastante ampla, poucos estudos que atendiam o desfecho desejado foram encontrados.

6 DISCUSSÃO

Se levarmos em consideração que o objeto do estudo incluía todas as possibilidades de tratamentos para lesões iniciais de cárie, pode-se dizer que o número de títulos que foi obtido ao final da seleção efetuada para esta revisão foi pequeno, o que nos leva a dividir esta discussão em duas partes: a primeira dedicada ao motivo de uma busca inicial tão extensa ter levado a um número final tão pequeno de títulos e a segunda dedicada aos achados relativos à efetividade do tratamento da cárie dentária não cavitada propriamente dito, objeto desta revisão.

Um motivo que levou à exclusão de estudos foi o método utilizado para o diagnóstico das lesões de cárie, seja no *baseline* ou no *follow-up*. Optou-se, nesta revisão por selecionar apenas as pesquisas que usaram exames clínicos ou radiográficos por serem estes os métodos mais testados e conhecidos e utilizados pelos profissionais de Odontologia. São métodos considerados simples, uma vez que o treinamento para a sua utilização se dá desde o início da formação profissional, além de acessíveis a todos os profissionais, especialmente os que atuam na atenção primária, incluindo serviços públicos de saúde. Dentre os índices utilizados pela maioria dos profissionais e pesquisadores está o CPOD/S, que conta com a indicação da OMS (PETERSEN *et al.*, 2013) e o ICDAS, que possui a capacidade de registrar as primeiras alterações no esmalte dentário (PITTS, 2009). Embora mais moderno e detalhado, apenas 3 dos estudos incluídos nesta revisão utilizaram o ICDAS, com a maioria optando pelo CPOD/S, mais antigo e experimentado. Apesar do ICDAS ser um índice robusto, capaz de classificar a atividade de cárie, este índice requer mais treinamento do avaliador, bem como o dente seco, limpo e iluminado para o exame (EKSTRAND, 2018). Em favor do CPOD/S conta o fato da calibração entre os avaliadores ser mais simples, e o exame ser mais fácil e desta forma, de melhor custo-efetividade, ainda que avalie a cárie apenas no seu estágio mais avançado, que é a cavidade (MELGAR, 2016). Desta forma, pode ser uma escolha mais conveniente para estudos clínicos. Walsh *et al.* (2022) validam esta escolha, uma vez que, ao analisar revisões sistemáticas que avaliaram diferentes métodos diagnósticos concluíram que os seus resultados foram similares, embora tenham registrado que, em termos de sensibilidade, a

imagem radiográfica apresentou uma performance inferior. Ainda assim, enfatizaram que o sumário das estimativas de especificidade foi semelhante para todas as tecnologias avaliadas. Por fim, estes autores concluíram que a utilização de novas tecnologias de diagnóstico traz pouco benefício na suplementação do exame tátil visual.

Outro motivo de exclusão dos títulos foi o desfecho diferente. A maioria dos autores utiliza como desfecho para os seus estudos a regressão das lesões brancas ao invés da progressão e, quando a progressão de cárie é utilizada como desfecho, esta é avaliada de forma indiscriminada, aceitando-se qualquer nível de progressão. A questão que se coloca aqui é que, sendo a cárie dentária uma disbiose, fruto de desequilíbrio e potencialmente reversível a partir do restabelecimento do equilíbrio do meio bucal, independente de intervenção, qualquer progressão que possa ser revertida pelo processo natural de des-remineralização do tecido dentário pode ser considerada um falso desfecho, uma vez que não resulta em um problema efetivo para o indivíduo que deva sofrer uma intervenção direcionada a si. Desta forma, há que se questionar a utilização de tal desfecho, tão amplamente utilizado e que leva a falsas conclusões de sucesso tanto quanto a tratamentos dispensáveis, que aumentam desnecessariamente os recursos gastos com esta condição.

A utilização do desfecho “progressão de cárie” de forma ampla e indiscriminada é tão comum que, mesmo nos títulos selecionados foi necessário depurar os dados que realmente importam, que são aqueles em que a progressão atinge o terço médio da dentina, de modo a indicar a necessidade de intervenção no elemento dentário. Autores como Skold *et al.* (2005) concluem pelo sucesso do tratamento estudado alegando que o grupo controle apresentou maior incidência de lesões em esmalte que o grupo testado, quando a progressão para dentina ou restaurações ocorridas nos grupos teste e controle foi pequena, variando entre 5 e 16%. Pode se alegar que a utilização do desfecho substituto neste caso se justifica, uma vez que, se há uma progressão, qualquer que seja ela, em se deixando seguir o curso do tempo sem intervenção, esta resultará em restauração ou perda do dente. A questão é que não necessariamente a progressão ocorrerá ou será impedida pelo tratamento proposto. Desta forma, não há como justificar utilizar progressão em qualquer nível como um desfecho substituto para o desfecho verdadeiro que é cavidade dentária. Um desfecho substituto só é considerado válido se a conclusão do estudo baseado no desfecho substituto corresponder a conclusão

do estudo baseado em um desfecho verdadeiro (HUJOEL *et al*., 1997). E isso, muitas vezes, não é válido para a cárie dentária, uma vez que, em nível de esmalte, esta progressão na maioria das vezes é paralisada ou revertida na ausência de tratamento.

São muitos os desfechos substitutos que têm levado a erros de diagnóstico ou tratamento ao longo dos anos. Fleming; DeMets (1996) pontuam que são muitas as explicações para o seu fracasso, sendo a mais plausível a de que a intervenção tenha mecanismos de ação não intencionais que são independentes do processo da doença e advogam a necessidade de métodos de validação estatísticos que envolvam metanálises para a adequada validação destes desfechos. Em Odontologia, a maior parte dos estudos que avaliam a utilização de desfechos substitutos estão concentrados nas alterações periodontais ou câncer bucal; ainda tem os que falam sobre a utilização da saliva como biomarcador. Neste caso, é possível encontrar autores que se referem a cárie dental (BUZALAF *et al*., 2020). Entretanto, pouco se discute sobre desfechos, verdadeiros e substitutos, para a cárie dentária.

Mattos-Silveira (2016), em sua tese, considera dois padrões de progressão, sendo que o primeiro padrão envolve somente progressão da lesão em esmalte e o segundo padrão, progressão para escores que envolvam dentina. Na ânsia de se prevenir a cavidade, os autores têm usado o desfecho substituto lesão em esmalte. Isto termina dando ao desfecho substituto, a mesma visibilidade que o desfecho verdadeiro, gerando confusão no que se refere à importância de um e de outro. Hujoel (2004) chama a atenção para o fato de que mudanças de opinião sobre como medir periodontite não são baseadas em evidências, mas em crenças. E que, mesmo quando há consenso sobre como a periodontite deve ser medida, não há consenso sobre o seu significado clínico. Tal afirmação encaixa-se perfeitamente no caso da cárie dentária, com o agravante de que, neste caso, a questão sequer é discutida.

A maneira que há de se definir a importância de um desfecho, e que o torna, em última instância, verdadeiro é a sua aplicabilidade clínica. Aliás, nenhum estudo pesquisado nesta revisão utilizou os desfechos verdadeiros dor de dente e perda do dente. Será que, na ânsia de tratar, não estamos sobre tratando? É necessário conhecer a efetividade dos tratamentos cada vez mais precoces, que vêm sendo propostos. Seguindo esta premissa, Baelum (2010) e Fejerskov *et al.*

(2013) concordam que o clínico, no seu processo de exame e diagnóstico, está formatado para pensar no diagnóstico e tratamento dentro de uma perspectiva de protocolo: *"this-lesion-needs-this-kind-of-treatment"*, e isto deve ser levado em consideração. Se considerarmos qualquer progressão da lesão como um desfecho substituto válido para cavidade dentária, que deve ser o desfecho verdadeiro para a cárie, para muitos clínicos isso pode naturalmente ser um sinal de necessidade de intervenção, o que traz o risco de tratamentos desnecessários.

É comum os autores citarem que os tratamentos propostos são melhores que o tratamento cirúrgico-restaurador, uma vez que são menos invasivos. O trabalho de Borges *et al.* (2012) é um exemplo. Entretanto, em muitos casos, mesmo estes tratamentos não se mostram justificáveis, uma vez que a simples higiene bucal, com dentifrício fluoretado apresenta resultados semelhantes. Por exemplo, Madlena *et al.* (2002) forneciam orientação de higiene bucal e dieta a cada 2 meses a todos os participantes do estudo e encontraram resultados semelhantes nos grupos pesquisados quando se excluiu lesões incipientes. Mohebbi *et al.* (2009) avaliaram exatamente o impacto da intervenção educacional e concluíram pela sua efetividade.

Na revisão sistemática objeto desta tese, houve a preocupação em se avaliar somente as intervenções que foram comparadas a placebo, não intervenção ou higiene bucal. Esta escolha se deu pois sabe-se que não é possível comparar qualquer que seja a intervenção com uma verdadeira não intervenção. A verdadeira não intervenção para esta pesquisa deveria incluir a não utilização de qualquer tipo de higiene bucal ou contato com fluoretos e não é factível encontrar pessoas que não façam uso, minimamente, de higiene bucal que, mesmo deficiente, tem algum valor na prevenção de cavidades de cárie (NYVAD, 2017). Para além do hábito de higiene bucal ser amplamente difundido por si só, há ainda a questão relacionada a presença do flúor nos cremes dentais e na água de abastecimento, uma recomendação corroborada pela OMS, além de questões éticas (WHO, 2020). Não seria ético, com o conhecimento atual solicitar que os participantes de uma pesquisa não utilizem qualquer forma de higiene bucal por um período suficiente para o desenvolvimento de lesão de cárie. Tampouco é factível controlar tudo que um indivíduo coloca na boca, de modo a ter certeza de que não houve qualquer contato dos elementos dentários com fluoretos. Este íon está presente não só em dentifrícios e água potável, mas também em alimentos e é uma forma de se intervir

no processo de des-remineralização que, quando em desequilíbrio leva a lesão de cárie, tanto assim que várias intervenções testadas incluem o fluoreto em suas diferentes formulações.

Arthur *et al.* (2018) não encontraram diferença significativa entre o grupo que sofreu intervenção com infiltrante resinoso e o grupo controle e, refletem se isso não se deve ao fato de ambos os grupos terem acesso a orientações sobre higiene bucal e dieta, além dos benefícios do flúor. A reflexão é pertinente, uma vez que é difícil encontrar indivíduos que não tenham nenhum acesso ao flúor e a medidas educativas atualmente, sem falar nas questões éticas que isso implicaria. Neste caso, a dúvida que se estabelece é qual o propósito de se investir em um produto com maior custo e desconforto para o paciente na sua execução se há uma solução mais simples e econômica como a empregada entre os indivíduos do grupo controle.

Esta dúvida também atinge os resultados informados por Jorge *et al.* (2019), que, além de concluírem pelo sucesso do infiltrante resinoso levando em consideração qualquer grau de progressão da lesão, expõem uma taxa de perda no estudo de 42% dos participantes, sendo a maioria deles excluídos porque o dente que participava do estudo exfoliou. Sendo a cárie uma alteração que pode ser de evolução lenta, ainda mais quando o indivíduo tem acesso a produtos contendo flúor largamente difundidos como o dentifrício, parece ser um custo desnecessário investir em produtos mais onerosos para dentes que logo estarão exfoliados.

No que se refere ao diamino fluoreto de prata, identificado por Mattos-Silveira (2016) como sendo uma intervenção efetiva e de baixo custo, chama a atenção o fato de haver somente um estudo presente na revisão.

Na maioria das intervenções avaliadas nos estudos incluídos nesta revisão sistemática, o resultado foi favorável. Entre os estudos que forneceram o resultado em número de lesões que progrediram para cavidade, poucos foram aqueles em que não houve nenhuma progressão no grupo de intervenção. O material avaliado de maior custo é o infiltrante resinoso. Proporcionalmente, seus resultados não pareceram melhores que os das demais intervenções.

Chama a atenção também a quantidade de estudos envolvendo o infiltrante resinoso, seis no total, pelo fato de só existir uma marca comercial deste produto, que é relativamente novo. Infelizmente nenhum dos estudos que avaliaram o infiltrante resinoso estava entre os que foram submetidos a metanálise, uma vez que todos apresentaram o resultado no formato de contagem de lesões que progrediram,

não havendo nenhum que tenha se utilizado de médias. Aliás, cabe ressaltar ainda o tamanho sempre pequeno das amostras dos estudos que investigaram os infiltrantes.

Quando se avalia os estudos que tiveram seus resultados submetidos à metanálise, verifica-se que embora o efeito a favor do tratamento de lesões não cavitadas de cárie tenha sido estatisticamente significativo, o tamanho do efeito foi pequeno: em média, entre menos 0,22 e menos 0,27 dente com cárie em dentina / cavitada. Diante deste pequeno efeito (além da baixa certeza da evidência), é inevitável que surja a questão relacionada ao custo-efetividade do tratamento. Este efeito, pequeno, ainda que estatisticamente significativo, ocorre com materiais de primeira linha, como é o caso do verniz fluoretado Duraphat®, utilizado nos estudos de Skold (2016), por exemplo.

À questão do custo, há que se somar o conforto e aceitabilidade dos usuários em relação aos tratamentos executados. Mattos-Silveira (2016) relatou que os pacientes dos grupos que receberam o diamino fluoreto de prata e fio dental relataram menos desconforto que os que foram submetidos a intervenção com o infiltrante resinoso. Deve ser mais confortável para o paciente ser submetido a procedimentos que possam ser realizados em seu lar, como a higiene bucal, ou mesmo na escola, no caso de crianças, como o proposto por Skold *et al.* (2005). Neste caso, ainda há o benefício adicional da atividade em grupo servir como apoio e estímulo.

Paris *et al.* (2020) levanta uma outra questão importante. Na amostra estudada a quantidade de dentes com diagnóstico D1(radiolucência no terço externo da dentina) no grupo teste foi consideravelmente maior do que no grupo controle, onde prevaleceram as lesões E2 (radiolucência envolvendo a metade interna do esmalte). Lesões D1 são mais propensas a cavitar que lesões E2, o que pode ter levado ao número encontrado de dentes do grupo teste com lesão D2 (radiolucência no terço médio da dentina). Ressalte-se que esta diferença não deveria ocorrer em estudos randomizados. Mattos-Silveira (2016) afirma que em seu estudo a progressão das lesões não estava associada com o grupo de tratamento, mas com a condição clínica inicial da lesão. Ou seja, além do que já foi discutido, há que se pensar que a expectativa para o sucesso do tratamento tenha relação com a profundidade inicial da lesão a ser tratada.

O tempo de acompanhamento não parece ter influenciado os resultados. Estudos como os de Memarpour et al. (2015), Detsomboonrat et al. (2016) e Sitthisettapong et al. (2012), apesar do pouco tempo de acompanhamento (12 meses) apresentaram resultados dissonantes entre si, sendo que os dois últimos tiveram peso pequeno na metanálise e não apresentaram diferença estatisticamente significante. O estudo de Memarpour *et al.* (2015), por sua vez, apresentou um resultado amplamente favorável à intervenção com higiene bucal e aconselhamento de dieta. No extremo oposto, o estudo de Truin *et al.* (2005), com 48 meses, apesar do resultado estatisticamente significante, teve seu intervalo de confiança muito próximo da nulidade, variando entre -0,87 e -0,01.

Embora o trabalho mais antigo seja de 1999, fica clara a concentração de estudos da última década, com 12 trabalhos. Levando-se em consideração que o tema cárie dentária não é algo novo, mas que a ideia de se reconhecer e tratar a lesão inicial de cárie o é, talvez possamos pensar no viés de suspeita do diagnóstico, especialmente nos estudos que se utilizaram apenas de exames clínicos nas suas avaliações. Uma avaliação mais otimista é a de que a qualidade das metodologias de estudo melhorou com o passar do tempo e o aumento da utilização de ensaios clínicos randomizados.

Em alguns estudos, pode-se pensar no viés de aderência, uma vez que se compreende atualmente a cárie como uma alteração onde os hábitos de higiene e alimentação tem muita influência, e esta influência é de conhecimento geral da população. Explica-se: ainda que o grupo controle não tenha sofrido nenhuma intervenção ou, que a intervenção seja a higiene bucal rotineira, sabe-se que os pacientes são influenciados a melhorar a sua higiene em razão da visita ao dentista. Se estes indivíduos têm que ir a um exame odontológico com uma maior frequência ou têm a consciência de estar participando de um experimento relacionado a cárie dentária, há uma tendência de que sejam estimulados indiretamente a melhorar a sua higiene bucal. Achilleos *et al.* (2019) e Gisselsson *et al.* (1999) examinaram os grupos de alto risco de cárie a cada 3 meses; Borges *et al.* (2012) e Detsomboonrat *et al.* (2016), o fizeram a cada 4 meses, por exemplo. Arslan *et al.* (2020), Madléna *et al.* (2002) e Jorge *et al.* (2019), por outro lado, examinaram os participantes a cada 12 meses. Cada um desses exames traz um reforço positivo no que se refere a bons hábitos de higiene e alimentação e o intervalo entre eles foi diferente nos estudos.

A qualidade dos estudos, avaliada através da análise do risco de viés e da certeza da evidência, foi um ponto a pedir atenção. Apenas 2 dos domínios avaliados tiveram baixo risco em mais da metade dos estudos: os vieses de detecção e de atrito. É preocupante que 13 em 19 estudos tenham apresentado problemas quanto à geração da sequência aleatorizada. Isso demonstra que os autores não se preocuparam em explicar de forma adequada como uma parte tão importante do método ou, simplesmente, não a executaram da forma adequada, o que prejudica a confiabilidade dos estudos. Também chama a atenção que a maioria dos estudos (15/19) não tenha o seu protocolo registrado, impossibilitando que se tenha a certeza de não ter havido alteração na proposta do estudo em função dos resultados observados. De alguma forma, este dado mostra-se incompatível com o achado relativo ao viés de atrito, que apresentou avaliação negativa somente para 4 estudos. Era de se esperar que as avaliações relativas ao viés de relato e ao viés de atrito mostrassem resultados mais próximos. É inegável que os problemas na avaliação do risco de viés impactam negativamente no resultado da análise. Um ponto a ser considerado aqui é a dificuldade de contato com os autores. Somente um dos nove autores contatados respondeu aos questionamentos feitos. Os demais não foram encontrados ou não responderam às mensagens enviadas. Desta forma, seus estudos podem ter sido mal avaliados pela ausência de informações precisas.

Por óbvio, estas mesmas questões impactaram na avaliação da certeza da evidência. Nenhuma intervenção apresentou alta certeza de evidência. Chama a atenção o tamanho das amostras dos estudos, especialmente nos que não puderam ser submetidos à metanálise, onde a maior amostra não chegou a 300 lesões somando os grupos teste e controle. O estudo que avaliou o selante resinoso apresentou resultados muito discrepantes em relação aos demais. Como somente um estudo da amostra selecionada avaliou este material, não foi possível verificar se esta questão era relativa ao estudo ou ao material investigado.

Os resultados da análise de risco de viés e da certeza de evidência, infelizmente, jogam luz sobre a qualidade ruim dos estudos selecionados. É impactante e, de certa forma frustrante, que, após um processo de depuração tão grande, com um número inicial de 4108 títulos para se atingir os 19 títulos que fizeram parte da amostra estes estudos apresentem tantos problemas relacionados a sua metodologia. Urge que os pesquisadores invistam cada vez mais no

aprimoramento da metodologia das suas pesquisas e que os periódicos tenham um olhar mais crítico para o método empregado.

CONCLUSÃO

Poucos estudos avaliaram a efetividade do tratamento não invasivo de lesões de cárie não cavitadas (mancha branca) em evitar cavidades ou restaurações. Dentre esses poucos estudos, o tratamento teve um efeito relativamente pequeno. O risco de viés nos estudos incluídos foi, de uma forma geral, alto ou moderado e a certeza da evidência foi baixa. Nenhum estudo avaliou a efetividade deste tratamento em evitar dor ou perda de dente. Portanto, a prática de identificar e tratar lesões de cárie não cavitadas (i.e., o tratamento precoce), embora comum e preconizada internacionalmente por dentistas e associações odontológicas, não tem sustentação científica suficiente.

É preciso conscientizar os pesquisadores acerca da importância de se utilizar desfechos verdadeiros da cárie dentária em seus estudos, para que seja possível conhecer a efetividade das diferentes intervenções precoces em evitar cavidades em dentina, restaurações, dor e perda de dentes.

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ANEXO 1 – REGISTRO PROSPERO

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

To enable PROSPERO to focus on COVID-19 submissions, this registration record has undergone basic automated checks for eligibility and is published exactly as submitted. PROSPERO has never provided peer review, and usual checking by the PROSPERO team does not endorse content. Therefore, automatically published records should be treated as any other PROSPERO registration. Further detail is provided here.

Citation

Paulo Nadanovsky, Ana Paula Santos, Alessandra Bomfim, Luciane Stochero. Effectiveness of different types of treatment for non-cavitated caries lesions in primary and permanent teeth.. PROSPERO 2021 CRD42021148844 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021148844

Review question

Are the different types of treatment for non-cavitated dental caries effective to avoid cavities in permanent and primary teeth?

Searches

The searches will be performed in the following databases: The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE via PubMed, EMBASE, Web of Science, Scopus, LILACS. Additional sources will include the Biblioteca Digital Brasileira de Teses e Dissertações (BDTD), and four registers of ongoing trials (Current Controlled Trials, ClinicalTrials.gov, EU Clinical Trials Register and the Brazilian register of clinical trials (REBEC)). Meeting abstracts of the International Association for Dental Research (2001-2019) and the European Organisation for Caries Research (1998-2019) will also be searched. References of eligible trials and systematic and narrative reviews on the subject will be checked in order to detect potential studies. The following dentistry journals will be handsearched: Caries Research, Community Dentistry & Oral Epidemiology, European Archives of Paediatric Dentistry, International Journal of Paediatric Dentistry, Journal of the American Dental Association, Journal of Dental Research, Journal of Dentistry for Children, Journal of Public Health Dentistry, Pediatric Dentistry and Journal of Dentistry. The grey literature will also be investigate through the OpenGrey site (http://www.opengrey.eu/).

Types of study to be included

Randomized controlled trials, individually or in groups where the different types of intervention for non-cavitated caries lesions were compared with each other, with placebo or with no intervention.

Condition or domain being studied

Dental caries, a non-communicable bacterial disease, capable of leading to the formation of a cavity in the teeth, cause pain and loss of primary and permanent teeth, and impact the quality of life of individuals.

Participants/population

Adults and children, including permanent and primary teeth, presenting with non-cavitated caries lesions.

Intervention(s), exposure(s)

All non-operative (non-invasive) caries treatment found in the literature, including treatment with infiltrating substances, fluorides in their different presentations, silver diamine fluoride, amorphous phosphorous calcium phosphate casein (CPP-ACP), xylitol, diet control, oral hygiene, resin-based or glass ionomer dental sealants, chlorhexidine-based substances, cariostatic agents, oral hygiene and professional prophylaxis.

Comparator(s)/control

All interventions presented and also placebo and no intervention.

Context

Studies conducted in schools and communities, as well as in clinical settings (hospitals, clinics, and any public or private health units).

Main outcome(s)

Cavitated caries lesions at dentine level, fillings, tooth loss and dental pain due to caries.

Measures of effect

No time limit for the follow-up.

The effect measure is the incidence of cavitated caries lesions at dentine level.

Additional outcome(s)

None.

Measures of effect

Not applicable.

Data extraction (selection and coding)

Two reviewers will independently extract the data using data extraction forms. In case of disagreement, another reviewer will be consulted and the dispute will be resolved by consensus. The authors of the included studies will be consulted by the authors of this review when there are incomplete or missing relevant data. The reasons for exclusion of studies in this phase will be documented.

Risk of bias (quality) assessment

Two reviewers will independently assess risk of bias. In case of disagreement, another reviewer will be consulted and the dispute shall be resolved by consensus. The potential risk of bias in the included studies will be assessed using the Cochrane Collaboration tool for assessing risk of bias. The evaluation involves six domains: random sequence generation; allocation concealment; blinding of participants and study personnel; blinding of outcome assessors; incomplete outcome data and selective reporting of results. Other potential sources of bias will also be assessed, such as comparability between groups at baseline and outcome diagnosis reliability. Each item will be classified as having low, high or unclear risk of bias. The low risk of bias is defined as a bias that is unlikely to seriously alter the results. The high risk of bias is defined as a bias that can seriously alter the results. The uncertain risk of bias will be considered as a bias that raises doubts about the results.

Strategy for data synthesis

If possible, meta-analyses will be performed in order to estimate pooled effect estimates (relative risk, prevented fraction, difference in means).

Analysis of subgroups or subsets

If appropriate and available data allow, subgroup analysis will be performed to evaluate the influence of tooth type (permanent or primary) on the results of the proposed treatments.

Contact details for further information

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Organisational affiliation of the review

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Review team members and their organisational affiliations

Professor Paulo Nadanovsky. Rio de Janeiro State University and Oswaldo Cruz Foundation
Dr Ana Paula Santos. Rio de Janeiro State University
Ms Alessandra Bomfim. Rio de Janeiro State University

Ms Luciane Stochero. Rio de Janeiro State University

Type and method of review
Epidemiologic, Intervention, Meta-analysis, Network meta-analysis, Prevention, Systematic review

Anticipated or actual start date
02 September 2019

Anticipated completion date
15 March 2021

Funding sources/sponsors
There are no funding sources or sponsors.

Conflicts of interest

Language
English

Country
Brazil

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
MeSH headings have not been applied to this record

Date of registration in PROSPERO
08 January 2021

Date of first submission
08 December 2020

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.
The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions
08 January 2021
08 January 2021

APÊNDICE 1 - ESTRATÉGIA DE BUSCA

Database/Date of search	**Strategy**
Medline/PubMed March 26th, 2020	#1 "Dental Caries"[Mesh] OR “dental decay”[TIAB] OR Caries[TIAB] OR carious[TIAB] OR “tooth decay”[TIAB] OR "Tooth Demineralization"[Mesh] OR “Tooth demineralization”[TIAB] OR “Tooth demineralisation”[TIAB] OR “initial caries”[TIAB] OR “enamel caries”[TIAB] OR “early caries”[TIAB] OR “early tooth decay”[TIAB] #2 non-cavitated[TIAB] OR noncavitated[TIAB] OR “white spot lesion”[TIAB] OR “White Spots”[TIAB] OR “White Spot”[TIAB] OR “white lesion”[TIAB] OR “white lesions”[TIAB] OR “initial caries”[TIAB] OR “enamel caries”[TIAB] OR “early caries”[TIAB] OR “early tooth decay”[TIAB] OR “caries reversal”[TIAB] OR “approximal caries”[TIAB] OR “demineralized lesions”[TIAB] OR “demineralised lesions”[TIAB] OR “enamel demineralisation”[TIAB] OR “enamel demineralization”[TIAB] OR “enamel white spot lesions”[TIAB] #3 (clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading] OR randomized controlled trial[Publication Type] #4 in vitro[Title]

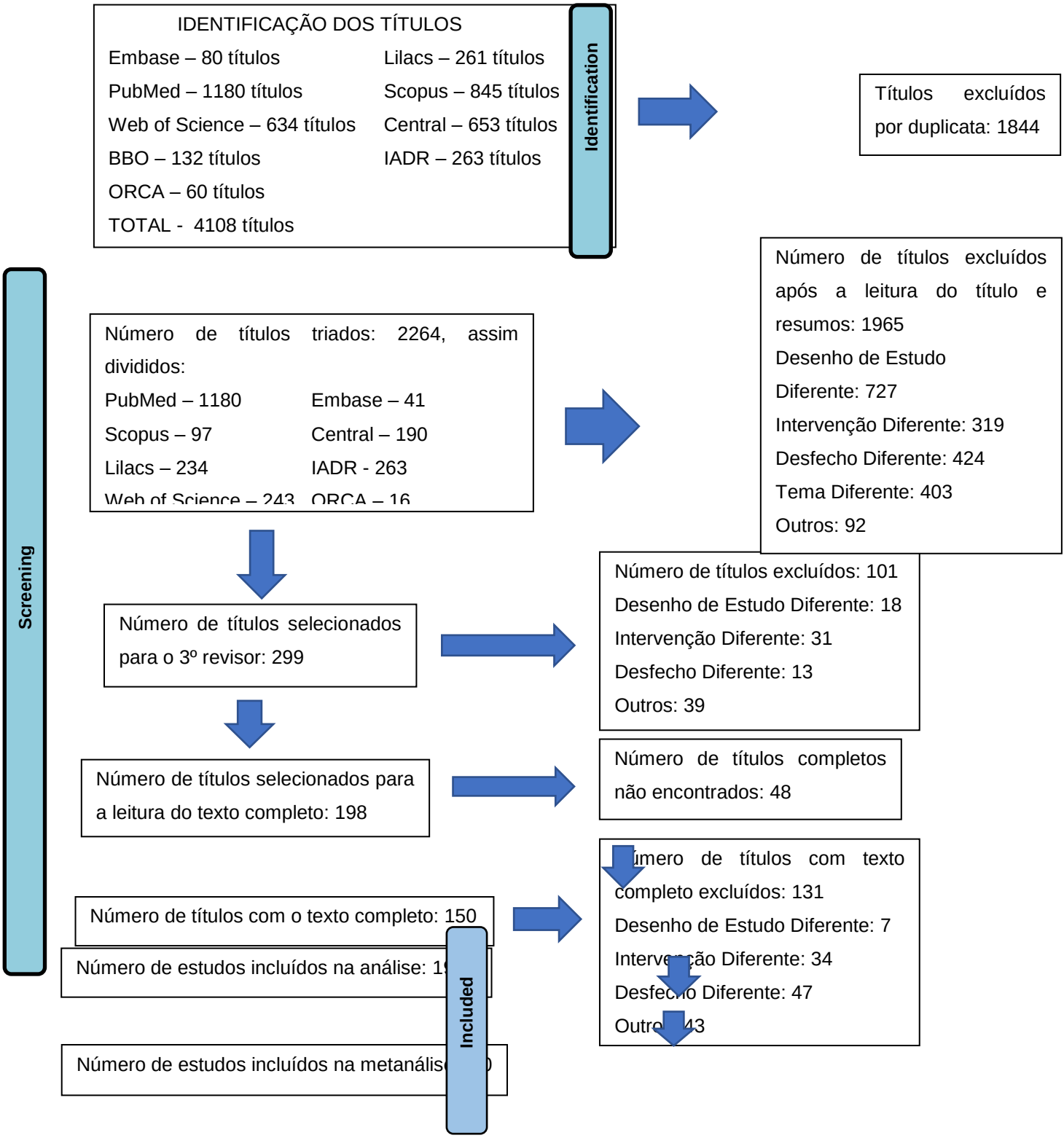
	#5 (#1 AND #2 AND #3) NOT #4
Embase April 24th, 2020	#1 'dental caries'/exp #2 ('dental decay' OR caries OR carious OR 'tooth decay' OR 'tooth demineralization' OR 'tooth demineralisation' OR 'initial caries' OR 'enamel caries' OR 'early caries' OR 'early tooth decay'):ti,ab,kw #3 (#1 OR #2) #4 ('non cavitated' OR noncavitated OR 'white spot lesion' OR 'white spots' OR 'white spot' OR 'white lesion' OR 'white lesions' OR 'initial caries' OR 'enamel caries' OR 'early caries' OR 'early tooth decay' OR 'caries reversal' OR 'approximal caries' OR 'demineralized lesions' OR 'demineralised lesions' OR 'enamel demineralisation' OR 'enamel demineralization' OR 'enamel white spot lesions'):ti,ab,kw #5 'clinical trial'/exp #6 ('clinical trial' OR random*):ti,ab,kw #7 – (#5 OR #6) #8 – (#3 AND #4 AND #7) #9 – #8 AND [embase]/lim
Web of Science April 25th, 2020	#1 TS=("dental decay" OR caries OR carious OR "Tooth decay" OR "tooth demineralization" OR "tooth demineralization" OR "initial caries" OR "enamel caries" OR "early caries" OR "early tooth decay") #2

	TS=(“non cavitated” OR noncavitated OR ”white spot lesion” OR ”white spots” OR ”white spot” OR ”white lesion” OR ”white lesions” OR ”initial caries” OR ”enamel caries” OR ”early caries” OR ”early tooth decay” OR ”caries reversal” OR ”approximal caries” OR ”demineralized lesions” OR ”demineralised lesions” OR ”enamel demineralisation” OR ”enamel demineralization” OR ”enamel white spot lesions”) #3 TS=("clinical trial" OR random*) #4 - (#1 AND #2 AND #3) (SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI)
Scopus April 25th, 2020	#1 TITLE-ABS-KEY ("dental decay" OR caries OR carious OR "Tooth decay" OR "tooth demineralization" OR "tooth demineralization" OR "initial caries" OR "enamel caries" OR "early caries" OR "early tooth decay") #2 TITLE-ABS-KEY ("non cavitated" OR noncavitated OR "white spot lesion" OR "white spots" OR "white spot" OR "white lesion" OR "white lesions" OR "initial caries" OR "enamel caries" OR "early caries" OR "early tooth decay" OR "caries reversal") OR TITLE-ABS-KEY ("approximal caries" OR "demineralized lesions" OR "demineralised lesions" OR "enamel demineralisation" OR "enamel demineralization" OR "enamel white spot lesions")) #3

		TITLE-ABS-KEY ("clinical trial" OR random*) #4 - (#1 AND #2 AND #3) #5 #4 AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "cp"))
	Central April 26th, 2020	#1 "dental decay" OR caries OR carious OR "Tooth decay" OR "tooth demineralization" OR "tooth demineralization" OR "initial caries" OR "enamel caries" OR "early caries" OR "early tooth decay" #2 "non cavitated" OR noncavitated OR "white spot lesion" OR "white spots" OR "white spot" OR "white lesion" OR "white lesions" OR "initial caries" OR "enamel caries" OR "early caries" OR "early tooth decay" OR "caries reversal" OR "approximal caries" OR "demineralized lesions" OR "demineralised lesions" OR "enamel demineralisation" OR "enamel demineralization" OR "enamel white spot lesions" #3 – (#1 AND #2)
	Lilacs and BBO May 20th, 2020	(tw:(carie OR caries OR carious OR cariosa OR cariado)) AND (tw:("non cavitated" OR noncavitated OR “no cavitada” OR “sem cavitacao” OR "white spots" OR "white spot" OR "white lesion" OR "white lesions" OR "manchas brancas" OR "manchas blancas" OR "initial caries" OR "enamel caries" OR "early caries" OR "early tooth decay" OR "Carie Precoce" OR "caries inicial" OR "Carie Incipiente" OR “caries temprana” OR "caries reversal" OR "approximal caries" OR "cárie incipiente" OR "lesiones cariosas" OR "lesiones de caries")) AND

	type_of_study:("clinical_trials"))

APÊNDICE 2 – FLUXOGRAMA PRISMA



APÊNDICE 3 – FIGURAS DO RESULTADO NÃO APRESENTADAS NO TEXTO

FIGURA 4 – Metanálise dos estudos com somente uma intervenção acrescidos dos estudos de Madlena et al. (dentifrício com fluoreto de amina + gel com fluoreto de amina vs hábitos orais usuais), Memarpour et al. (verniz fluoretado vs nenhuma intervenção) e Mohebbi et al. (panfleto + lembrete vs nenhuma intervenção).

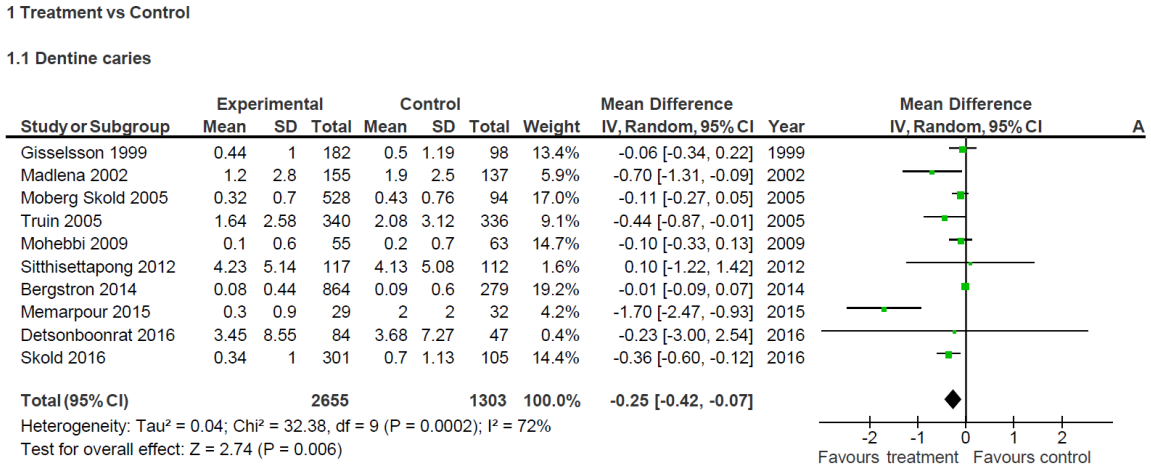


FIGURA 5 – Metanálise dos estudos com somente uma intervenção acrescidos dos estudos de Madlena et al. (dentifrício com fluoreto de amina + gel placebo vs hábitos

orais usuais), Memarpour et al. (verniz fluoretado vs nenhuma intervenção) e Mohebbi et al. (panfleto + lembrete vs nenhuma intervenção).

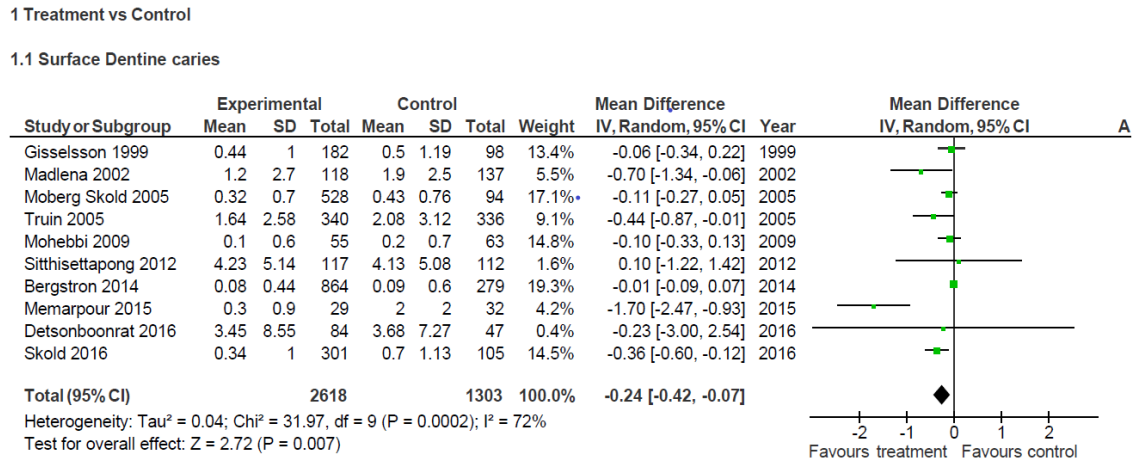


FIGURA 6 – Metanálise dos estudos com somente uma intervenção acrescidos dos estudos de Madlena et al. (dentifrício com fluoreto de amina + gel com fluoreto de amina vs hábitos orais usuais), Memarpour et al. (CPP-ACP vs nenhuma intervenção) e Mohebbi et al. (panfleto vs nenhuma intervenção).

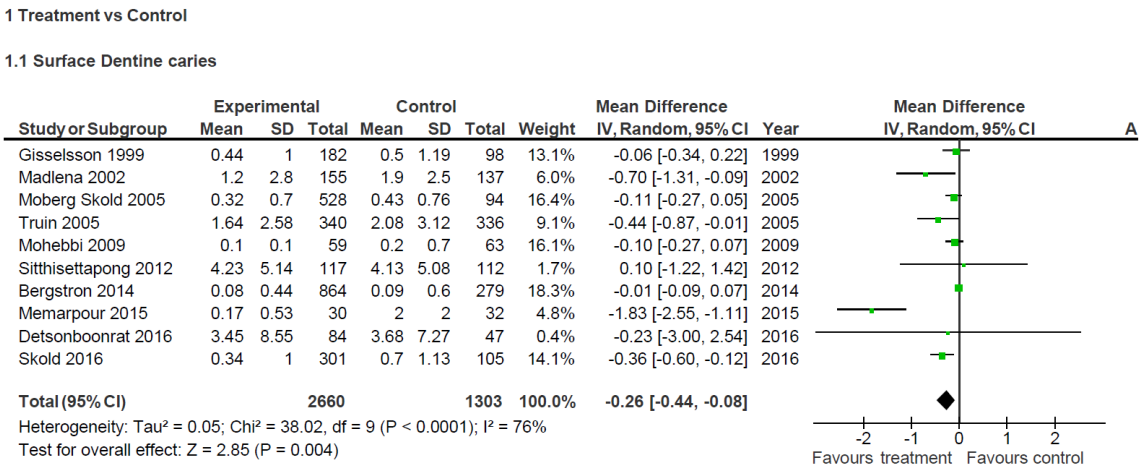


FIGURA 7 – Metanálise dos estudos com somente uma intervenção acrescidos dos estudos de Madlena et al. (dentifrício com fluoreto de amina + gel com fluoreto de amina vs hábitos orais usuais), Memarpour et al. (CPP-ACP vs nenhuma intervenção) e Mohebbi et al. (panfleto vs nenhuma intervenção).

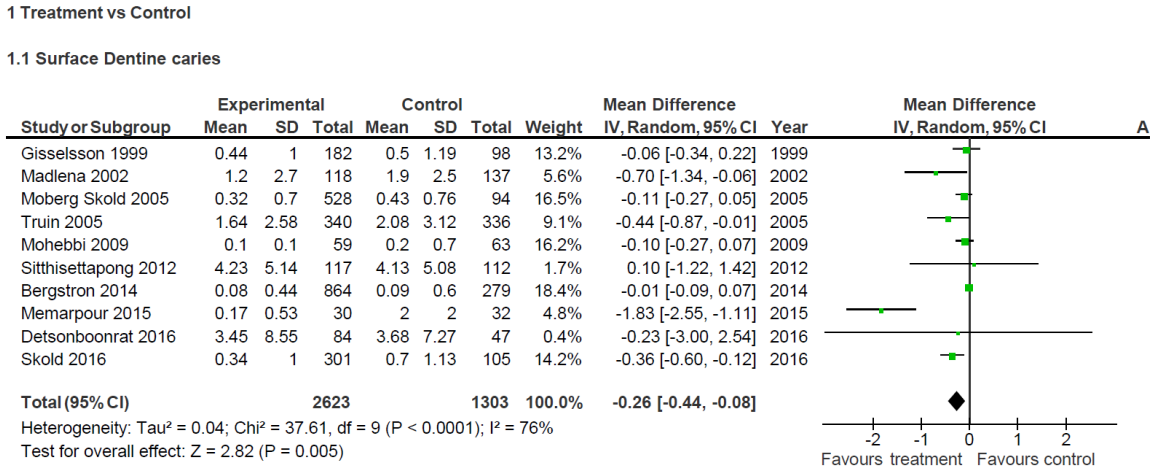


FIGURA 8 – Metanálise dos estudos com somente uma intervenção acrescidos dos estudos de Madlena et al. (dentifrício com fluoreto de amina + gel com fluoreto de amina vs hábitos orais usuais), Memarpour et al. (higiene bucal + aconselhamento de dieta vs nenhuma intervenção) e Mohebbi et al. (panfleto + lembrete vs nenhuma intervenção).

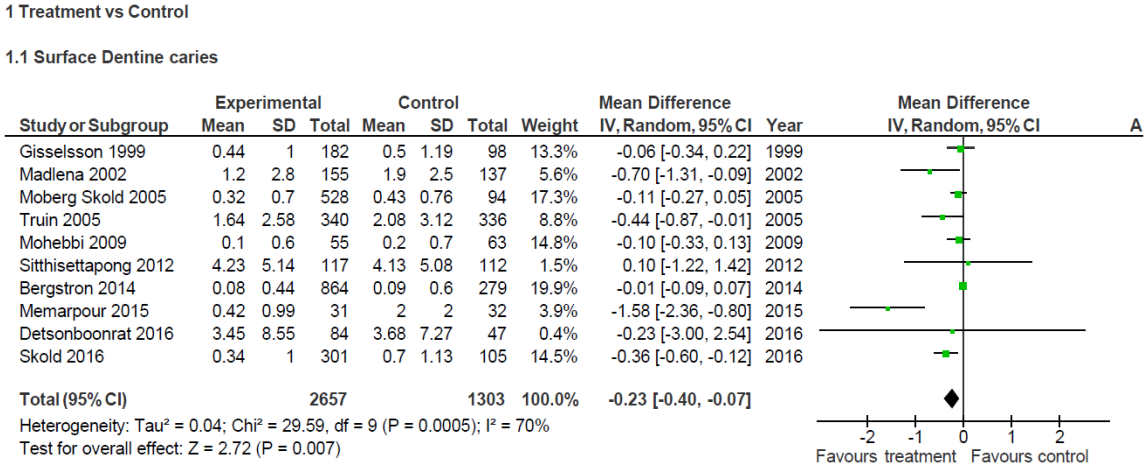


FIGURA 9 – Metanálise dos estudos com somente uma intervenção acrescidos dos estudos de Madlena et al. (dentifrício com fluoreto de amina + gel placebo vs hábitos orais usuais), Memarpour et al. (higiene bucal + aconselhamento de dieta vs nenhuma intervenção) e Mohebbi et al. (panfleto + lembrete vs nenhuma intervenção).

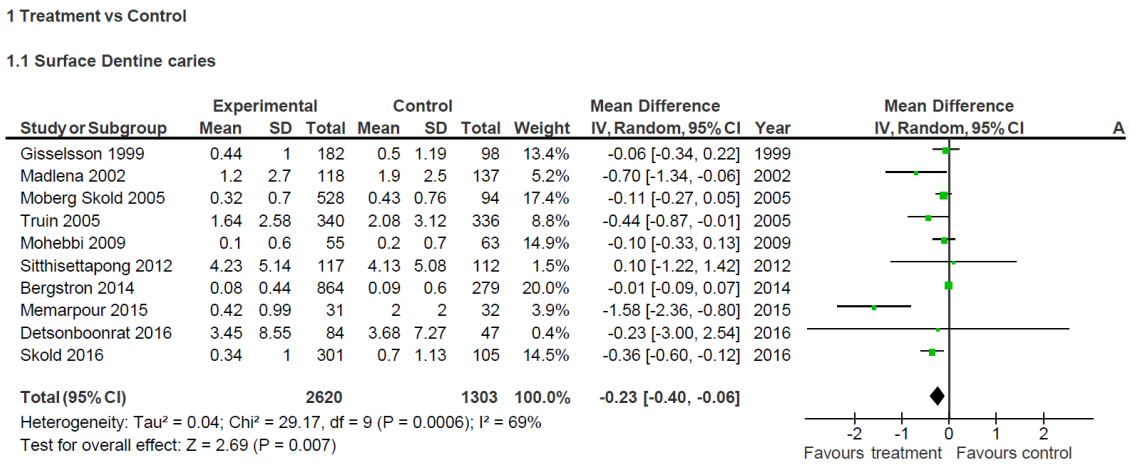


FIGURA 10 – Metanálise dos estudos com somente uma intervenção acrescidos dos estudos de Madlena et al. (dentifrício com fluoreto de amina + gel com fluoreto de amina vs hábitos orais usuais), Memarpour et al. (higiene bucal + aconselhamento de dieta vs nenhuma intervenção) e Mohebbi et al. (panfleto vs nenhuma intervenção).

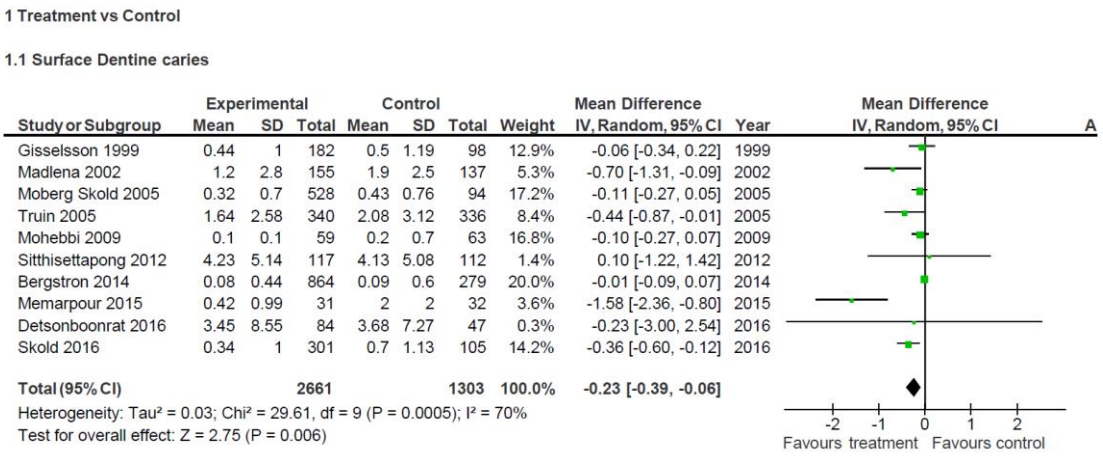


FIGURA 11 – Metanálise dos estudos com somente uma intervenção acrescidos dos estudos de Madlena et al. (dentifrício com fluoreto de amina + gel placebo vs hábitos orais usuais), Memarpour et al. (verniz fluoretado vs nenhuma intervenção) e Mohebbi et al. (panfleto vs nenhuma intervenção).

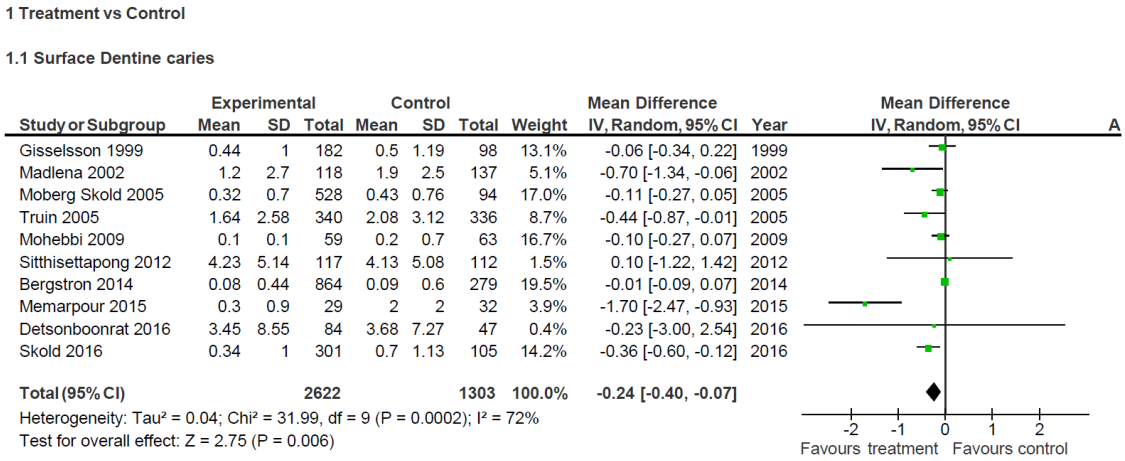


FIGURA 12 – Metanálise dos estudos com somente uma intervenção acrescidos dos estudos de Madlena et al. (dentifrício com fluoreto de amina + gel com fluoreto de amina vs hábitos orais usuais), Memarpour et al. (verniz fluoretado vs nenhuma intervenção) e Mohebbi et al. (panfleto vs nenhuma intervenção).

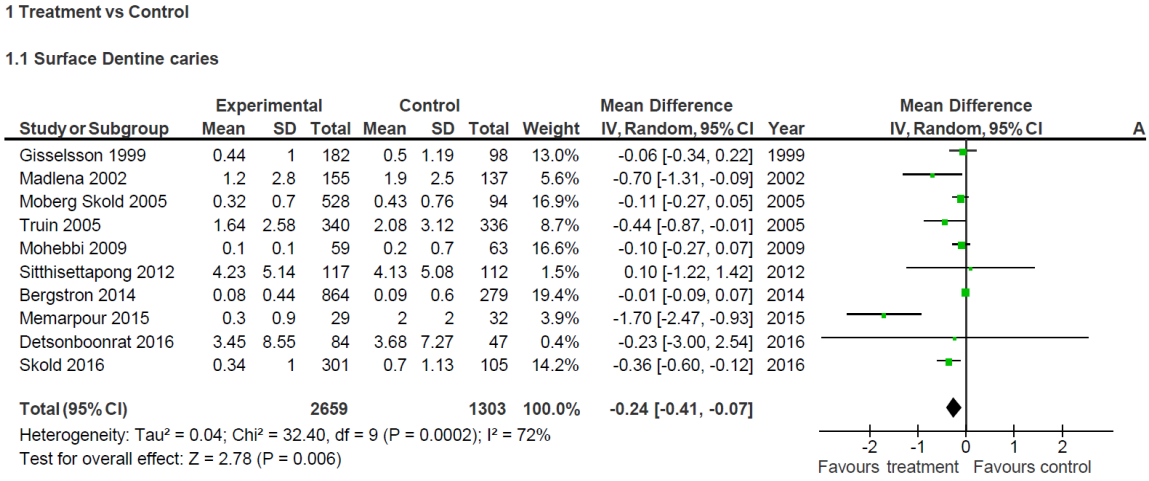


FIGURA 13 – Metanálise dos estudos com somente uma intervenção acrescidos dos estudos de Madlena et al. (dentifrício com fluoreto de amina + gel com fluoreto de amina vs hábitos orais usuais), Memarpour et al. (CPP-ACP vs nenhuma intervenção) e Mohebbi et al. (panfleto + lembrete vs nenhuma intervenção).

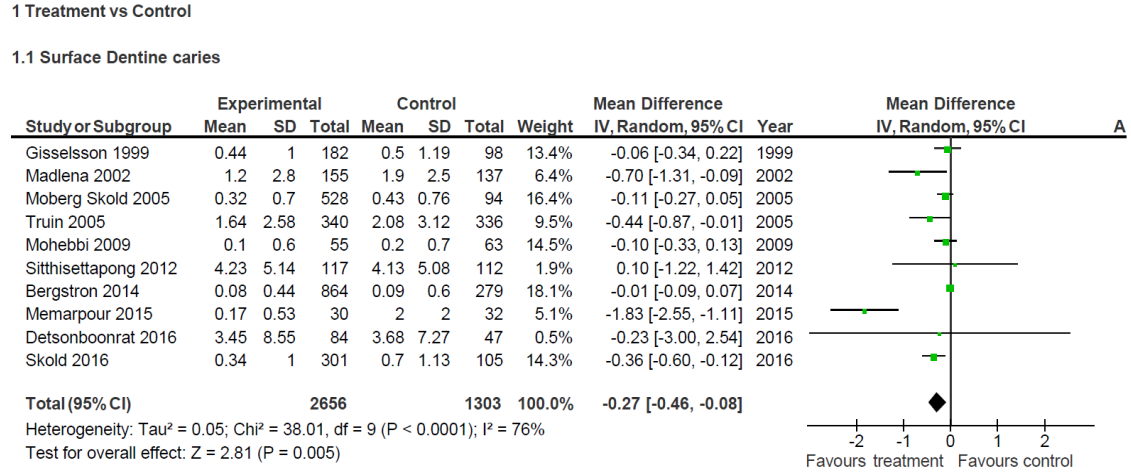


Gráfico 1: Avaliação de risco de viés (RoB2) dos diferentes domínios, com dados percentuais dos julgamentos realizados

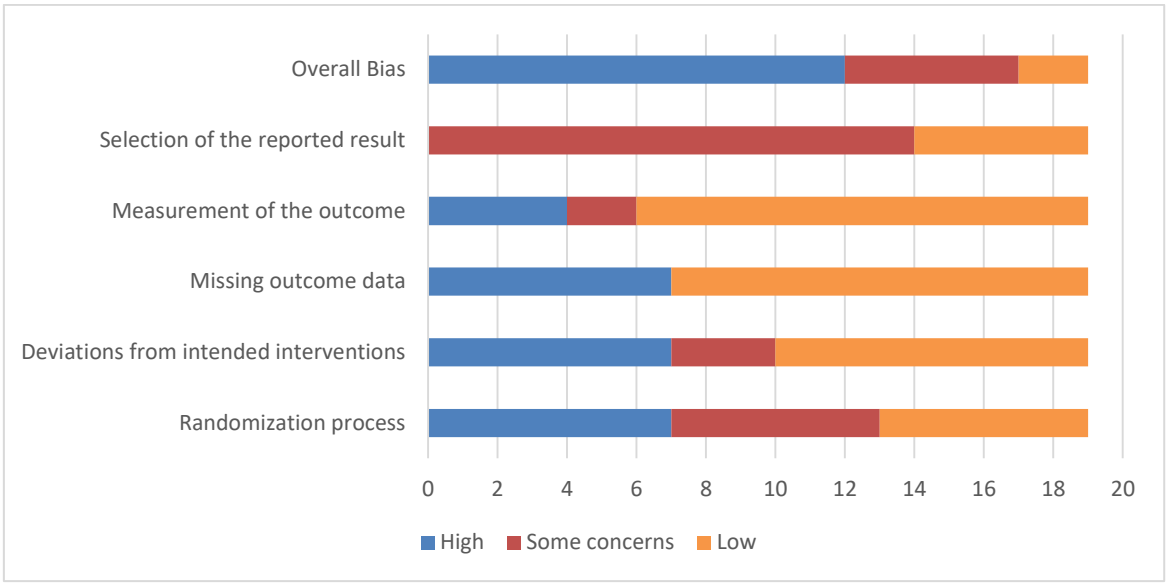

Overall Bias
Selection of the reported result
Measurement of the outcome
Missing outcome data
Deviations from intended interventions
Randomization process
0
2
4
6
8
10
12
14
16
18
20
High
Some concerns
Low

FIGURA 14: Avaliação do risco de viés de cada um dos 19 estudos incluídos (RoB 2)

APÊNDICE 4 – Formulários da análise de viés

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)
TEMPLATE FOR COMPLETION

Edited by Julian PT Higgins, Jelena Savović, Matthew J Page, Jonathan AC Sterne
on behalf of the RoB2 Development Group

Version of 22 August 2019

The development of the RoB 2 tool was supported by the MRC Network of Hubs for Trials Methodology Research (MR/L004933/2- N61), with the support of the host MRC ConDuCT-II Hub (Collaboration and innovation for Difficult and Complex randomised controlled Trials In Invasive procedures - MR/K025643/1), by MRC research grant MR/M025209/1, and by a grant from The Cochrane Collaboration.

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Legenda:

Y – yes (sim)

PY – probably yes (provavelmente sim)

N – no (não)

PN – probably no (provavelmente não)

NI – not informed (não informado)

Study details

Reference	ACHILLEOS, E, et al. Clinical Evaluation of Two Different Prevention Programs in Adults Depending on Their Caries Risk Profile: One-Year Results. Oper Dent. v. 44, n. 2, p. 127-137, 2019.

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: Caries management protocol Comparator: Control protocol

Specify which outcome is being assessed for risk of bias	Development of incipient caries lesions
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Table 6

Is the review team's aim for this result…?

- ☐ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- X to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one

must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	"…the randomization process was as follows: the first patient who took part in the study of each patient risk group was included in the intervention group and the second in the control group and the sequence continued in this way."	Y / PY / PN / N / NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y / PY / PN / N / NI

1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	The only information offered on the characteristics of the sample was age, which ranged between 20 and 62 years (average of 30 years) and gender: 9 men and 35 women.	Y / PY / PN / N / NI
Risk-of-bias judgement	Randomization is not good, and the differences reported between groups are few.	Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	**Comments**	**Response options**
2.1. Were participants aware of their assigned intervention during the trial?	"Protocols were applied by the same examiner who conducted the evaluations."	Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	"All the different medical conditions of the patients were included, except for those who were pregnant, patients who were in cancer therapy at the time of the study, or those with systematic diseases or who had taken medicines that influence the saliva."	NA / Y / PY / PN / N / NI

2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	The authors did not report anything that could suggest it. However, "protocols were applied by the same examiner who conducted the evaluations."	NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	Nothing was reported, however, the procedures that differed between the groups essentially depended on the operators, not requiring the participation of the participants.	NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	The authors did not inform nothing that suggests yes or no. However, six patients, from 50, withdrew from the study before the one-year recall. It is not a high number.	NA / Y / PY / PN / N / NI
Risk-of-bias judgement	There are problems about blindness.	Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options

3.1 Were data for this outcome available for all, or nearly all, participants randomized?	The data for lesions at baseline and 1 year follow-up is in tables 5 and 6.	Y / PY / PN / N / NI
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA / Y / PY / PN / N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement	Lesions data were provided.	Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	**Comments**	**Response options**

4.1 Was the method of measuring the outcome inappropriate?	The authors used ICDAS codes to measure the changes of lesions.	Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	"Protocols were applied by the same examiner who conducted the evaluations."	Y / PY / PN / N / NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		NA / Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement	The method that is not well described does not allow for an adequate assessment of the existence of bias in the outcome.	Low / High / Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	The authors did not inform the clinical trial register.	Y / PY / PN / N / NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	"The changes for each lesion from the baseline examination to the one-year recall were recorded."	Y / PY / PN / N / NI
5.3 ... multiple eligible analyses of the data?	"The nonparametric Wilcoxon test was applied to the two visits (baseline and one year) in each group for comparing the number of lesions." The authors did not refer to any other statistical method that could the choosed.	Y / PY / PN / N / NI
Risk-of-bias judgement	The authors did not inform the clinical trial register.	Low / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement	Blindness and lack of information are problems.	Low / High / Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Study details

Reference	ARSLAN, S; KAPLAN, M.H. The Effect of Resin Infiltration on the Progression of Proximal Caries Lesions: A Randomized Clinical Trial. Med Princ Pract. v. 29, n.3, p. 238-243, 2020.

Study design

☐ Individually-randomized parallel-group trial

☐ Cluster-randomized parallel-group trial

X Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: Resin infiltration + oral hygiene Comparator: oral hygiene

Specify which outcome is being assessed for risk of bias	Caries progression
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Table 3

Is the review team's aim for this result…?

☐ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)

X to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one

must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Domain 1a: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	"Each patient included in the study had two proximal lesions and was assigned to the control group or to the test group by flipping a coin. If more than two lesions were present, the test and control teeth were selected by	Y / PY / PN / N / NI

1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	the lottery method. The tooth numbers were placed in a jar and mixed thoroughly, after which a researcher chose numbers in a blinded fashion. The first number chosen was in the control group and the second number chosen was in the test group. This lottery method was continued until the selection was completed." "Flipping a coin" is a very vulnerable method to allocation hiding.	Y / PY / PN / N / NI
1.3 Did baseline differences between intervention groups at the start of the first period suggest a problem with the randomization process?	"The study design was a split-mouth controlled randomized clinical trial."	Y / PY / PN / N / NI
Risk-of-bias judgement	Random method presented. Split-mouth study, so no differences between groups characteristics. However, "Flipping a coin" is a very vulnerable method to allocation hiding. **For ROB2's algorithm, the result was HIGH.**	Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain S: Risk of bias arising from period and carryover effects

Signalling questions	Comments	Response options
S.1 Was the number of participants allocated to each of the two sequences equal or nearly equal?	Split-mouth study, so no differences between groups characteristics.	Y/PY/PN/N/NI

S.2 If N/PN/NI to S.1: Were period effects accounted for in the analysis?		NA/Y/PY/PN/N/NI
S.3 Was there sufficient time for any carryover effects to have disappeared before outcome assessment in the second period?	Split-mouth study. Same time.	Y/PY/PN/N/NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from period and carryover effects?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during each period of the trial?	There was no mock treatment for the control group. Nothing was said about controls procedures. "In the test group, the treatment was conducted using rubber-dam isolation and plastic wedges."	Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during each period of the trial?		Y / PY / PN / N / NI

2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced between interventions?	It was a split-mouth trial.	NA / Y / PY / PN / N / NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	The authors didn't mention. They described the technique, that is correct. However, failures are important for the results of this kind of treatment.	NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	This procedure must be performed by a trained professional. Thus, there is no way that the patient's non-adherence to the procedure performed can interfere with the result. The only issue that could occur would be non-cooperation in the case of young children, which was not reported.	NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement	There was no mock treatment for the control groups. 26,8% of the patients refused to participate in the control appointments. However, it was a split-mouth study. **For ROB2's algorithm, the result was LOW.**	Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Risk of bias due to missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	"Of 640 patients, 56 met the inclusion criteria, gave their informed consent and were enrolled in the study. But, at the end of the year only 41 patients participated in the evaluation (15 patients refused to participate in the control appointments)."	Y / PY / PN / N / NI
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA / Y / PY / PN / N
3.3 If N/PN to 3.2 Could missingness in the outcome depend on its true value?		NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement	It is a split-mouth study, so the missing are balanced.	Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	"After 1 year, patients were called back for a follow-up examination. Standardized digital bitewing radiographs were obtained using the same individual holders and settings as during the baseline examination."	Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between interventions within each sequence?	"After 1 year, patients were called back for a follow-up examination. Standardized digital bitewing radiographs were obtained using the same individual holders and settings as during the baseline examination."	Y / PY / PN / N / NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	"Radiographs and DSR images were read by one experienced clinical examiner (intra-examiner reliability was assessed), who was blinded with regard to the test and control lesions."	NA / Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement	Measures are appropriate. Examiner was blinded.	Low / High / Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	The data and outcome are in accordance with the registered project. (TCTR identification number: 20190406001)	Y / PY / PN / N / NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	The data and outcome are in accordance with the registered project. (TCTR identification number: 20190406001)	Y / PY / PN / N / NI
5.3 ... multiple eligible analyses of the data?	The data and outcome are in accordance with the registered project. (TCTR identification number: 20190406001)	Y / PY / PN / N / NI
5.4 Is a result based on data from both periods sought, but unavailable on the basis of carryover having been identified?	It is a split-mouth study. Same time.	Y / PY / PN / N / NI
Risk-of-bias judgement	The data and outcome are in accordance with the registered project. (TCTR identification number: 20190406001)	Low / High / Some concerns

Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement	**For ROB2's algorithm, the result was SOME CONCERNS.**	Low / High / Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Study details

Reference	ARTHUR, R. et al. Proximal carious lesions infiltration – a 3-year follow-up study of a randomized controlled clinical trial. Clin Oral Invest. v. 22, n. 1, p. 469-474, 2018.

Study design

☐ Individually-randomized parallel-group trial

☐ Cluster-randomized parallel-group trial

X Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: resin infiltration + oral hygiene Comparator: oral hygiene

Specify which outcome is being assessed for risk of bias	Caries progression
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Table 1 / Figure 1

Is the review team's aim for this result…?

☐ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)

X to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one

must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Domain 1a: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	"This was a double-blind split-mouth placebo-controlled randomized clinical trial." The authors didn't explain how they made the randomization.	Y / PY / PN / N / NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y / PY / PN / N / NI

1.3 Did baseline differences between intervention groups at the start of the first period suggest a problem with the randomization process?	"Considering a power of 80 and 5% of significance, 22 pairs of lesions were considered necessary to conduct the study. Considering a drop-out rate of 30% for the 5-year follow-up (estimative based on unpublished data of our group), 32 pairs of lesions would be necessary. During the screening process, 36 pairs of lesions were included in this study." In addition, it is a split-mouth trial.	Y / PY / PN / N / NI
Risk-of-bias judgement	The authors did not explain the randomization process.	Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain S: Risk of bias arising from period and carryover effects

Signalling questions	Comments	Response options
S.1 Was the number of participants allocated to each of the two sequences equal or nearly equal?	Split-mouth study. Same time.	Y/PY/PN/N/NI
S.2 If N/PN/NI to S.1: Were period effects accounted for in the analysis?		NA/Y/PY/PN/N/NI

S.3 Was there sufficient time for any carryover effects to have disappeared before outcome assessment in the second period?	Split-mouth study. Same time.	Y/PY/PN/N/NI
Risk-of-bias judgement	Split-mouth study. Same time.	Low / High / Some concerns
Optional: What is the predicted direction of bias arising from period and carryover effects?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during each period of the trial?	"In order to assure volunteer blinding, lesions assigned to placebo treatment (n = 36) were subjected to the clinical steps described above, but water was used instead of acid etching and resin infiltrant. Rubber dam was used in all clinical procedures." "Except for the operator (RTC), all the other investigators were kept blind to treatment assignment of the NCPL."	Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during each period of the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced between interventions?	It was a split-mouth trial.	NA / Y / PY / PN / N / NI

2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	The authors didn't mention. They described the technique, that is correct. However, failures are important for the results of this kind of treatment.	NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	This procedure must be performed by a trained professional. Thus, there is no way that the patient's non-adherence to the procedure performed can interfere with the result. The only issue that could occur would be non-cooperation in the case of young children, which was not reported.	NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement	It is a split-mouth trial, participants are blinding, mock treatment were used.	Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Risk of bias due to missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	"At follow-up (April 2014 to April 2015), 17 out 22 patients enrolled at baseline were clinically and radiographically examined (47% male and 53%female; 27 out 36 pairs of lesions)."	Y / PY / PN / N / NI

3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA / Y / PY / PN / N
3.3 If N/PN to 3.2 Could missingness in the outcome depend on its true value?		NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement	77% of the lesions were analysed at the follow-up.	Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	"At the 3-year follow-up, volunteers were recalled to clinical and radiographic examination by one operator (JCDP) who was blinded with regard to the allocation of test/placebo treatments."	Y / PY / PN / N / NI

4.2 Could measurement or ascertainment of the outcome have differed between interventions within each sequence?	"At the 3-year follow-up, volunteers were recalled to clinical and radiographic examination by one operator (JCDP) who was blinded with regard to the allocation of test/placebo treatments."	Y / PY / PN / N / NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	"At the 3-year follow-up, volunteers were recalled to clinical and radiographic examination by one operator (JCDP) who was blinded with regard to the allocation of test/placebo treatments."	NA / Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement	Bite wings radiographs are an adequate method to evaluate caries progression in proximal lesions. Moreover, the operator was blinded.	Low / High / Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	The authors did not inform the clinical trial register.	Y / PY / PN / N / NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	The authors did not inform the clinical trial register.	Y / PY / PN / N / NI
5.3 ... multiple eligible analyses of the data?	The authors did not inform the clinical trial register.	Y / PY / PN / N / NI
5.4 Is a result based on data from both periods sought, but unavailable on the basis of carryover having been identified?	The authors did not inform the clinical trial register.	Low / High / Some concerns
Risk-of-bias judgement		Low / High / Some concerns

Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement	**For ROB2's algorithm, the result was SOME CONCERNS.**	Low / High / Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Study details

Reference	BORGES, B.C.D. et al. Arrest of non-cavitated dentinal occlusal caries by sealing pits and fissures: a 36-month, randomized controlled clinical trial. International Dental Journal, v. 62, n. 5, p. 251-255, 2012.

Study design

X Individually-randomized parallel-group trial

☐ Cluster-randomized parallel-group trial

☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: sealant + oral hygiene Comparator: oral hygiene

Specify which outcome is being assessed for risk of bias	arresting non-cavitated dentin lesions
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Table 2 ("Clinical progression was defined by the presence of visible cavitation and/or sensitivity during follow-up.")

Is the review team's aim for this result…?

☐ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)

X to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one

must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	"Each eligible tooth was assigned a number; these numbers were noted on individual pieces of paper which were subsequently put into a sealed opaque envelope. An external examiner withdrew one paper at a time and allocated 30 teeth to each group." It is not clear if this procedure was made immediately before the procedure.	Y / PY / PN / N / NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y / PY / PN / N / NI

1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Demographic data for the subjects included in this study was demonstrated on table 1.	Y / PY / PN / N / NI
Risk-of-bias judgement	It is not explained the timing of the randomization.	Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	**Comments**	**Response options**
2.1. Were participants aware of their assigned intervention during the trial?	Nothing is said about participant's blinding. It is impossible to the operator to be blind in this kind of procedure.	Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	"All patients received oral hygiene instructions that 11 included the Fones technique for daily tooth brushing and the use of dental floss after meals. In addition, the operator recorded all possible fluoride sources used."	NA / Y / PY / PN / N / NI

2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	The authors described the technique for the procedure, that was correct.	NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	This tested procedure must be performed by a trained professional. Thus, there is no way that the patient's non-adherence to the procedure performed can interfere with the result.	NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement	Nothing is said about participant's blinding.	Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options

3.1 Were data for this outcome available for all, or nearly all, participants randomized?	11% of participants were lost at the 8-month recall appointment. Moreover, all the losses occurred in the control group.	Y / PY / PN / N / NI
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	Although the losses occurred only in the control group, the difference in the result between the groups was quite striking and left no doubt.	NA / Y / PY / PN / N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement	11% of participants were lost at the 8-month recall appointment. Moreover, all the losses occurred in the control group. **For ROB2's algorithm, the result was LOW.**	Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	"One experienced and calibrated examiner evaluated the radiographs at 12, 24 and 36 months."	Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	"The examiner paired the radiographs and evaluated them blindly in a dark room using a negatoscope, a 2x magnifying glass and a millimetre ruler."	Y / PY / PN / N / NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	"The examiner paired the radiographs and evaluated them blindly in a dark room using a negatoscope, a 2x magnifying glass and a millimetre ruler."	NA / Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	The protocol number were not avaiable.	Y / PY / PN / N / NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	The protocol number were not avaiable.	Y / PY / PN / N / NI
5.3 ... multiple eligible analyses of the data?	The protocol number were not avaiable.	Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement	**For ROB2's algorithm, the result was SOME CONCERNS.**	Low / High / Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Study details

Reference	DETSOMBOONRAT, P. et al. Similar 1-year caries increment after use of fluoride or non-fluoride toothpaste in infants and toddlers. Fluoride, v. 49, n. 3, p. 313-326, 2016.

Study design

- ☐ Individually-randomized parallel-group trial
- X Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: 500 ppm toothpaste Comparator: 1000 ppm toothpaste

Specify which outcome is being assessed for risk of bias	Caries increment
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Tables 5 (baseline) and 8 (12 months follow-up)

Is the review team's aim for this result…?

- ☐ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- X to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one

must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Domain 1a: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1a.1 Was the allocation sequence random?	"Three different toothpastes in three different colored packages were randomly assigned to each group by one investigator."	Y / PY / PN / N / NI
1a.2 Was the allocation sequence concealed until clusters were enrolled and assigned to interventions?	The authors did not explain how the randomization was done.	Y / PY / PN / N / NI

1a.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Table 1 shows comparisons between the 3 groups at baseline.	Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 1b: Risk of bias arising from the timing of identification or recruitment of participants in a cluster-randomized trial

Signalling questions	Comments	Response options
1b.1 Were all the individual participants identified and recruited (if appropriate) before randomization of clusters?	Nothing was said about it.	Y/PY/PN/N/NI
1b.2 If N/PN/NI to 1b.1: Is it likely that selection of individual participants was affected by knowledge of the intervention assigned to the cluster?	"The subjects were divided into three clusters based on their village areas to eliminate the risk of the subjects sharing different toothpastes in the nearby village." The clusters were formed by proximity. The interventions were randomized between the formed groups. Nothing is said about the time of randomization.	NA/Y/PY/PN/N/NI

1b.3 Were there baseline imbalances that suggest differential identification or recruitment of individual participants between intervention groups?	"In terms of the socio-demographic characteristics, there was a statistically significant difference among three groups in the age of the primary caregivers. The primary caregivers in the 1000 ppm group were younger than those in the other two groups. For other variables, there was no difference between the three groups through statistical analysis."	Y/PY/PN/N/NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the timing of identification and recruitment of participants?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	"...the blinded respective toothpaste for each group..." "Three different toothpastes in three different colored packages were randomly assigned to each group by one investigator"	Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA / Y / PY / PN / N / NI

2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	"The subjects were divided into three clusters based on their village areas to eliminate the risk of the subjects sharing different toothpastes in the nearby village."	NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	The 173 primary caregivers and children were allocated into the 3 groups (1000 ppm: n=53; 500 ppm: n=59, xylitol: n=61) at baseline. One-hundred and thirty-one dyads (1000 ppm: n=37; 500 ppm: n=47, xylitol: n=47) completed the trial (response rate = 75.7%). The 41 lost cases included 12 cases who moved out of the villages, 27 cases who did not attend appointments, and 2 cases who became seriously ill."	NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	"The 173 primary caregivers and children were allocated into the 3 groups (1000 ppm: n=53; 500 ppm: n=59, xylitol: n=61) at baseline… Therefore, 131 dyads were included in the final analysis."	NA / Y / PY / PN / N / NI
Risk-of-bias judgement	**For ROB2's algorithm, the result was HIGH.**	Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Risk of bias due to missing outcome data

Signalling questions	Comments	Response options

3.1a Were data for this outcome available for all clusters that recruited participants?	"The 173 primary caregivers and children were allocated into the 3 groups (1000 ppm: n=53; 500 ppm: n=59, xylitol: n=61) at baseline. One-hundred and thirty-one dyads (1000 ppm: n=37; 500 ppm: n=47, xylitol: n=47) completed the trial (response rate = 75.7%)." The authors were expected a high dropout rate.	Y / PY / PN / N / NI
3.1b Were data for this outcome available for all, or nearly all, participants within clusters?	"The 173 primary caregivers and children were allocated into the 3 groups (1000 ppm: n=53; 500 ppm: n=59, xylitol: n=61) at baseline. One-hundred and thirty-one dyads (1000 ppm: n=37; 500 ppm: n=47, xylitol: n=47) completed the trial (response rate = 75.7%)."	Y / PY / PN / N / NI
3.2 If N/PN/NI to 3.1a or 3.1b: Is there evidence that the result was not biased by missing data?	"The 41 lost cases included 12 cases who moved out of the villages, 27 cases who did not attend appointments, and 2 cases who became seriously ill."	NA / Y / PY / PN / N
3.3 If N/PN to 3.2 Could missingness in the outcome depend on its true value?	"The 173 primary caregivers and children were allocated into the 3 groups (1000 ppm: n=53; 500 ppm: n=59, xylitol: n=61) at baseline. One-hundred and thirty-one dyads (1000 ppm: n=37; 500 ppm: n=47, xylitol: n=47) completed the trial (response rate = 75.7%)."	NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	"The oral examination was conducted by one pediatric dentist who did not know which group the children were assigned to." "The classification of dental findings was modified from Warren et al. as follows: unerupted tooth (U), normal enamel surface (S), demineralization but no loss of enamel structure (d1), caries lesion with loss of tooth structure (d2), filled surface without evidence of secondary caries (f), missing tooth due to caries (m). The severity of ECC was determined using dmfs (including and excluding white lesions) and incremental dmfs (including and excluding white lesions)."	Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	"The oral examination was conducted by one pediatric dentist who did not know which group the children were assigned to."	Y / PY / PN / N / NI
4.3a If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware that a trial was taking place?		NA / Y / PY / PN / N / NI
4.3b If Y/PY/NI to 4.3a: Were outcome assessors aware of the intervention received by study participants?	"The oral examination was conducted by one pediatric dentist who did not know which group the children were assigned to."	NA / Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3b: Could assessment of the outcome have been influenced by knowledge of intervention received?	"The oral examination was conducted by one pediatric dentist who did not know which group the children were assigned to."	NA / Y / PY / PN / N / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI

Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	The protocol number is not avaiable.	Y / PY / PN / N / NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	The protocol number is not avaiable.	Y / PY / PN / N / NI
5.3 ... multiple eligible analyses of the data?	The protocol number is not avaiable.	Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement	**For ROB2's algorithm, the result was SOME CONCERNS.**	Low / High / Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Study details

Reference	GISSELSSON, H.; BIRKHED, D; EMILSON, C.G. Effect of professional flossing with NaF or SnF_2 gel on approximal caries in 13-16-year-old schoolchildren. Acta Odontol Scand, v.57, n. 2, p. 121-125, 1999.

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental:	Flossing with fluoride content gel	Comparator:	Flossing with a placebo gel

Specify which outcome is being assessed for risk of bias	Caries incidence
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Table 3

Is the review team's aim for this result…?

- ☐ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- X to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one

must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

x Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	"They were randomly allocated to 3 gel groups." The authors did not explain how randomization was done.	Y / PY / PN / N / NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y / PY / PN / N / NI

1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	"They belonged to 26 separate school classes, and the 3 groups were evenly distributed in every class."	Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	"A placebo gel was used as a control." "The different gels were marked 1, 2, and 3, and the study was carried out double-blind. All gels were manufactured and packed in identical bottles."	Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA / Y / PY / PN / N / NI

2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	"The gel treatment of the 280 children was carried out by 3 dental nurses, and every nurse treated children from all the groups."	NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	At the start of the study, 8 individuals did not want to participate. During the following 3 years, 29 children moved from the area or preferred to visit a private dentist.	NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options

3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Response rate = 88,3%	Y / PY / PN / N / NI
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	The authors did not inform from which group the children belonged.	NA / Y / PY / PN / N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	"During the following 3 years, 29 children moved from the area or preferred to visit a private dentist." Why they preferred visit a private dentist?	NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	**Comments**	**Response options**

4.1 Was the method of measuring the outcome inappropriate?	"Bitewing radiographs were then taken in all children except 10 (thus, n = 270) in whom approximal caries lesions were judged not to be present." "All children were examined with bitewing radiographs at 15 and 16 years of age, and most of them at 14."	Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	"…altogether 36 surfaces per child, were diagnosed on the bitewing radiographs by one of the authors (H.G.)."	Y / PY / PN / N / NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	There is no information about the blindness of the assessor.	NA / Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	There is no information about the blindness of the assessor.	NA / Y / PY / PN / N / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement	**For ROB2's algorithm, the result was HIGH.**	Low / High / Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	The protocol number is not avaiable.	Y / PY / PN / N / NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	The protocol number is not avaiable.	Y / PY / PN / N / NI
5.3 ... multiple eligible analyses of the data?	The protocol number is not avaiable.	Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Study details

Reference	JORGE, R.C. et al. Randomized controlled clinical trial of resin infiltration in primary molars: a 2 years follow-up. J Dent, v. 90, Nov, 2019.

Study design

☐ Individually-randomized parallel-group trial

☐ Cluster-randomized parallel-group trial

X Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: resin infiltration + flossing Comparator: flossing

Specify which outcome is being assessed for risk of bias	Caries progression
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Table 3

Is the review team's aim for this result…?

☐ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)

X to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one

must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Domain 1a: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	"For the randomization into test or control group, the selected teeth were organized according to the sequence from tooth 55 to 65 in the upper arch and from 75 to 85 in the lower arch. The first tooth in the sequence was allocated by flipping a coin to test or control and the other tooth was automatically allocated to the other group." "Flipping a coin" is a very vulnerable method to allocation hiding.	Y / PY / PN / N / NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y / PY / PN / N / NI

1.3 Did baseline differences between intervention groups at the start of the first period suggest a problem with the randomization process?	The 2 treatments occurred at the same time.	Y / PY / PN / N / NI
Risk-of-bias judgement	"Flipping a coin" is a very vulnerable method to allocation hiding.	Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain S: Risk of bias arising from period and carryover effects

Signalling questions	Comments	Response options
S.1 Was the number of participants allocated to each of the two sequences equal or nearly equal?	Split-mouth study.	Y/PY/PN/N/NI
S.2 If N/PN/NI to S.1: Were period effects accounted for in the analysis?		NA/Y/PY/PN/N/NI
S.3 Was there sufficient time for any carryover effects to have disappeared before outcome assessment in the second period?	Split-mouth study	Y/PY/PN/N/NI

Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from period and carryover effects?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during each period of the trial?	The period is the same. This is a split-mouth study. And the authors did not tell anything about mock treatment.	Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during each period of the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced between interventions?	Split-mouth study. Same time.	NA / Y / PY / PN / N / NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	The treatment (resin infiltration) of the test lesions was performed by a single trained investigator following the manufacture's intruction for the infiltration technique (low viscosity resin - Icon, DMG®, Hamburg, Germany).	NA / Y / PY / PN / N / NI

2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	The flossing activity depends on the collaboration of caregivers. However, it is a split-mouth study; this problem tends to be balanced in the 2 groups.	NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement	**For ROB2's algorithm, the result was HIGH.**	Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Risk of bias due to missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Response rate = 84%	Y / PY / PN / N / NI
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	"As one of the reasons for dropout was the exfoliation of the teeth, it somehow explains the higher baseline mean age among the dropouts." 7 lost contact; 1 moved; 13 tooth exfotiation	NA / Y / PY / PN / N

3.3 If N/PN to 3.2 Could missingness in the outcome depend on its true value?		NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement	Although the response rate, the major dropouts were because of tooth exfotiation.	Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	Digital bitewing radiographs were taken at baseline and repeated after 12 and 24-months.	Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between interventions within each sequence?	Split-mouth study.	Y / PY / PN / N / NI

4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Pair-wise reading was assessed by one calibrated examiner, blind in relation to test and control lesions (intra and inter examiner reliability was 95.8%, kappa 0.90; and 90%, kappa 0.75, respectively), and in a randomized order, regardless of the participant number and group.	NA / Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options

5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	The trial is registered in clinicaltrials.gov (NCT01726179).	Y / PY / PN / N / NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		Y / PY / PN / N / NI
5.3 ... multiple eligible analyses of the data?		Y / PY / PN / N / NI
5.4 Is a result based on data from both periods sought, but unavailable on the basis of carryover having been identified?	Split-mouth study. Same period.	Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement	**For ROB2's algorithm, the result was HIGH.**	Low / High / Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Study details

Reference	MADLÉNA, M. et al. Effect of Amine Fluoride Toothpaste and Gel in High Risk Groups of Hungarian Adolescents: Results of a Longitudinal Study. Caries Res. V. 36, n. 2, p. 142-146, 2002.

Study design

- ☐ Individually-randomized parallel-group trial
- X Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental:	Amine fluoride toothpaste + amine fluoride gel	Comparator:	Amine fluoride toothpaste + placebo gel

Specify which outcome is being assessed for risk of bias	Caries increment
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Tables 2 and 3

Is the review team's aim for this result…?

- ☐ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- X to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one

must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Domain 1a: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1a.1 Was the allocation sequence random?	"The adolescents were randomly divided into test and control groups by clusters (school classes) in both cities." The authors did not explain how the randomization was done or if it was done before clusters were enrolled and assigned to interventions.	Y / PY / PN / N / NI
1a.2 Was the allocation sequence concealed until clusters were enrolled and assigned to interventions?		Y / PY / PN / N / NI

1a.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	"Table 1 shows the demographic summary: number of participants, distribution according to sex and age, in the different groups at baseline and after 2 years."	Y / PY / PN / N / NI
Risk-of-bias judgement	**For ROB2's algorithm, the result was SOME CONCERNS.**	Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 1b: Risk of bias arising from the timing of identification or recruitment of participants in a cluster-randomized trial

Signalling questions	Comments	Response options
1b.1 Were all the individual participants identified and recruited (if appropriate) before randomization of clusters?	The authors did not inform it.	Y/PY/PN/N/NI
1b.2 If N/PN/NI to 1b.1: Is it likely that selection of individual participants was affected by knowledge of the intervention assigned to the cluster?	"The examination sites were two Hungarian cities; 261 of the participating children lived in Budapest, the capital, and 325 children in Debrecen, the second largest city in the north-eastern part of the country."	NA/Y/PY/PN/N/NI

1b.3 Were there baseline imbalances that suggest differential identification or recruitment of individual participants between intervention groups?	"Table 1 shows the demographic summary: number of participants, distribution according to sex and age, in the different groups at baseline and after 2 years."	Y/PY/PN/N/NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the timing of identification and recruitment of participants?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	"One test group received Elmex toothpaste (GABA International Ltd., Basel, Switzerland) for unsupervised home use twice daily, and Elmex gel for unsupervised use once a week (test group A). The other test group received Elmex toothpaste and a placebo gel for unsupervised home use (test group B)."	Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	The authors did not inform anything that suggest it.	NA / Y / PY / PN / N / NI

2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	"All the pupils participating in the study were regularly motivated and instructed, and advised on diet bimonthly."	NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	The dropout was about 30%.	NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	The authors did not inform anything that suggest it.	NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Risk of bias due to missing outcome data

Signalling questions	Comments	Response options
3.1a Were data for this outcome available for all clusters that recruited participants?		Y / PY / PN / N / NI

3.1b Were data for this outcome available for all, or nearly all, participants within clusters?	The dropout was about 30%.	Y / PY / PN / N / NI
3.2 If N/PN/NI to 3.1a or 3.1b: Is there evidence that the result was not biased by missing data?	Table 1 shows that losses were not evenly distributed between genders.	NA / Y / PY / PN / N
3.3 If N/PN to 3.2 Could missingness in the outcome depend on its true value?	There is no way to know. The authors said nothing to suggest that the outcome could be changed, but nothing to suggest that it could not.	NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	"The examinations were carried out by two calibrated dentists. The intra- and inter-examiner calibrations were performed at the beginning of the study, and repeated each year." "Clinical examinations were performed in a dental chair with the help of a plain dental mirror and a dental probe, using the lighting attached to the unit, according to the standard methods and criteria of the World Health Organization."	Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	The authors did not say anything about blindness of the dentists who made the examinations.	Y / PY / PN / N / NI
4.3a If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware that a trial was taking place?	The examinations were carried out by two calibrated dentists.	NA / Y / PY / PN / N / NI
4.3b If Y/PY/NI to 4.3a: Were outcome assessors aware of the intervention received by study participants?	The authors did not say anything about blindness of the dentists who made the examinations.	NA / Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3b: Could assessment of the outcome have been influenced by knowledge of intervention received?	The authors did not say anything about blindness of the dentists who made the examinations.	NA / Y / PY / PN / N / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns

Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	the clinical trial register was not provided.	Y / PY / PN / N / NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	the clinical trial register was not provided.	Y / PY / PN / N / NI
5.3 ... multiple eligible analyses of the data?	the clinical trial register was not provided.	Y / PY / PN / N / NI

Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

tudy details

Reference	MATTOS-SILVEIRA, Juliana. Diamino fluoreto de prata – uma nova proposta para o tratamento não operatório de lesões proximais em molares decíduos: estudo clínico randomizado. 2016. Tese (Doutorado) – Curso de Odontologia (Odontopediatria), Universidade de São Paulo, São Paulo, 2016.

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: Silver diamine fluoride 30% Comparator: Resin infiltration

Specify which outcome is being assessed for risk of bias	Caries progression
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Table 5.4, 5.5, 5.6 and 5.7

Is the review team's aim for this result…?

- ☐ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- X to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one

must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

☐ Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
X "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	"A alocação dos participantes em cada grupo foi feita aleatoriamente por uma lista de randomização gerada por um software específico (Medcal software verssion 12.4.0.0, Ostende, Belgica). Assim, a sequencia gerada pela randomização foi distribuída em envelopes opacos e lacrados, que foram abertos pelo operador no momento do tratamento."	Y / PY / PN / N / NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y / PY / PN / N / NI

1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	"No início do estudo os responsáveis responderam a um questionário socioeconômico e com questões referentes às características individuais dos participantes."	Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	**Comments**	**Response options**
2.1. Were participants aware of their assigned intervention during the trial?	"O objetivo do placebo foi tentar cegar os participantes e seus responsáveis em relação ao grupo de tratamento ao qual foram alocados, no intuit de que os participantes e seus responsáveis se sentissem igualmente tratados. Por outro lado, sabe-se que trata-se de um placebo imperfeito, pous um dos tratamentos requer uso de anestesia local e isolamento absoluto, o que seria eticamente inaceitável em uma intervenção placebo."	Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA / Y / PY / PN / N / NI

2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	The proposed treatments are well described, with no error.	NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	2 interventions need a professional to be done. In this way, the issue of non-adherence becomes meaningless. The control was dental hygiene. Therefore, the risk of non-adherence is common to all groups.	NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	**Comments**	**Response options**

3.1 Were data for this outcome available for all, or nearly all, participants randomized?	"Apenas 7% dos participantes perderam todos os retornos para avaliação de cárie. As taxas de perda de seguimento foram de 15% aos 12 meses e de 24% aos 24 meses, sendo semelhantes entre os grupos, em ambos os períodos. O principal motivo de perda de seguimento foi o não comparecimento à consulta agendada."	Y / PY / PN / N / NI
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	"Apesar das perdas, as caracteristicas da amostra reavaliada foram semelhantes aquelas dos participantes que não se pôde reavaliar, quando considerados: sexo, idade, renda e risco."	NA / Y / PY / PN / N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement	**For ROB2's algorithm, the result was LOW.**	Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	**Comments**	**Response options**

4.1 Was the method of measuring the outcome inappropriate?	"Dois examinadores foram treinados para detectar lesões de cárie utilizando o ICDAS..." "De igual modo, os examinadores foram treinados para avaliar a profundidade das lesões de cárie em radiografias interproximais de dentes decíduos, de acordo com os escores propostos por Ekstrand et al..."	Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	"Os examinadores desconheciam o tratamento recebido pelos participantes, os quais também não foram informados em relação a alocação dos grupos."	Y / PY / PN / N / NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	"Os examinadores desconheciam o tratamento recebido pelos participantes, os quais também não foram informados em relação a alocação dos grupos."	NA / Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	"... está registrado no ClinicalTrials.gov, número NCT01477385..."	Y / PY / PN / N / NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	All results obtained seems to be presented.	Y / PY / PN / N / NI
5.3 ... multiple eligible analyses of the data?	All results obtained seems to be presented.	Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns

Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Study details

Reference	MEMARPOUR, M. et al. Efficacy of Fluoride Varnish and Casein Phosphopeptide-Amorphous Calcium Phosphate for Remineralization of Primary Teeth: A Randomized Clinical Trial. Med Princ Pract, v. 24, n. 3, p. 231-237, 2015.

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: Fluoride varnish Comparator: CPP-ACP

Specify which outcome is being assessed for risk of bias	Caries progression
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Table 3

Is the review team's aim for this result…?

- ☐ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- X to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one

must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	"At baseline and follow-up appointments, a staff member at the health clinic selected children by means of a block randomization method with the help of a random number table."	Y / PY / PN / N / NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y / PY / PN / N / NI

1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	"There were no significant differences between groups in terms of sex ratio (p = 0.280) or mean age (p = 0.657)."	Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	**Comments**	**Response options**
2.1. Were participants aware of their assigned intervention during the trial?	"The examiners and the parents were blinded as to which group each child had been randomly assigned." In control group, a placebo, water-based, was used.	Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA / Y / PY / PN / N / NI

2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	In groups 3 and 4 some children dropout because did not follow instructions.	NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Nothing was mentioned.	NA / Y / PY / PN / N / NI
Risk-of-bias judgement	**For ROB2's algorithm, the result was HIGH.**	Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	**Comments**	**Response options**

3.1 Were data for this outcome available for all, or nearly all, participants randomized?	13% of the participants dropout.	Y / PY / PN / N / NI
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	Children in 2 groups dropout because did not follow instructions or declined to participate. It did not happen in the other 2 groups.	NA / Y / PY / PN / N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	The numbers of children who left because did not follow instructions or declined to participate is almost half of the dropouts.	NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	"For each child, the dmft index was recorded. This index is defined as 'd' which indicates a decayed tooth, 'm' a missing tooth due to decay and 'f' a filled tooth."	Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	"The examiners and the parents were blinded as to which group each child had been randomly assigned." "To ensure consistency, a pretest was done by both examiners…"	Y / PY / PN / N / NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	"The examiners and the parents were blinded as to which group each child had been randomly assigned."	NA / Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	The research protocol was approved by the Human Ethics Review Committee of the Faculty of Dentistry, Shiraz University of Medical Sciences, and the Iranian Registry of Clinical Trials (code: IRCT201207077402N2).	Y / PY / PN / N / NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		Y / PY / PN / N / NI
5.3 ... multiple eligible analyses of the data?		Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Study details

Reference	PARIS, S. et al. Seven-year-efficacy of proximal caries infiltration - Radomized clinical trial. J Dent, v. 93, p. 103277, 2020.

Study design

- ☐ Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- X Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: Resin infiltration Comparator: Mock infiltration

Specify which outcome is being assessed for risk of bias	Caries progression
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Figure 1

Is the review team's aim for this result…?

- ☐ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- X to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one

must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Domain 1a: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	"For each patient, one (15 patients) or two pairs (7 patients) of interproximal lesions with scores E2 or D1 were chosen by the investigator based on site of lesion occurrence. From each pair, 1 lesion was allocated to the "test" and 1 to the "control" group, respectively, by computer-generated randomly permuted blocks (generated by WH, sealed in envelopes)."	Y / PY / PN / N / NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y / PY / PN / N / NI

1.3 Did baseline differences between intervention groups at the start of the first period suggest a problem with the randomization process?	"At baseline, mean age (range) of participants was 25 (20-34) yrs, with 14/22 (64%) females and 8/22 (36%) males. Mean DMFT (SD) was 6.7 (3.1). At baseline, 32% of participants had a low, 36% a moderate, 23% an increased, and 9% a high caries risk. In mean (SD), the chance to avoid new caries (CAC = 1-caries risk) was 60 (22%). Papillary bleeding was observed adjacent to 38% of control and 35% of test lesions. No surface breakdown was observed."	Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain S: Risk of bias arising from period and carryover effects

Signalling questions	Comments	Response options
S.1 Was the number of participants allocated to each of the two sequences equal or nearly equal?	It is a split mouth study.	Y/PY/PN/N/NI
S.2 If N/PN/NI to S.1: Were period effects accounted for in the analysis?		NA/Y/PY/PN/N/NI

S.3 Was there sufficient time for any carryover effects to have disappeared before outcome assessment in the second period?	It is a split mouth study.	Y/PY/PN/N/NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from period and carryover effects?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during each period of the trial?	"To avoid behavioral changes of participants with regard to oral hygiene, we did not inform them about the treatment allocation of their teeth. To ensure blinding, we performed a placebo treatment on control teeth: Instead of HCl-gel and infiltrant, water was used." It is impossible to the operator being blind because of the characteristics of the testing procedure.	Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during each period of the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced between interventions?	Split mouth study. Mock treatment.	NA / Y / PY / PN / N / NI

2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	The test procedure was correctly explained.	NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	Split mouth study. The losses are balanced.	NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Risk of bias due to missing outcome data

Signalling questions	Comments	Response options

3.1 Were data for this outcome available for all, or nearly all, participants randomized?	27% dropped out.	Y / PY / PN / N / NI
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	"One patient with one lesion pair had dropped out of the analyses at the 18-month follow-up, because the control lesion had been restored by another dentist, while the respective test lesion showed progression with pair-wise comparison and DSR. Another lesion pair dropped out of analysis because both the control and the test lesion had been restored by another dentist as observed at the 36 months' evaluation, because the control lesion was symptomatic on cold stimuli (both lesions had shown no progression at 18-month follow-up). Additionally, five lesion pairs could only be evaluated after shorter observation times (one - 18 months, four - 36 months). From these 4/5 control and 0/5 test lesions had progressed at the last (18 or 36 months) follow-up. After 18 months one patient having one lesion pair that showed progression (both test and control) was referred to restorative treatment, which was included in the seven-year analysis as failure."	NA / Y / PY / PN / N
3.3 If N/PN to 3.2 Could missingness in the outcome depend on its true value?	Several teeth dropped out of the study because they were restored by other dentists.	NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns

Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	Several teeth dropped out of the study because they were restored by other dentists.	Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between interventions within each sequence?	"…two clinical investigators (SP and KB), who were blinded with respect to treatment allocation."	Y / PY / PN / N / NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	"…two clinical investigators (SP and KB), who were blinded with respect to treatment allocation."	NA / Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI

Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	**Comments**	**Response options**
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	"Due to the start in 2006 registration was not mandatory and also not seen as necessary retrospectively." The trial do not have a trial registration.	Y / PY / PN / N / NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		Y / PY / PN / N / NI

5.3 ... multiple eligible analyses of the data?		Y / PY / PN / N / NI
5.4 Is a result based on data from both periods sought, but unavailable on the basis of carryover having been identified?	Split mouth study. Same time.	Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		Low / High / Some concerns

Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Study details

Reference	MOBERG SKÖLD, U.M., et al. Approximal Caries Development in Adolescents with Low to Moderate Caries Risk after Different 3-Year School-Based Supervised Fluoride Mouth Rinsing Programmes. Caries Res, v.39, n. 6, p. 529-535, 2005.

Study design

X Individually-randomized parallel-group trial

☐ Cluster-randomized parallel-group trial

☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: Fluoride mouth rinse Comparator: Not rinse

Specify which outcome is being assessed for risk of bias	Caries progression
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Figure 2 / table 2

Is the review team's aim for this result…?

☐ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)

X to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options

1.1 Was the allocation sequence random?	"Adolescents of five different secondary schools in Mölndal were randomised into five different groups (every school included had five classes within the age group)."	Y / PY / PN / N / NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	The authors did not explain how the randomization was done.	Y / PY / PN / N / NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	"Adolescents of five different secondary schools in Mölndal were randomized into five different groups (every school included had five classes within the age group). Caries prevalence at baseline showed no statistically significant differences between the five groups."	Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	**Comments**	**Response options**
2.1. Were participants aware of their assigned intervention during the trial?	"The same dental nurse supervised all rinses in all the schools throughout the study."	Y / PY / PN / N / NI

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	"The subjects in groups 1–4 rinsed for 1 min in their classroom. The rinse used was 10 ml of a 0.2% neutral NaF solution (Meda AB, Stockholm, Sweden). The adolescents did not brush their teeth before rinsing and they were told not to eat or drink anything for 1 h afterwards. All participants attended dental clinics for regular check-ups once a year and they were given prophylactic treatment according to their actual caries risk. The dentists who treated them had no knowledge to which group they belonged."	NA / Y / PY / PN / N / NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	Mouth rinses is a simple procedure.	NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	Reasons for dropping out include: less rinses than stipulated, refused to rinse, change class, school or moved out from the area, missed or inafequate quality of bitewing radiographs.	NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Reasons for dropping out include: less rinses than stipulated, refused to rinse, change class, school or moved out from the area, missed or inafequate quality of bitewing radiographs. The authors provide the numbers, too.	NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns

Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	"One hundred and sixty-six subjects (21%) were excluded from the study for various reasons; thus the results are based on 622 adolescents."	Y / PY / PN / N / NI
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	The most common reason for drop out was "less rinses than stipulated".	NA / Y / PY / PN / N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Reasons for dropping out include: less rinses than stipulated, refused to rinse, change class, school or moved out from the area, missed or inafequate quality of bitewing radiographs.	NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	"Four bitewing radiographs were taken at baseline and after the 3-year-trial by the children's dentists after instruction by an oral radiologist. The bitewing radiographs were scored and analysed according to an index by Gröndahl et al. [1977]. Two of the authors (E.B. and U.M.S.) read the radiographs simultaneously, using a light desk and a magnifying viewer [Mattsson, 1953]. A consensus of each code was reached. The authors did not know to which group the adolescents belonged."	Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	"The authors did not know to which group the adolescents belonged."	Y / PY / PN / N / NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	"The authors did not know to which group the adolescents belonged."	NA / Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	The clinical trial register was not presented.	Y / PY / PN / N / NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		Y / PY / PN / N / NI
5.3 ... multiple eligible analyses of the data?		Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Study details

Reference	SKÖLD, U.M. Approximal caries increment in relation to baseline approximal caries prevalence among adolescents in Sweden with and without a school-based fluoride varnish programme. Community Dental Health, v. 33, n. 4, p. 281-285, 2016.

Study design

X Individually-randomized parallel-group trial

☐ Cluster-randomized parallel-group trial

☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: Fluoride varnish programme Comparator: No fluoride varnish

Specify which outcome is being assessed for risk of bias	Caries progression
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Figure 1

Is the review team's aim for this result…?

☐ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)

X to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one

must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	"In each area, the adolescents were randomly allocated within each school class into four different groups with respect to the F varnish application..."	<u>Y / PY</u> / PN / N / NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	How randomization was done are not explain.	<u>Y / PY</u> / PN / N / NI

1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	The randomization process was not explained.	Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	**Comments**	**Response options**
2.1. Were participants aware of their assigned intervention during the trial?	It is not said the participants were blind. "Three trained dental nurses and one dental hygienist performed all the treatments by working in teams of 2. They visited the schools with a simple mobile unit of a sun chair and a trolley containing a fi shing box with all the necessary material and used the room of the school nurse."	Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	Nothing is said about this.	NA / Y / PY / PN / N / NI

2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	The procedure is easy to do and well explained. "The adolescents came in groups of 4 to the treatment from the classroom, brushed their teeth with a toothbrush but without any toothpaste and then lay down in the chair. Cotton rolls were placed in the vestibulum of the upper and the lower jaw and the approximal surfaces were cleaned with a dental floss. Fluoride varnish was applied to the approximal surfaces with a 1.2-ml syringe (fitted with an Ultra Dent Microtip needle: Ultra Dent, South Jordan, Utah, USA) using both buccal and lingual approaches. All the approximal surfaces, from the distal surface of the canines to the mesial surface of the second molars, were treated and a total amount of 0.3 ml varnish was used. The patients were told not to eat any hard food products that day and not to brush their teeth until the next day."	NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	Nothing is said about this	NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Nothing is said about this	NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Response rate – 88%	Y / PY / PN / N / NI
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	"Ninety-six of the adolescents did not complete the study; the reasons were in most cases moving away from the area and secondly not attending all treatment sessions."	NA / Y / PY / PN / N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	"Not attending all treatment sessions" may indicate little concern with oral health and influence caries progression results.	NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	"Four bitewing radiographs each from baseline and at the end of the study were taken by the ordinary dentists at the different public dental clinics and these dentists were given prior appropriate education in the standardised method by two oral radiologists." "These check-ups took place at an interval of 12-18 months for more than 70% of the adolescents, as the caries risk assessed by the dentists at the public dental clinics was considered to be low or medium. The dentists did not know to which group the adolescents belonged."	Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	"The dentists did not know to which group the adolescents belonged." However, the authors did not say anything about blindness of the radiographs assessors.	Y / PY / PN / N / NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		NA / Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	"The dentists did not know to which group the adolescents belonged." However, the authors did not say anything about blindness of the radiographs assessors.	NA / Y / PY / PN / N / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns

Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	The clinical trial register was not informed.	Y / PY / PN / N / NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	The clinical trial register was not informed.	Y / PY / PN / N / NI
5.3 ... multiple eligible analyses of the data?	The clinical trial register was not informed.	Y / PY / PN / N / NI

Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Study details

Reference	MOHEBBI, S.Z. et al. A Cluster Randomized Trial of Effectiveness of Educational Intervention in Primary Health Care on Early Childhood Caries. Caries Res, v. 43, n. 2, p. 110 – 118, 2009.

Study design

- ☐ Individually-randomized parallel-group trial
- X Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: Pamphlet and reminder Comparator: Pamphlet only

Specify which outcome is being assessed for risk of bias	Caries increment
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Table 5

Is the review team's aim for this result…?

- ☐ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- X to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one

must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Domain 1a: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1a.1 Was the allocation sequence random?	"Using a list provided by the Ministry of Health and Medical Education, we randomly selected 18 of 102 public health centres in Tehran city."	Y / PY / PN / N / NI

1a.2 Was the allocation sequence concealed until clusters were enrolled and assigned to interventions?	"Health centres were randomly assigned to the three arms: two intervention (A and B) groups and one control (C) group. Consequently, 6 centres were devoted to each group. The randomization was assigned with a table of random numbers. The randomization and intervention processes were supervised by a dentist (A.A.) uninvolved in the clinical examinations and interviews."	Y / PY / PN / N / NI
1a.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	The interview used the structured questionnaire covering background factors including the child's gender and date of birth, the mother's age, family income and parents' level of education assessed separately for father and mother using a 7-point scale ranging from illiterate to doctoral degree. The parents' level of education was defined as the highest level of either parent's education. The question about family income per month was open-ended. The parents' level of education and family income as the most commonly applied indicators for the socio-economic status of a family were included.	Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 1b: Risk of bias arising from the timing of identification or recruitment of participants in a cluster-randomized trial

Signalling questions	Comments	Response options
1b.1 Were all the individual participants identified and recruited (if appropriate) before randomization of clusters?	"At baseline, all target age children visiting the centre on these days were selected, resulting in 10–15 children per centre."	Y/PY/PN/N/NI
1b.2 If N/PN/NI to 1b.1: Is it likely that selection of individual participants was affected by knowledge of the intervention assigned to the cluster?	"The subjects were entered into a database with a numerical code only."	NA/Y/PY/PN/N/NI
1b.3 Were there baseline imbalances that suggest differential identification or recruitment of individual participants between intervention groups?	"For the present intervention, a sample size of 240 participants (80/study arm, 6 health centres/arm; _ = 0.05, twosided, power = 80%, 25–30% attrition, prevalence of 5–10% for dentinal or enamel caries in 1-year-olds) was chosen to detect a 20% difference in caries prevalence between the intervention and control groups."	Y/PY/PN/N/NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the timing of identification and recruitment of participants?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	The mothers received or not a pamphlet and a call.	Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	"The subjective evaluation of the study was carried out as a short interview by means of the two following questions asked from the mother: (1) How satisfied were you with the pamphlet? and (2) How much did the pamphlet influence your oral health behaviour? The response was given on a 6-point scale from 'very much' to 'very little', respectively. The response included the alternative of 'no opinion'."	NA / Y / PY / PN / N / NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	The drop-outs (n = 65) were not different from those who attended the outcome examinations (n = 177) in terms of the baseline percentage of children with dt (3 vs. 2%) and de (8 vs. 9%), number of dt (! 0.1 vs. ! 0.1) and de (0.1 vs. 0.2), number of teeth (6.1 vs. 6.3), and background factors.	NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns

Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Risk of bias due to missing outcome data

Signalling questions	Comments	Response options
3.1a Were data for this outcome available for all clusters that recruited participants?		Y / PY / PN / N / NI
3.1b Were data for this outcome available for all, or nearly all, participants within clusters?	Response rate = 73%	Y / PY / PN / N / NI
3.2 If N/PN/NI to 3.1a or 3.1b: Is there evidence that the result was not biased by missing data?	The drop-outs (n = 65) were not different from those who attended the outcome examinations (n = 177) in terms of the baseline percentage of children with dt (3 vs. 2%) and de (8 vs. 9%), number of dt (0.1 vs. 0.1) and de (0.1 vs. 0.2), number of teeth (6.1 vs. 6.3), and background factors.	NA / Y / PY / PN / N
3.3 If N/PN to 3.2 Could missingness in the outcome depend on its true value?		NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI

Risk-of-bias judgement	**For ROB2's algorithm, the result was LOW.**	Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	"Dental examination was carried out with the help of a headlamp and a standard plane dental mirror with the mother and examiner sitting in a knee-to-knee position. Every tooth was recorded as present when visible in the mouth, otherwise as absent. After cleaning and drying with gauze and a sterile cotton sponge, the surfaces were visually examined. If in doubt, a WHO probe was gently used. The criteria for caries diagnoses met WHO recommendations."	Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	"…the examining dentist, one of the authors (S.Z.M.), remained blinded to the allocation of groups throughout the study."	Y / PY / PN / N / NI
4.3a If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware that a trial was taking place?	"…the examining dentist, one of the authors (S.Z.M.), remained blinded to the allocation of groups throughout the study."	NA / Y / PY / PN / N / NI

4.3b If Y/PY/NI to 4.3a: Were outcome assessors aware of the intervention received by study participants?	"…the examining dentist, one of the authors (S.Z.M.), remained blinded to the allocation of groups throughout the study."	NA / Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3b: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	**Comments**	**Response options**
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	The clinical trial register was not informed.	Y / PY / PN / N / NI

Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		Y / PY / PN / N / NI
5.3 ... multiple eligible analyses of the data?		Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Study details

Reference	MORGAN, M.V., et al. The Anticariogenic Effect of Sugar-Free Gum Containing CPP-ACP Nanocomplexes on Approximal Caries Determined Using Digital Bitewing Radiography. Caries Res, v. 42, n. 3, p. 171-184, 2008.

Study design

- ☐ Individually-randomized parallel-group trial
- X Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: CPP-ACP gum Comparator: Control gum

Specify which outcome is being assessed for risk of bias	Caries progression
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Tables 6 and 8

Is the review team's aim for this result…?

- ☐ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- X to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one

must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Domain 1a: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1a.1 Was the allocation sequence random?	all subjects (unit of randomization) who had fulfilled the entry criteria were stratified into two groups (caries-free/non-caries-free). Each school was randomized separately following the completion of the baseline clinical and	Y / PY / PN / N / NI

1a.2 Was the allocation sequence concealed until clusters were enrolled and assigned to interventions?	radiographic examinations at the school. The study sponsor was notified of the numbers in each group and they assigned the blocks of product codes to be used for the caries-free subjects and the non-caries free subjects (as the study sponsor was based in the USA, the blinded packaged product had been shipped to Australia by air freight in advance of randomization). Within each stratum the product codes were then randomly assigned to the subjects by the study statistician (G.G.A.).	Y / PY / PN / N / NI
1a.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Table 3	Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 1b: Risk of bias arising from the timing of identification or recruitment of participants in a cluster-randomized trial

Signalling questions	Comments	Response options

1b.1 Were all the individual participants identified and recruited (if appropriate) before randomization of clusters?	"The study sponsor was notified of the numbers in each group and they assigned the blocks of product codes to be used for the caries-free subjects and the noncaries- free subjects (as the study sponsor was based in the USA, the blinded packaged product had been shipped to Australia by air freight in advance of randomization)."	Y/PY/PN/N/NI
1b.2 If N/PN/NI to 1b.1: Is it likely that selection of individual participants was affected by knowledge of the intervention assigned to the cluster?		NA/Y/PY/PN/N/NI
1b.3 Were there baseline imbalances that suggest differential identification or recruitment of individual participants between intervention groups?		Y/PY/PN/N/NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the timing of identification and recruitment of participants?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	"The subjects, the clinical examiners and those involved in distributing the test products were not aware of which chewing gum the subject was assigned. The	Y / PY / PN / N / NI

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	investigators were provided with sealed code break envelopes, which could be used in a medical emergency. These were audited and returned unopened to the study sponsor at the completion of the study."	Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA / Y / PY / PN / N / NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	"The gum allocation was only divulged by the study sponsor upon completion of all data queries and the locking of the databases."	NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	"The most common reasons for subject non-completion were that the subject had transferred to a non-participating school, the subject's school withdrew from the study, the subject received fixed orthodontic appliances or the subject discontinued participation for personal reasons."	NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Risk of bias due to missing outcome data

Signalling questions	Comments	Response options
3.1a Were data for this outcome available for all clusters that recruited participants?	Response rate = 64%	Y / PY / PN / N / NI
3.1b Were data for this outcome available for all, or nearly all, participants within clusters?	Response rate = 64%	Y / PY / PN / N / NI
3.2 If N/PN/NI to 3.1a or 3.1b: Is there evidence that the result was not biased by missing data?	The children who violated the protocol were excluded.	NA / Y / PY / PN / N
3.3 If N/PN to 3.2 Could missingness in the outcome depend on its true value?	Figure 1 The missingness was equilibrate in both groups.	NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement	**For ROB2's algorithm, the result was LOW.**	Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	"Caries progression on approximal surfaces was estimated from the radiographs using the scoring system described by Pitts [1985]."	Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	The subjects, the clinical examiners and those involved in distributing the test products were not aware of which chewing gum the subject was assigned.	Y / PY / PN / N / NI
4.3a If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware that a trial was taking place?	The subjects, the clinical examiners and those involved in distributing the test products were not aware of which chewing gum the subject was assigned.	NA / Y / PY / PN / N / NI
4.3b If Y/PY/NI to 4.3a: Were outcome assessors aware of the intervention received by study participants?		NA / Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3b: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns

Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	**Comments**	**Response options**
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	the clinical trial register was not informed.	Y / PY / PN / N / NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		Y / PY / PN / N / NI
5.3 ... multiple eligible analyses of the data?		Y / PY / PN / N / NI

Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		Low / High / Some concerns

Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Study details

Reference	Peters, M.C. et al. Efficacy of Proximal Resin Infiltration on Caries Inhibition: Results from a 3-Year Randomized Controlled Clinical Trial. J Dent Res, v. 98, n. 13, p. 1497-1502, 2019.

Study design

- ☐ Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- X Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: resin infiltration Comparator: mock infiltration

Specify which outcome is being assessed for risk of bias	Caries progression
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Table 4

Is the review team's aim for this result…?

- ☐ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- X to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one

must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Domain 1a: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	"If multiple eligible lesions were present, a standardized process was used to avoid selection bias. To determine which lesions would be included the following order of priority was applied: (1) similar lesion depth (E2/D1), (2)	Y / PY / PN / N / NI

1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	similar tooth type (premolar/molar), (3) lesion location: preference for (a) same arch left/right, over (b) two arches left/right, over (c) same quadrant." "Computer-generated randomization (MCP [24]) assigned RI and C allocation (concealed until start of treatment). The lesion with the lowest tooth number (Universal Numbering System) was randomly allocated to RI or C, the other lesion allocated to the second strategy."	Y / PY / PN / N / NI
1.3 Did baseline differences between intervention groups at the start of the first period suggest a problem with the randomization process?	Split mouth study.	Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain S: Risk of bias arising from period and carryover effects

Signalling questions	Comments	Response options
S.1 Was the number of participants allocated to each of the two sequences equal or nearly equal?	Split-mouth study	Y/PY/PN/N/NI

S.2 If N/PN/NI to S.1: Were period effects accounted for in the analysis?		NA/Y/PY/PN/N/NI
S.3 Was there sufficient time for any carryover effects to have disappeared before outcome assessment in the second period?	Split-mouth study. Same time.	Y/PY/PN/N/NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from period and carryover effects?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during each period of the trial?	Both patients and evaluators were blinded to the allocation. The procedure needs an operator to be done.	Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during each period of the trial?		Y / PY / PN / N / NI

2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced between interventions?	Split mouth study.	NA / Y / PY / PN / N / NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	The sequence of the test procedure and the mock treatment are well explained.	NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	Split mouth study.	NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Risk of bias due to missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Radiographs of 32 (76%) participants were available for 2-year review.	Y / PY / PN / N / NI

3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA / Y / PY / PN / N
3.3 If N/PN to 3.2 Could missingness in the outcome depend on its true value?		NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options

4.1 Was the method of measuring the outcome inappropriate?	"At the 2-year recall, standardized digital bitewing radiographs were taken from both RI and C study teeth using the individually customized sensor holder. Study surfaces on coded radiographic images (viewed at 8" x 11" enlargement) were visually scored for lesion depth (categories E2/D1/D2-Rest) by two independent masked examiners (ARH, MCP)."	Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between interventions within each sequence?	"Discrepancies in assessment were resolved by consensus."	Y / PY / PN / N / NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	"Study surfaces on coded radiographic images (viewed at 8" x 11" enlargement) were visually scored for lesion depth (categories E2/D1/D2-Rest) by two independent masked examiners (ARH, MCP)."	NA / Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	(ClinicalTrials.gov NCT01584024)	Y / PY / PN / N / NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	The results are in accordance with the clinical trial register.	Y / PY / PN / N / NI
5.3 ... multiple eligible analyses of the data?	The results are in accordance with the clinical trial register.	Y / PY / PN / N / NI
5.4 Is a result based on data from both periods sought, but unavailable on the basis of carryover having been identified?	Split mouth study	Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns

Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Study details

Reference	SITTHISETTAPONG, T. et al. Effect of CPP-ACP Paste on Dental Caries in Primary Teeth: A Randomized Trial. J Dent Res, v. 91, n. 9, p. 847-852, 2012.

Study design

X Individually-randomized parallel-group trial

☐ Cluster-randomized parallel-group trial

☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: CPP-ACP toothpaste Comparator: Placebo toothpaste

Specify which outcome is being assessed for risk of bias	Caries incidence
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Table 2

Is the review team's aim for this result…?

☐ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)

X to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one

must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	"After baseline ICDAS, children were systematically allocated to two groups, and the allocation of treatment to each group was done randomly. The allocation of experimental or control group was determined by an assistant	Y / PY / PN / N / NI

1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	who was not involved in the clinical aspects of the study, to reduce potential biases." "To facilitate the logistics involving participation of children from 10 schools, within each province, sequential identification numbers were assigned to the alphabetical lists of participants' names (1-191 and 1-107, respectively). Randomly, those with odd ID numbers were assigned to the experimental treatment, and those with even ID numbers to the control treatment."	Y / PY / PN / N / NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	"At baseline, the two groups were comparable in terms of potential confounders with respect to age, gender, eating behaviors, toothbrushing behavior, and parents' socio-economic status, except that more children in the experimental group reported falling asleep with a bottle (p = 0.008)."	Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	**Comments**	**Response options**
2.1. Were participants aware of their assigned intervention during the trial?	"Those in the experimental group were assigned to receive 10% w/v CPP-ACP paste, Tooth Mousse® (GC Corporation, Tokyo, Japan) daily; those in the control	Y / PY / PN / N / NI

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	group received a placebo paste that had identical packaging, color, and taste, since it was prepared and provided by the same manufacturer." "All staff, teachers, and participating children were blinded to the group assignment and did not know which paste is more effective in caries prevention. The paste code was retained by the manufacturer and broken only after analysis of the study results."	Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA / Y / PY / PN / N / NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	"The paste was applied by trained teachers every school day, using each child's coded paste, following toothbrushing with fluoridated toothpaste after lunch."	NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	"Two major reasons for drop-out were children's transfer to higher level schools and families moving out of the area."	NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	"After 1 yr, 229 children remained in the study; the drop-out rates of the experimental and the control groups were 22.0% and 23.3% (p = 0.79)."	Y / PY / PN / N / NI
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	"…the drop-out rates of the experimental and the control groups were 22.0% and 23.3% (p = 0.79)." "Two major reasons for drop-out were children's transfer to higher level schools and families moving out of the area." " …more children in the experimental group reported falling asleep with a bottle (p = 0.008). However, this was not diagnosed as a risk factor for all caries outcome measures of this study."	NA / Y / PY / PN / N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	"Dental caries clinical examinations were conducted according to ICDAS II criteria that classify severity of dental lesions, ranging from the early clinically visible change in enamel to extensive cavitation, and presenting 6 stages of the caries process in ordinal code."	Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	"All children were examined at the nursery schools by one pediatric dentist who was blinded to the child's group assignment. The ICDAS training exercise was carried out 3 days before the examinations. Intra-examiner reliability, based on approximately 10% of the children and computed by the weighted kappa statistic at baseline, 6 mos, and 1 yr, was high: 0.80, 0.79, and 0.87, respectively."	Y / PY / PN / N / NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	"All staff, teachers, and participating children were blinded to the group assignment and did not know which paste is more effective in caries prevention. The paste code was retained by the manufacturer and broken only after analysis of the study results."	NA / Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns

Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	The trial register was not informed.	Y / PY / PN / N / NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	The trial register was not informed.	Y / PY / PN / N / NI
5.3 ... multiple eligible analyses of the data?	The trial register was not informed.	Y / PY / PN / N / NI

Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement	**For ROB2's algorithm, the result was HIGH.**	Low / High / Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Study details

Reference	TRUIN, G.J., VAN'T HOF, M.A. Caries Prevention by Profissional Fluoride Gel Application on Enamel and Dentinal Lesions in Low-Caries Children. Caries Res, v. 39, n. 3, p. 236-240, 2005.

Study design

X Individually-randomized parallel-group trial

☐ Cluster-randomized parallel-group trial

☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: Neutral fluoride gel Comparator: Placebo gel

Specify which outcome is being assessed for risk of bias	Caries increment
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Table 1 and 4

Is the review team's aim for this result…?

☐ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)

X to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one

must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	"By drawing a random unmarked envelope containing the allocation to one of the treatments, the participants were randomly assigned to either the placebo or fluoride application."	Y / PY / PN / N / NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y / PY / PN / N / NI

1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	"Table 1 shows that 42% of the initially selected 1,610 subjects refused to participate in the study. This was mainly due to the fact that parents preferred an 'active' fluoride gel instead of a placebo treatment."	Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	**Comments**	**Response options**
2.1. Were participants aware of their assigned intervention during the trial?	"In order to enhance study blindness, the placebo as well as the fluoride treatment were represented by two colour codes. Consequently, the study included four colour-coded study groups (red, yellow, green, blue) consisting of two placebo and two fluoride groups. All four gels were identical regarding packing, taste, colour, and consistency. The study was conducted double-blind. Only the pharmacist who prepared the four colourmasked gels and the chief analyst of the laboratory that regularly verified the presence of fluoride from samples applied in the clinics were acquainted with the content of each of the gels."	Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA / Y / PY / PN / N / NI

2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	"Intervention was undertaken according to a written protocol for regular semi-annual dental check-ups and treatment."	NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	"Table 1 shows that 42% of the initially selected 1,610 subjects refused to participate in the study. This was mainly due to the fact that parents preferred an 'active' fluoride gel instead of a placebo treatment."	NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	"No relevant differences were found between the treatment groups for both the background variables and prognostic factors."	NA / Y / PY / PN / N / NI
Risk-of-bias judgement	**For ROB2's algorithm, the result was SOME CONCERNS.**	Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options

3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Response rate = 87,45%	Y / PY / PN / N / NI
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	"The fact that the 'intention-to treat' analysis and the 'per protocol' analysis showed similar results indicates that the study was not sensitive to non-adherence."	NA / Y / PY / PN / N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement	**For ROB2's algorithm, the result was LOW.**	Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	Clinical examinations were carried out in accordance with a written protocol for visual inspection of the dentition and bitewing radiography of the posterior approximal tooth surfaces. Intensive calibration sessions preceding the examinations were conducted by the well trained principal investigator	Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	"The intra-observer agreement of the principal examiner in the permanent (n = 5,757 surfaces) and primary (n = 4,924 surfaces) dentition was 0.96 (SE = 0.01) and 0.94 (SE = 0.01), respectively. The inter-observer agreement between the principal examiner and the other examiners in the permanent (n = 6,834 surfaces) and primary (n = 5,392 surfaces) dentition was 0.95 (SE = 0.01) and 0.90 (SE = 0.01), respectively."	Y / PY / PN / N / NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	"The study was conducted double-blind. Only the pharmacist who prepared the four colourmasked gels and the chief analyst of the laboratory that regularly verified the presence of fluoride from samples applied in the clinics were acquainted with the content of each of the gels."	NA / Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns

Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	**Comments**	**Response options**
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	The trial register was not informed.	Y / PY / PN / N / NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	The trial register was not informed.	Y / PY / PN / N / NI
5.3 ... multiple eligible analyses of the data?	The trial register was not informed.	Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns

Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Study details

Reference	BERGSTRÖM, E.K. et al. Approximal caries increment in adolescents in a low caries prevalence area in Sweden after a 3.5-year school-based fluoride varnish programme with Bifluorid 12 and Duraphat. Community Dent Oral Epidemiol, v. 42, n. 5, p. 404 – 411, 2014.

Study design

X Individually-randomized parallel-group trial

☐ Cluster-randomized parallel-group trial

☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: Bifluorid 12 varnish Comparator: Duraphat varnish

Specify which outcome is being assessed for risk of bias	Caries increment
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Figure 3 and table 3

Is the review team's aim for this result…?

☐ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)

X to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one

must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	"This was a randomized controlled trial, RCT, which meant that all adolescents in seven secondary schools were randomly selected on an individual basis within each school class in every single school into four	Y / PY / PN / N / NI Fiquei entre PY e NI

1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	different groups.' Ele reforça que foi randomizado, mas não detalha, por isso acho que seria melhor colocar "NI" Mas também essa informação aqui pode ajudar a deduzir que foi aleatório: "Those who chose to participate in the study could therefore belong to one of the four groups" "…the randomization into the four groups was done before the parents and children had accepted to participate in the study."	Y / PY / PN / N / NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	"During the 3.5-year study, the dental nurses/hygienists had to report any eventually adverse side-effects caused by the F varnish programme."	Y / PY / PN / N / NI
Risk-of-bias judgement	**For ROB2's algorithm, the result was SOME CONCERNS.**	Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	**Comments**	**Response options**
2.1. Were participants aware of their assigned intervention during the trial?	The authors did not inform this.	Y / PY / PN / N / NI

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	"Furthermore, the awareness that adolescents in the control group were excluded from the F varnish treatment at school might affect the preventive measures performed at home even more for these individuals." Entendo que formalmente eles não tinham consciência, mas os autores discutem essa questão.	Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA / Y / PY / PN / N / NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	The procedure is simple and well explained. "The F varnish programme was performed by 20 well-educated dental nurses or dental hygienists with long experience of F varnish applications at school, all from the three Public Dental Clinics in the municipality."	NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	Figure 1	NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Figure 1	NA / Y / PY / PN / N / NI
Risk-of-bias judgement	**For ROB2's algorithm, the result was SOME CONCERNS.**	Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Response rate = 70,5%	Y / PY / PN / N / NI
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	The drop outs were balanced.	NA / Y / PY / PN / N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement	**For ROB2's algorithm, the result was LOW.**	Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / 9Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	"Four bitewing radiographs were taken at baseline and after 3.5 years on all the participants at the Public Dental Clinics at the regular dental check ups."	Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		Y / PY / PN / N / NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	"All radiographs were analysed blindly at one and the same occasion at the end of the study side by side and for each surface by two of the authors (CG and E-KB) who had to come to a joint conclusion."	NA / Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement	**For ROB2's algorithm, the result was SOME CONCERNS.**	Low / High / Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	The trial register was not informed.	Y / PY / PN / N / NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	The trial register was not informed.	Y / PY / PN / N / NI
5.3 ... multiple eligible analyses of the data?	The trial register was not informed.	Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

APÊNDICE 5 – Manuscrito Publicado

O manuscrito publicado, intitulado *“Calcium and vitamin D supplementation and/or periodontal therapy in the treatment of periodontitis among Brazilian pregnant women: protocol of a feasibility randomised controlled trial (the IMPROVE trial)”,* é parte do projeto de pesquisa inicial para esta tese de doutorado, que era o desenvolvimento de um estudo clínico randomizado realizado em parceria com o Instituto de Nutrição Josué de Castro, da Universidade Federal do Rio de Janeiro (UFRJ). O tema estudado foi a suplementação de cálcio e vitamina D associados à terapia periodontal para a melhoria do perfil metabólico de gestantes. O objetivo era associar estratégias de intervenção para a melhoria da nutrição e da saúde bucal a fim de diminuir desigualdades de saúde em áreas desfavorecidas, como comunidades carentes.

A hipótese de pesquisa era de que a terapia periodontal associada ao consumo de leite fortificado com cálcio e vitamina D seria capaz de otimizar o tratamento periodontal, melhorando o perfil metabólico e inflamatório das gestantes com periodontite e, desta forma, reduzindo as intercorrências maternas e fetais.

Inicialmente, desenvolveu-se um estudo de viabilidade que aconteceu no município de Duque de Caxias, em unidades de saúde pertencentes ao SUS, com o objetivo de verificar a viabilidade de se recrutar gestantes para o estudo, investigar a interação entre aderência e resposta ao tratamento, avaliar a aceitabilidade das participantes ao leite fortificado e ao desenho do estudo e identificar as principais barreiras e facilitadores para a implementação da intervenção, entre outros.

O projeto incluiu pesquisadores do Instituto de Nutrição da UFRJ, do Reino Unido e da Dinamarca.

O estudo teve apoio do CNPQ e financiamento da Fundação Dinamarquesa de Pesquisas de Lácteos através da *Arla Foods Ingredients*. A ideia inicial é que esta empresa fornecesse os sachês com o leite em pó enriquecido para o estudo, que seriam importados da Dinamarca. Vários problemas burocráticos enfrentados na liberação junto ao ministério da agricultura impediram a importação do leite, uma vez que o produto, perecível, não conseguiria chegar ao Brasil dentro do prazo de validade após o atraso causado pelos empecilhos no trâmite alfandegário. Somado a isso, outras questões relativas ao financiamento envolveram a desvalorização da libra esterlina, moeda utilizada para o financiamento, em razão do processo de saída

da Reino Unido da União Europeia, diminuindo o valor disponibilizado para o projeto. Para solucionar o problema foi preciso pesquisar no mercado nacional um leite em pó enriquecido com cálcio e vitamina D que pudesse substituir o produto europeu, o que foi bem-sucedido.

A população do estudo foi composta por mulheres adultas (18 a 39 anos) grávidas, consideradas de baixo risco, atendidas no SUS. A seleção das participantes foi feita através de questionários contendo informações tais como condição socioeconômica, hábitos etílico e de fumar, atitudes alimentares, condição geral de saúde física, mental e bucal, entre outros.

Participei da parte operacional do projeto propriamente dita, com a responsabilidade pela calibração dos profissionais responsáveis pelo exame odontológico das voluntárias, atuação na seleção das participantes do estudo, capacitação dos profissionais envolvidos com o tratamento periodontal e acompanhamento da evolução dos grupos para o qual as mulheres foram randomizadas, além de reuniões com a gestão da unidade e profissionais envolvidos no atendimento das participantes, bem como com os demais pesquisadores participantes do projeto.

O atraso no desenvolvimento do projeto (pelos motivos relatados acima), impediu que, por questões de prazo para a conclusão do doutorado, fosse possível dar continuidade à participação nas demais fases do projeto.

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Pilot and Feasibility Studies

STUDY PROTOCOL Open Access

Calcium and vitamin D supplementation and/or periodontal therapy in the treatment of periodontitis among Brazilian pregnant women: protocol of a feasibility randomised controlled trial (the IMPROVE trial)

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Abstract

Background: Periodontitis is a common oral inflammation, which is a risk factor for adverse pregnancy outcomes. Intakes of vitamin D and calcium are inversely associated with occurrence and progression of periodontitis. This study aims to assess the feasibility of a multi-component intervention, including provision of milk powder supplemented with calcium and vitamin D and periodontal therapy (PT), for improving maternal periodontal health and metabolic and inflammatory profiles of low-income Brazilian pregnant women with periodontitis.

Methods: The IMPROVE trial is a feasibility randomised controlled trial (RCT) with a 2 × 2 factorial design with a parallel process evaluation. Pregnant women with periodontitis, aged 18–40 years and with < 20 gestational weeks ($n = 120$) were recruited and randomly allocated into four groups: (1) fortified sachet (vitamin D and calcium) and powdered milk plus PT during pregnancy, (2) placebo sachet and powdered milk plus PT during pregnancy, (3) fortified sachet (vitamin D and calcium) and powdered milk plus PT after delivery and (4) placebo sachet and powdered milk plus PT after delivery. Dentists and participants are blinded to fortification. Acceptability of study design, recruitment strategy, random allocation, data collection procedures, recruitment rate, adherence and attrition rate will be evaluated. Data on serum levels of vitamin D, calcium and inflammatory biomarkers; clinical periodontal measurements; anthropometric measurements; and socio-demographic questionnaires are collected at baseline, third trimester and 6–8 weeks postpartum. Qualitative data are collected using focus group, for analysis of favourable factors and barriers related to study adherence.

(Continued on next page)

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Discussion: Oral health and mineral/vitamin supplementation are much overlooked in the public prenatal assistance in Brazil and of scarcity of clinical trials addressing these issues in low and middle-income countries,. To fill this gap the present study was designed to assess the feasibility of a RCT on acceptability of a multi-component intervention combining conventional periodontal treatment and consumption of milk fortified with calcium-vitamin D for improving periodontal conditions and maternal metabolic and inflammation status, among Brazilian low-income pregnant women with periodontitis. Thus, we hope that this relatively low-cost and safe multicomponent intervention can help reduce inflammation, improve maternal periodontal health and metabolic profile and consequently prevent negative gestational outcomes.

Trial registration: NCT, NCT03148483. Registered on May 11, 2017.

Keywords: Calcium, Feasibility randomised controlled trial, Milk, Pregnant women, Periodontal therapy, Vitamin D

Strengths and limitations of this study

- To the best of our knowledge, this is the first feasibility trial to explore the acceptability of a multi-component intervention combining milk powder supplemented with calcium and vitamin D and periodontal therapy in Brazilian pregnant women.
- This study will contribute to the limited literature on the impact of milk intake, supplementation of calcium and vitamin D and periodontal therapy for improving maternal metabolic and inflammation status and periodontal health.
- The evaluation process includes qualitative data to support the assessment of barriers and facilitators related to the study feasibility.
- Follow-up for this study is limited to 6–8 weeks after birth due to study budget and timeframe. Ideally, longer-term follow-up would be preferable to allow for the initial effect of the intervention to be assessed in both mothers and infants.

Background

Periodontitis is an inflammatory disease defined as a bacterial gum infection causing a breakdown of soft tissue and loss of tooth-supporting bone [1]. If untreated, periodontitis can cause tooth loss potentially resulting in low self-esteem, impaired speech and chewing and reduced ability to eat healthy and nutritious food [2]. Periodontitis is one of the most common oral conditions and is prevalent in both developed and developing countries reaching approximately 20–50% of the global population [3]. Pregnant women, due to hormonal changes, are prone to develop periodontitis or existing periodontitis may worsen with the progression of pregnancy [4]. In Brazil, the prevalence of moderate periodontitis among pregnant women has been estimated to be between 11% and 47% [5–8].

The inflammatory burden induced from periodontitis may have repercussions beyond the oral cavity, leading to low-grade systemic inflammatory status and metabolic disturbances, which can affect the course of gestation [9]. Increased levels of pro-inflammatory mediators such as interleukin-6 (IL-6), C-reactive protein (CRP) and matrix metalloproteinase 9 (MMP-9) have been observed among people with periodontitis [10–12].

Systematic reviews have shown that women with periodontitis are at higher risk of delivering preterm (< 37 weeks gestation) and low-birth-weight (< 2.5 kg) babies, [13–15] both of which are among the leading causes of neonatal deaths [16]. The biological mechanism underlying the link between periodontitis and adverse pregnancy outcomes is not fully known [17]. Periodontitis may cause bacterial translocation through blood circulation or production of inflammatory mediators associated with premature rupture of membranes and onset of delivery [18]. Additionally, it may initiate and propagate a framework for insulin resistance and ultimately the manifestation of gestational diabetes [9]. The vertical transmission of oral pathogenesis is also a concern, as children of mothers with periodontitis are at higher risk of acquiring periodontal pathogens [19].

Randomised controlled trials (RCT) investigating whether non-surgical periodontal therapy (PT) during pregnancy has the potential of reducing miscarriage, preterm birth and low-birth-weight incidence have shown conflicting results [20–23]. However, the majority of the RCTs have found no significant effect [20, 22, 23], probably due to the PT not being intense or early enough to prevent disease progression, suggesting that ongoing periodontal maintenance treatment throughout gestation might be needed [24].

The active form of vitamin D has an important action in relation to regulating calcium and skeletal homeostasis and also acts as an anti-inflammatory and anti-microbial agent that may be beneficial to periodontal health by antibiotic effects on periodontopathogens and inhibition of inflammatory mediators that contribute to the periodontal destruction [25]. Besides vitamin D, calcium

has also been associated with lower occurrence of periodontitis, probably by prevention of alveolar bone loss and better natural dentition, i.e. the higher calcium consumption is associated with lower loss of tooth [26].

Calcium and vitamin D co-supplementation have been hypothesised to act in synergy rather than independently [27], since 1,25-dihydroxyvitamin D acts on the small intestine and kidneys to increase absorption of calcium [25]. Previous studies in an adult Danish population have shown that intakes of calcium within recommendations (1000 and 1200 mg/day for men aged 51–70 and > 70 years, respectively, and 1200 mg/d for women aged ≥ 51 years) are associated with lower risk of periodontitis and tooth loss only among those with higher intake of vitamin D (> 6.8 μg/d) [28, 29]. These studies suggest that calcium obtained from dairy sources was associated with benefits for periodontal health. In addition, a non-randomised clinical trial performed among Indian adults found that the group taking vitamin D (250 IU/day) and calcium (500 mg/day) supplementation for 3 months developed better periodontal health (higher bone density and lower gingival bleeding index) than the group that did not take supplementation [30]. However, larger studies are needed to evaluate the effectiveness of this strategy in pregnant women.

In Brazil, the prevalence of vitamin D insufficiency (defined as 25(OH) D levels < 20 ng/mL.) in pregnant women ranges from 16.1 to 43% [31, 32]. Moreover, mean calcium consumption among adult Brazilian women is only 476 mg/d [33], which is below the dietary recommendations of 1000 mg/d [34].

Considering the high prevalence of periodontitis and vitamin D insufficiency and low calcium consumption among Brazilian pregnant women, the purpose of this study is to assess the feasibility and acceptability of a multi-component intervention, including provision of milk powder supplemented with calcium and vitamin D and periodontal therapy (PT), for improving maternal periodontal health and metabolic and inflammatory profiles.

Objectives

The primary and secondary objectives are described in Table 1.

Methods/design

Study design and setting

The IMPROVE trial is a 2 × 2 factorial feasibility RCT with a parallel process evaluation, i.e. the groups are not cross-over [35], conducted among pregnant women with an existing diagnosis of periodontitis. During recruitment, participants are allocated to one of four intervention arms using a permutated block randomisation matrix (Fig. 1). The arms are as follows:

Table 1 Objectives of the IMPROVE feasibility trial

Primary	Secondary
1. Feasibility of recruitment strategy for local health service and participants	1. Estimates of effect size and variability to enable accurate sample size and power calculations for a definitive RCT
2. Time necessary to recruit participants	2. Identification of any differences across age groups and other socio-demographic factors with regards to attrition rate
3. Acceptability of the study design and random allocation	3. Identification of key barriers and enablers to adoption, and large-scale implementation, of the IMPROVE trial are
4. What the most appropriate inclusion/exclusion criteria are	4. Definition of required for economic analysis and if they can be collected reliably
5. Estimates of compliance, satisfaction, follow- up and attrition rates	5. The capacity of the research team to embed this study into routine practice in the Public Health Centres
	6. To determine the initial effects of the intervention, time and intervention-time interaction on inflammatory biomarkers concentrations and periodontitis status

1) Semi-skimmed powdered milk fortified with additional sachet of 500 mg calcium and 500 IU vitamin D and early PT (PT during pregnancy)
2) Semi-skimmed powdered milk fortified with additional sachet of 500 mg calcium and 500 IU vitamin D and late onset PT (PT after delivery)
3) Semi-skimmed powdered milk with placebo sachet and early PT
4) Semi-skimmed powdered milk with placebo sachet and late onset PT

The 2 × 2 design allows gathering evidence to feed into an adequately powered RCT to test two different hypotheses, so the four arms will enable estimation of the approximated effect that the specific combinations of the intervention components add to improving concentrations of maternal blood metabolic/inflammation markers and periodontal status.

Baseline data was collected up to second trimester (T0), with follow-up at third trimester (T1) and 6–8 weeks postpartum (T2).

Questionnaire data

At the three points (T0–T2), the pregnant women with periodontitis diagnosis answer questionnaires about sleep [36], physical activity level [37], frequency of food consumption [38], smoking habits, alcohol consumption, maternal conditions (general questionnaire), pregnancy complications, sunlight exposure, mental health [39], health general [40] and social support [41]. At the baseline, women also provided socioeconomic information. A specific questionnaire on Oral Health Impact Profile

	STUDY PERIOD			
	Enrolment	**Prior-allocation**	***Post-allocation***	**Close-out**
TIMEPOINT	***-t1***	***T0 Baseline***	***T1 Beginning of the 3rd Trimester until delivery***	***T2 6–8 weeks postpartum***
ENROLMENT:				
Eligibility screen	X			
Informed consent	X			
Periodontitis diagnosis		X		
Allocation			X	
INTERVENTIONS:				
Supplementation[†] +PT during pregancy[‡]			←	
Placebo[†] +PT during pregancy[‡]			←	
Supplementation[†] + postpartum PT[‡]			←	→
Placebo[†] + postpartum PT[‡]			←	→
ASSESSMENTS:				
Socioeconomic assessment		X		
Anthropometry		X	X	X
Blood pressure		X	X	X
Blood/Urine collection*		X	X	X
Questionnaires responses**		X	X	X
Periodontitis evaluation		X		X
Focus group**	X			
Baby blood collection (filter paper)*****			←	→

PT = Periodontal Treatment; [†]Powdered milk and vitamin/ calcium or placebo sachets are delivered monthly. [‡]The number of visits from dentist for periodontal treatment during pregnancy depends of severity of periodontitis. After discharge of dental treatment pregnant women will receive maintenance dental evaluation every two months. *Maternal blood levels of biomarkers of inflammation (C reactive protein, interleukin-6 and Matrix metallopeptidase 9); blood levels of 25-hydroxy vitamin D, glucose, insulin, calcium, parathyroid hormone, lipids (HDL, LDL and triglycerides) and urinary calcium and creatinine levels. **Oral health impact profile, smoking habits, alcohol consumption, maternal conditions, sleeping habits, pregnancy complications, solar exposure, mental health (depression), physical activity level, frequency of food consumption, general health and social support. ***Focus groups were also performed before recruitment among pregnant women who are cared for at the health centre in Duque de Caxias. ****Collected until 7 days postpartum (Baby vitamin D and calcium levels)

Fig. 1 SPIRIT flow diagram of the IMPROVE feasibility trial

(OHIP) [42] was administered at baseline (T0) and 6–8 weeks postpartum (T2) (Fig. 1).

Biomarkers and measures

Anthropometric (height and weight) and blood pressure are measured in T0–T2. Maternal blood samples were collected in the morning after 12-h overnight fast in the T0, T1 and after delivery (T2) for analysis of biochemical markers. Also 24-h urine is collected at three-time points (T0–T2) for analysis of urinary calcium and creatinine. Prior to the urine collection, all participants are carefully instructed regarding the specific procedures. The blood and urine samples are stored in a freezer with a temperature of − 80 °C until analysis in the Institute of Nutrition Josué de Castro at the Federal University of Rio de Janeiro.

Recruitment period and setting

The participant recruitment period started in April 2017 and ended in May 2018 with follow-up scheduled until February 2019. The study is conducted in the Municipal Health Centre of Duque de Caxias, Rio de Janeiro/Brazil. This public health centre offers prenatal care for low-risk pregnant women, child health programmes, as well as a clinical laboratory. The population assisted by this centre is of low income and most of them live in the surrounding slums.

Duque de Caxias is a city in the metropolitan region located geographically in the Rio de Janeiro state with approximately 900,000 inhabitants [43]. Duque de Caxias presents a neonatal mortality rate of 12.1 per 1000 live births, 0.7% of maternal deaths investigated and 20.4% of families covered by the family health strategy [44]. These programmes are targeted at families that live under adverse conditions and whose nutritional status is impacted by multiple constraints such as living with some degree of food insecurity (limited access to adequate quantity and quality of food) [45].

The latitude of Duque de Caxias is 22° 47′ S. This area of Brazil is usually sunny all year round. The climate is tropical and summers are hot and humid, while the winters are mild and with more restricted rainfall. The pollution index in this city is high according to the recommendations of the World Health Organization (mean annual concentrations of inhalable particles of diameter less than 10 μm < 20 μg/m^3 [46], with a mean estimate of 45.9 (SD 21.6) μg/m^3 between the years 2000–2008 [47].

Participants and eligibility criteria

The study population includes low-risk adult pregnant women, with periodontitis, attending the prenatal care in the Municipal Health Centre of Duque de Caxias, Rio de Janeiro/Brazil. Inclusion and exclusion criteria are described in Table 2.

Recruitment

In the first prenatal visit a member of the research team introduced pregnant women to the study and invited those initially interested in taking part to answer a preliminary checklist for eligibility, except for the diagnostic of periodontitis. After this, women were screened for syphilis and HIV, as part of the routine pre-natal care. Those who were preliminarily eligible and tested negative for syphilis and HIV were then invited to book a dental examination. Those who screened positive for periodontitis were provided with an informed consent form and included in the study (Fig. 2).

Randomisation, allocation concealment and blinding

To avoid information bias, regarding influence of interviewer by knowledge of group allocation of participants, randomisation took place after baseline assessment. An online randomisation system with a random mixture of permuted block sizes, stratifying participants by current smoking habit (yes vs. no) was provided and concealed by *Sealed Envelope Ltdtm*.

Due to the nature of the intervention (early vs. late PT), complete blinding of the intervention was not possible. However, dentists and participants were blinded to group allocation regarding milk fortification. Outcome assessment is blinded, and the dentist performing the final periodontal examination is not aware of group allocation regarding both placebo or fortified sachet and PT before or after delivery.

Interventions

Participants were advised to take two servings of a powdered vitamin D and calcium plus semi-skimmed milk daily during breakfast and afternoon snack or supper to avoid concomitant intake of the prenatal iron supplements routinely prescribed for consumption with hot main meals (e.g. lunch or dinner). Twenty grams (20 g) of powdered semi-skimmed milk (of a commercial brand available in Brazil) is mixed with a sachet (2 g), containing calcium (CAPOLAC 500 mg) [48] and vitamin D_3 (500 IU), to be reconstituted in 200 mL of potable water for each serving or other preparations (i.e. to consume with kneaded fruits, fruit smoothies, yogurt, porridge, etc.). Sachets with vitamin D/calcium and milk powder were provided monthly to participants in the fortified group during routine prenatal visits.

In the first dental session, a full periodontal examination was repeated to allow comparison with the first examination done during recruitment (screening) and check the agreement between the two dentists. After that, conventional non-surgical PT, consisting of

Table 2 Inclusion and exclusion criteria for the IMPROVE feasibility trial

Inclusion criteria	Exclusion criteria
1. Aged ≥ 18 years at the time of recruitment	1. Positive diagnosis of HIV/AIDS, syphilis, psychosis, diabetes before pregnancy, thyroid disease, or any disorder causing vitamin D hypersensitivity (e.g. sarcoidosis and other lymphomatous disorders)
2. > 20 weeks gestation at first prenatal visit	2. Lactose intolerance, milk allergy, history of renal stones or family history of renal stone and hyperparathyroidism
3. Positive diagnosis of periodontitis (≥ 1 tooth with at least one site with ≥ 4 mm of clinical attachment loss (CAL) and presence of bleeding on probing)	3. Extensive dental cavity (crowns of several teeth destroyed by caries) and loss of tooth structure or use of fixed dental braces
4. Cognitively and physically able to complete an interview and oral examination and willing to participate, including provision of blood samples.	4. Use of antibiotics or any immune-suppressants or medication known to affect vitamin D/calcium metabolism
	5. Consumption of ≥ 4 servings/day of dairy products or taking vitamin D supplements > 400 IU/day

prophylactic dental polishing to remove the sticky bacterial film that forms on the teeth overtime, scaling and root planning, as necessary, was undertaken throughout pregnancy, up to delivery (Fig. 1). The periodontal treatment is carried out at the Municipal Health Centre of Duque de Caxias. The treatment is performed by a qualified and trained dentist who was not involved in the screening procedure and was blind regarding group allocation.

PT started right after the randomisation to ensure early therapy initiation for the relevant treatment arms. The number of treatment sessions depended on the severity of the disease. However, participants were allowed up to five treatment sessions. In each session, participants also received personalised oral hygiene instructions. Standard fluoride toothpaste, without any additional component that could interfere in results, a toothbrush and dental floss were provided to all participants. Monitoring sessions (reassessment of dental conditions) were taken at 2-month interval. If necessary, PT and oral hygiene instructions were repeated.

All participants were advised not to alter their routine physical activity throughout the study and not to consume any supplements other than the ones provided by the clinics. Throughout pregnancy, participants were allowed to consume 400 μg/d folic acid and 60 mg/d

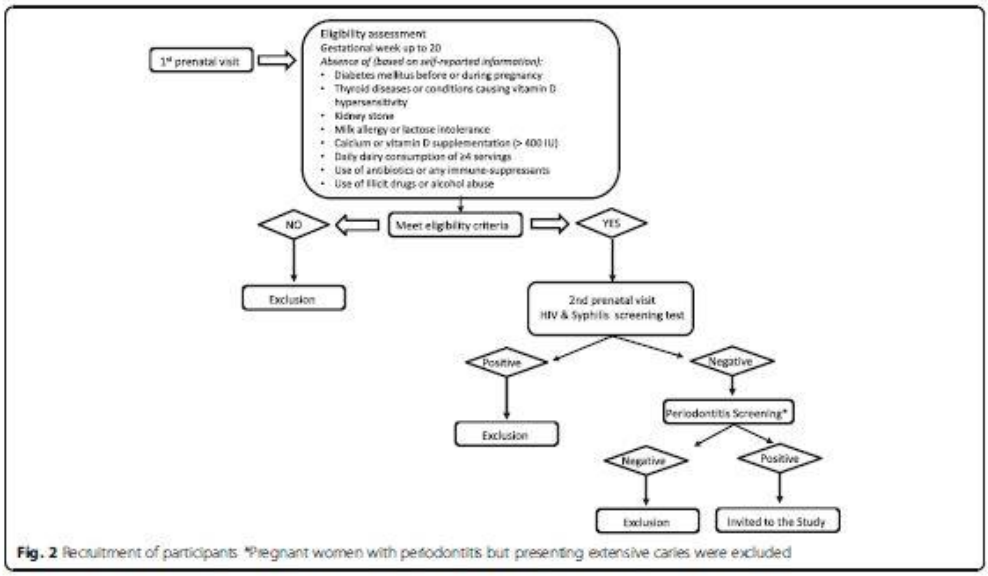

Fig. 2 Recruitment of participants. *Pregnant women with periodontitis but presenting extensive caries were excluded

ferrous sulphate, as provided during standard prenatal care in Brazil.

Control group

The control group are the women assigned to the semi-skimmed powdered milk with non-fortified sachet (placebo) with similar colour, flavour, smell and texture as well as before and after dilution than fortified sachet, during pregnancy and late onset PT (after delivery). Late-onset PT starts after postpartum assessment, as part of the routine dental care in the prenatal clinic. This strategy is considered a more acceptable approach in comparison to offering no PT intervention, since the possibility of being assigned to an 'untreated' group could limit recruitment and is more ethical.

All participants were informed about the benefits of dairy food intake during pregnancy and given a brochure to take home with general information about healthy diet and oral health hygiene instructions once they entered the study.

Dental examination

After initial screening, participants underwent a full periodontal examination at baseline (T0) and postpartum (T2). Periodontal examination was performed in full mouth at six sites per tooth (known as mesiobuccal, mid-buccal, distobuccal, mesiolingual, mid-lingual and distolingual), using North Carolina periodontal probes, dental mirror and gauze, but without X-rays. The model chosen is justified because no partial record model presents reliability to replace full mouth examination [49]. The T0 and T2 evaluations take place in the recruitment room, using a simple chair and a forehead flashlight. Maintenance examinations are performed to assess the periodontal status of those who had finished the treatment during pregnancy, and these examinations are done every 2 months. Data collection included gingival bleeding on probing, probing depth, cementoenamel junction-gingival margin distance (CAL) and dental mobility. A tailored form was developed to register the data. Oral examination and treatment procedures were performed by calibrated and trained dentists. The dentists always calibrated their probing force using a scale right before the clinical examination. The recommended probing force was approximately 20 g of pressure [50].

Process evaluation of qualitative data

Focus group discussions were held prior to trial recruitment to discuss issues regarding recruitment strategy, study design and data collection. In addition, group discussions were held throughout the study (second and third trimester) to assess potential barriers and facilitators to the intervention and data collection.

The process evaluation included qualitative data from focus group and interviews [51, 52].

To perform a content analysis [53], the specific process evaluation frame was developed including two major categories: (1) dietetics abilities to understand the way the women organise daily use of milk sachet with their habitual food and (2) health care and identification of their existing social support network in health care. The evaluation frame was used to generate content associated with two major categories. Six themes were derived from two categories: (1) how to make and consume the food; sharing of the food with other family members; and (2) intolerances social support network and challenges in social life, access to health unit and identification of events related to pain and discomfort. All researchers were trained to fill into a frame of content previously structured with data related to pregnant women's speeches associated to the six themes described above. Initially, one pilot focus group was performed with five women of similar socioeconomic conditions to those attending the health clinic where the present study is taking place. After some adjustments in the content of questions, the data was coded into themes and classified into three levels to identify favourable factors and health events: favourable, not favourable and neutral.

Second focus group regarding the culinary knowledge, health care practices including oral health and network social support at Duque de Caxias territory was performed prior to recruitment with 13 pregnant women attending the health centre. Thus, in the present study, we evaluated some of the barriers and enablers to participation, recruitment and intervention delivery, as well as the difficulties to go to the health unit.

Group discussions were held during the study after recruitment to assess potential barriers and facilitators to the intervention delivery and data collection. These group discussions provided qualitative data about potential acceptability. Additionally, monthly individual meetings were organised in the health centre with participants throughout the study to complement and update the qualitative data collection. Sentences and phases were registered and added into the frame, and frequency of occurrences, the patterns and the sequence of data are analysed. These data were then used to assist follow-up management and improve compliance with the intervention (e.g. suggestions on how to overcome reported barriers regarding milk consumption or monotonous diet). At the end of each participant's involvement in the study, they were asked to complete an anonymous evaluation questionnaire to gain insights about women's participation experience, acceptability and compliance to the study protocol.

Adherence

Adherence were routinely assessed counting the unused sachets monthly, i.e. number of returned sachet by pregnant women in their monthly visit. SMS reminders to consume the sachets and milk were sent (once a week) to participants to help prevent attrition. A surplus of plain milk powder was provided to all women with young children to ensure dose fidelity. Acceptance of the intervention was evaluated via a questionnaire comprising questions about quality of taste (both milk powder with fortified and placebo sachet), possible difference in taste between those provided by the study and the commercial ones that they had tried. The amount of sachet consumed and suggested time of consumption, as well as the continuation of the program were evaluated.

Moreover, in the focus group, the issues raised regarding barriers to comply with the intervention protocol were addressed (e.g. new recipes are provided to women who complain about monotonous diet; possibility of home delivery of the powdered milk and sachet, etc.).

A social media group in a free mobile app was created to promote participant engagement and peer interaction. This strategy may reduce the attrition rate and improve the commitment with the project.

Outcome measures

Primary outcome measures

1) Feasibility (acceptability of study design, recruitment strategy, random allocation and data collection procedures).

Feasibility will be evaluated using mixed methods to explore intervention delivery, participants' acceptability, challenges and issues faced during the study and recommended changes to the study design. Moreover, the number of protocol deviation; an estimate of the cost of carrying out the study; time required for recruitment, data collection, and analysis will be evaluated.

2) Recruitment rate

The total number of participants recruited into the study, number of participants recruited per month, number of invited women, and number of excluded participants before and after the dental screening and reasons for exclusion.

3) Adherence

Percentage of sachet consumed during the study per group (based on the number of returned sachet by pregnant women in their monthly visit); average number of follow-up visits, percentage of participants who provide full data at baseline throughout pregnancy and up to 6–8 weeks postpartum.

4) Attrition rate

Number of dropouts in each study arm and reasons for dropout.

Secondary outcome measures

1) Changes in mean and SD of percentage of sites with bleeding on probing (BOP) and CAL between postpartum and baseline
2) Changes in maternal blood levels of biomarkers of inflammation (CRP, IL-6 and MMP-9)
3) Changes in maternal blood levels of 25(OH) D, glucose, insulin, calcium, parathyroid hormone and lipids (HDL, LDL and triglycerides)
4) Neonatal blood levels of 25(OH) D and calcium

Sample size

This is a feasibility study, and thus the final sample size will be determined by the number of participants that are feasible to recruit within the timescale and budget of the project. For feasibility studies, a minimum of 12 subjects per group is proposed by Julious [54], and a total sample size of 70 subjects is proposed by Teare et al. [55] for a continuous outcome. Since we are planning a 2×2 factorial RCT, a sample size of 120 (30 per group), would be enough to detect a realistic event and allowing for 58% dropout rates (considering a sample size of 70), with sufficient precision and minimal bias for the estimates, as well as the existence of an additive interaction between the two interventions.

Patient and public involvement

Initially, we held meetings with directors and health professionals at the centre to get details on the prenatal care routine and logistics, socioeconomic and demographic profile of service users, numbers of pregnant women attending per month, and whether the centre offered free dental treatment and nutritional counselling for pregnant women. Subsequently, managers and health professionals at the centre were consulted on how to implement the project with minimal interference in their routine practice. Also, informal consultations with female heath care users ($n = 4$) and pregnant women ($n = 15$) attending the centre were performed to know their opinion about the study, if they considered it interesting for the population, if they had any suggestions on how the project could be implemented, how researchers could invite pregnant women to participate, how the pregnant women would adhere to the proposed protocol, if they would consume the milk and if

they had any suggestion on how the team could help in the maintenance of the consumption until the end of the gestation. The views and suggestion of health care professionals and service users were taken into consideration during the implementation of the project.

Statistical analysis

Baseline characteristics of participants will be summarised using descriptive statistics (i.e. means and standard deviations for normally distributed continuous variables, medians and ranges for skewed continuous variables, frequencies and proportions for categorical/binary variables), for all four intervention arms and total sample. All analyses will be according to the intention-to-treat approach, including all participants, regardless of adherence to the study protocol. To determine the effects of the intervention, time and group-time interaction on outcomes (inflammatory biomarker concentrations and periodontitis status), one-way repeated measures ANOVA will be used. Intervention will be regarded as a between-subject factor and time with three-time points (T0, T1 and T2) as a within-subject factor. Mean change of biomarker concentrations, number of sites with bleeding on probing and clinical attachment level (periodontal status) will be compared between the four treatment groups using ANCOVA, adjusted for their baseline values. A P value < 0.05 will be considered statiscally significant.

Data management

Questionnaires (quantitative data) are performed directly using RedCap software (Research Electronic Data Capture), with features that minimises data entry errors and facilitates conversion to other statistical software for data analysis. Questionnaires were designed specifically so that data entry in RedCap was made as accurate as possible.

Questionnaires are peer reviewed before data entry to search for missing data, erroneous values and inconsistency. The identified problems are being solved (data cleaning) using Stata 12 software (Stata Corp 12, TX, USA). Quantitative data are being held in Stata data file (.dta), which has the capacity to store hundreds of variables. Stata software is widely used in research and files can be easily converted into other formats via Stata transfer software. Qualitative interviews are being audio recorded (with full participant consent) and stored in MP3 files. Transcripts are analysed by thematic content analysis and Nvivo software for supporting qualitative analysis is used.

All laboratory specimens, evaluation forms, reports, and other records are identified in a manner designed to maintain participant confidentiality. All records are kept in secure cabinets with limited access. Clinical information cannot be released without the written permission of the participant, except as necessary for monitoring and auditing by the sponsor and regularity authorities. The investigator and the study site staff involved in this study are not allowed to disclose or use for any purpose other than performance of the study.

Computers used to collate the data have limited access measures via user names and passwords. Published results will not contain any personal data that could allow the identification of individual participants. All confidential data (name, address, etc.) are archived separately from research data. Data are housed on a secure server protected by university firewalls and are subject to backups.

Conditions for discontinuation of participation in this clinical trial

1. If a pregnant woman withdraws consent for participation in the clinical trial
2. If a participant is diagnosed after recruitment with serious kidney disease, or other disease (i.e. lactose intolerance, milk protein intolerance), which vitamin D/calcium supplementation or milk consumption are not recommended

Protocol amendments

The Ethics Committee will be informed if any amendments of the protocol are planned, and these amendments will only be implemented after approval.

Follow-up of adverse events

No risky procedure will be employed in this study, and the proposed interventions are considered safe for both the mother and the foetus. However, calcium supplementation in pregnancy may cause constipation. To circumvent this potential side effect, women are being advised to drink enough fluids throughout the study.

Studies have shown that foetal excess of vitamin D metabolites are unlikely to occur when maternal concentrations are within a normal range [56]. Therefore, offering a dose of 1000 IU vitamin D to women during pregnancy would be unlikely to cause any toxicity effect. Recent studies have not identified adverse effects in pregnant women and/or their children with the ingestion of vitamin D supplementation above 1000 IU daily administered during pregnancy [57–59]. Furthermore, the maximum tolerable upper intake level of vitamin D in pregnant women is 4000 IU/day. This quantity of vitamin D a day to pregnant women not only was associated with any toxicity but that it also was associated with better birth outcomes, i.e. improvement in gestational age at birth [34].

In a Cochrane review, the authors concluded that vitamin D supplementation, alone or in combination with calcium and micronutrients, and the low side effect

profile of vitamin D is a cost-effective measure and favourable for use in under-resourced settings [60].

Regarding PT, it has been speculated whether periodontal mechanical manipulation would cause bacteraemia, which itself could initiate the pathway leading to adverse pregnancy outcomes [24]. However, a large RCT showed that rates of adverse outcomes did not differ significantly between women who received treatments and those who did not require treatment. Use of topical or local anaesthetics during root planning was not associated with an increased risk of experiencing adverse outcomes. The authors concluded that essential dental treatment for moderate-to-severe caries or fractured or abscessed teeth and periodontal treatment are safe for pregnant women [61].

Venipuncture in newborns is impractical and collection of cord blood imposes a logistic burden to the hospital staff. Alternatively, drops of neonatal capillary blood will be collected via heel prick for measurement of calcium and 25(OH) D concentrations at the routine neonatal check-up. This test is harmless, with minimal discomfort. The amount of blood taken is too small to be likely to have any adverse effects.

Despite the minimal risks anticipated for this study, any adverse event or serious adverse event will be described according to its relatedness with the interventions, for both the total sample and by treatment arms, in the final study report.

Dissemination plan and impact

The main results of this study will be presented to the director, participants, prenatal nurses and physician of the Municipal Health Centre of Duque de Caxias, Rio de Janeiro/Brazil, through a workshop given by the researchers. The results will also be presented at national and international conferences and published in scientific journals in accordance with the CONSORT statement [62] and its extensions relating to non-pharmacological studies [63, 64] and TIDieR (template for intervention description and replication) [65] guidelines for intervention description and replication. Additionally, the results of this feasibility clinical trial could inform the study design of a full RCT in pregnant women with periodontitis.

Discussion

Periodontitis and vitamin D deficiency among pregnant women have been highly associated with adverse maternal-foetal outcomes including increased risk of delivering preterm and low-birth-weight newborns [13–15]. Despite the evidence on negative pregnancy outcomes, the prevalence of periodontitis and maternal vitamin D deficiency is still high in both developing countries and developed countries.

There is no consensus between studies that evaluate the association between PT alone during pregnancy with improvements of periodontitis [20–23]. However, some authors have observed that the occurrence of periodontitis is less frequent among adults consuming calcium within recommendations and higher quantities of vitamin D [28, 29] and that vitamin D and calcium co-supplementation seems to improve metabolic profile of pregnant women [27]. Moreover, there is limited but suggestive evidence of positive association between milk consumption and foetal growth and infant birthweight in healthy Western populations [66].

Due to the fact that oral health and mineral/vitamin supplementation are still overlooked in the prenatal assistance in Brazilian and there is scarcity of clinical trials addressing both oral health and calcium and vitamin D deficiency, the present study was designed for assessing the feasibility of a RCT on acceptability of a multi-component intervention combining conventional periodontal treatment and milk fortified with calcium-vitamin D intake for improving periodontal conditions and maternal metabolic and inflammation status, among Brazilian low-income pregnant women with periodontitis.

Policy makers, administrators and clinicians need to take the necessary steps to eliminate this easily preventable threat to mothers and infants. Thus, we hope that this relatively low-cost and safe multicomponent intervention can help reduce inflammation and improve maternal periodontal.

Abbreviations

BOP: Bleeding on probing; CAL: Clinical attachment loss; CRP: C-reactive protein; IL-6: Interleukin-6; IMPROVE: This feasibility randomised controlled trial; MMP-9: Matrix metalloproteinase 9; OHIP: Oral Health Impact Profile; PT: Periodontal therapy; RCT: Randomised controlled trials; TIDieR: Template for intervention description and replication health and metabolic profile and consequently prevent negative gestational outcomes

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Availability of data and materials

The datasets used during the current study are available from the corresponding authors on request.

Authors' contributions

PGC wrote the initial draft and revised, edited, discussed and organised the final version of the manuscript. ARA, BLH and GK designed the study, wrote the initial draft and organised the final version of the manuscript. MCVC designed the qualitative protocol to this study. PN, CB, MMS, MBTC, NAS, AFB, RRM, MFH, GLA and ARB revised and helped in the organisation of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The study was presented to and approved by the director of the health centre where it is being conducted. Recruitment started after the IMPROVE trial protocol was submitted and approved by the Ethics Committee of School Maternity of the Federal University of Rio de Janeiro-Brazil on April 27, 2016 (certificate number 1.516.656). The study is being conducted according to the principles of Good Clinical Practice and the Declaration of Helsinki. Explanation of study procedures is given verbally to all participants and a written copy is provided in the patient information sheet. Study participation began after receipt of informed written consent. The trial was registered in the ClinicalTrials.gov database (NCT, NCT03148483. Registered 11 May 2017, https://clinicaltrials.gov/ct2/show/NCT03148483) and its recruitment began on May 2017.

Consent for publication
No applicable.

Competing interests
The authors declare that they have no competing interests.

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