Universidade do Estado do Rio de Janeiro

Centro Biomédico

Faculdade de Ciências Médicas

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O impacto do tratamento com espuma densa eco-guiada na insuficiência venosa crônica

Rio de Janeiro

2024

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Tese apresentada, como requisito parcial para obtenção de título de Doutor, ao Programa de Pós-graduação em Ciências Médicas da Universidade do Estado do Rio de Janeiro.

Orientador: Prof. Dr. Carlos Eduardo Virgini-Magalhães

Rio de Janeiro

2024

CATALOGAÇÃO NA FONTE
UERJ/ REDE SIRIUS/ CB/A

A524 Amorim, Cláudia Salvador
O impacto do tratamento com espuma densa eco-guiada na insuficiência venosa crônica / Cláudia Salvador Amorim. – 2024.
70 f.

Orientador: Prof. Dr. Carlos Eduardo Virgini-Magalhães

Tese (Doutorado) – Universidade do Estado do Rio de Janeiro, Faculdade de Ciências Médicas. Pós-Graduação em Ciências Médicas.

1. Escleroterapia – Métodos – Teses. 2. Insuficiência venosa – Terapia – Teses. 3. Doenças Vasculares – Terapia – Teses. I. Virgini-Magalhães, Carlos Eduardo. II. Universidade do Estado do Rio de Janeiro. Faculdade de Ciências Médicas. III. Título.

CDU 616.1

Bibliotecário: Felipe Caldonazzo CRB7/7341

_____ _____

Assinatura Data

Cláudia Salvador Amorim

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Aprovada em 19 de julho de 2024.

Banca Examinadora: _____

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Rio de Janeiro

2024

DEDICATÓRIA

À minha família, que sempre foi o alicerce da minha jornada, expresso minha mais profunda gratidão. Vocês foram meu porto seguro e minha fonte de motivação em cada etapa desse caminho. Em especial, gostaria de agradecer ao meu pai, Jove Claudio Ferreira Amorim (*in memorium*) . Foi ele quem, desde cedo, plantou em mim a semente da curiosidade e o amor pelo conhecimento. Sua busca incessante pela inteligência e sabedoria foi a luz que guiou meus passos e me inspirou a trilhar o caminho da ciência. Pai, suas lições foram muito além das palavras; foram exemplos vivos de dedicação, perseverança e paixão pelo saber. Cada conquista minha é também sua, pois sem o seu apoio e incentivo, este sonho não teria se concretizado. A minha mãe, Terezinha, e aos meus irmãos, Marcos e Bruno, e Leandro meu companheiro de jornada, minha eterna gratidão pelo amor e apoio incondicional. A todos os membros da minha família, em especial minha avó Adelaide (*in memorium*) e meu avô Salvador por todo orgulho e confiança que tiveram em mim, meu reconhecimento pelo carinho, paciência e compreensão ao longo desses anos de estudos e pesquisas. Vocês me deram forças nos momentos de fraqueza e celebraram comigo cada vitória, por menor que fosse. É graças a vocês que hoje posso olhar para trás e ver o quão longe cheguei.

AGRADECIMENTOS

Gostaria de expressar meu profundo agradecimento ao meu chefe e orientador, Carlos Eduardo Virgini-Magalhães. Sua orientação e apoio foram fundamentais ao longo de todo o processo do meu doutoramento. Agradeço pela sua liderança, pelo compartilhamento de seu vasto conhecimento e pela dedicação em proporcionar um ambiente propício para o desenvolvimento acadêmico e profissional.

Agradeço também ao meu colega Douglas Poschinger. Sua colaboração e disposição para ajudar foram inestimáveis durante este período. Agradeço pelo suporte técnico, pela troca de ideias e pela parceria ao enfrentar os desafios que surgiram ao longo da pesquisa.

A verdadeira ciência é aquela que transforma o sofrimento humano em esperança, elevando a qualidade de vida através do conhecimento e inovação.

Autor desconhecido

RESUMO

AMORIM, Cláudia Salvador. **O impacto do tratamento com espuma densa eco-guiada na insuficiência venosa crônica**. 2024. 70 f. Tese (Doutorado em Ciências Médicas) – Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 2024.

A presente tese de doutorado compreende três estudos que abordam diferentes aspectos do tratamento da insuficiência da veia safena magna (VSM) e da doença venosa crônica (DVC), contribuindo para a compreensão aprofundada dessas condições e fornecendo subsídios valiosos para práticas terapêuticas com o tratamento com espuma densa eco-guiada. O primeiro estudo, "Intervenção Ambulatorial Combinada para Grandes Diâmetros da VSM", investigou a viabilidade da intervenção ambulatorial combinada em pacientes com grandes diâmetros da VSM, incluindo aqueles com úlceras abertas. Os resultados sugeriram que essa abordagem é segura, eficaz e viável, proporcionando melhorias na qualidade de vida até o terceiro ano de seguimento dos pacientes. O segundo estudo ,"Escleroterapia com Espuma Densa Eco-guiada (EEE) para Manejo da Dor na DVC", destacou a eficácia do EEE no manejo da dor em pacientes com DVC e insuficiência da VSM. Esta abordagem se revelou valiosa em estágios diversos da DVC, oferecendo uma alternativa quando a ablação endotérmica não é possível. Além disso, a melhora clínica não se correlacionou exclusivamente com os padrões de oclusão da veia axial, enfatizando a importância de fatores como sexo, idade e classificação clínica no resultado. O último estudo, "Concentrações de Espuma de Polidocanol (POL) na Veia Safena Magna (VSM)", investigou a eficácia das concentrações de espuma de polidocanol (POL) a 1%, 2% e 3% no tratamento da insuficiência da VSM. Embora todas as concentrações tenham mostrado eficácia na melhoria dos escores de dor venosa (EVA) e severidade clínica (VCSS), a concentração de 1% de POL esteve associada a um maior número de sessões e sugeriu uma tendência a pigmentação mais frequente, especialmente em VSM de maior calibre. Em conjunto, esses estudos indicam a importância da personalização do tratamento para a insuficiência da VSM e DVC. A técnica ambulatorial combinada se mostrou uma opção segura e eficaz, mesmo em pacientes sintomáticos com grandes diâmetros da VSM, ressaltando a relevância do tratamento da doença axial com varicosidades, apesar das condições anatômicas desfavoráveis. Essa abordagem integrada pode fornecer resultados clinicamente significativos e duradouros, abrindo caminho para práticas terapêuticas mais eficientes e individualizadas.

Palavras-chave: escleroterapia com espuma densa eco-guida; doença venosa crônica; veia safena magna.

ABSTRACT

AMORIM, Cláudia Salvador. *The Impact of Eco-Guided Foam Treatment on Chronic Venous Insufficiency*. 2024. 70 f. Tese (Doutorado em Ciências Médicas) – Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 2024.

The present doctoral thesis comprises three studies addressing different aspects of the treatment of great saphenous vein (GSV) insufficiency and chronic venous disease (CVD), contributing to a thorough understanding of these conditions and providing valuable insights for therapeutic practices with echo-guided foam sclerotherapy. The first study, "Combined Ambulatory Intervention for Large Great Saphenous Vein", investigated the feasibility of combined ambulatory intervention in patients with large GSV diameters, including those with open ulcers. Results suggested that this approach is safe, effective, and feasible, leading to improvements in the patients' quality of life up to the third year of follow-up. The second study, "Echo-Guided Foam Sclerotherapy for Pain Management in Chronic Venous Disease" highlighted the effectiveness of echo-guided foam sclerotherapy in managing pain in patients with CVD and GSV insufficiency. This approach proved valuable in various stages of CVD, providing an alternative when endothermal ablation is not possible. Furthermore, clinical improvement did not exclusively correlate with axial vein occlusion patterns, emphasizing the importance of factors such as gender, age, and clinical classification in the outcome. The last study, "Polidocanol Foam Concentrations in the Great Saphenous Vein (GSV)", investigated the efficacy of polidocanol foam concentrations (POL) at 1%, 2%, and 3% in GSV insufficiency treatment. While all concentrations demonstrated efficacy in improving venous pain scores (Visual Analog Scale) and clinical severity (Venous Clinical Severity Score), the 1% POL was associated with a higher number of sessions and suggested a trend toward more frequent pigmentation, especially in larger GSV. Collectively, these studies underscore the importance of personalized treatment for GSV insufficiency and CVD. The combined ambulatory technique proved to be a safe and effective option, even in symptomatic patients with large GSV diameters, emphasizing the relevance of treating axial disease with varicosities despite unfavorable anatomical conditions. This integrated approach can yield clinically significant and enduring results, paving the way for more efficient and individualized therapeutic practices.

Keywords: echo-guided foam sclerotherapy; chronic venous insufficiency; great saphenous vein.

LISTA DE ABREVIATURAS E SIGLAS

AVVQ	*Aberdeen Varicose Vein Questionnaire*
CEAP	Clínica Etiologia Anátomo Patologia
ECD	*EcoColorDoppler*
EL	*Endolaser*
EEE	Escleroterapia com Espuma Eco-Guiada
EVA	Escala Visual Analógica
HUPE	Hospital Universitário Pedro Ernesto
JSF	Junção Safeno-Femoral
POL	Polidocanol
PPC	Policlínica Piquet Carneiro
RF	Radiofrequência
SISREG	Sistema de Regulação
VCSS	*Venous Clinical Severity Score*
VSM	Veia Safena Magna

SUMÁRIO

INTRODUÇÃO

A doença venosa crônica dos membros inferiores é uma das mais prevalentes no mundo além de ser responsável por um impacto significativo na qualidade de vida dos pacientes que a apresentam. Acometendo mais de 50% da população brasileira, o quadro clínico pode variar desde telangiectasias até úlceras cutâneas em atividade[1-3].

A dor nos membros inferiores é a queixa mais frequente na doença venosa crônica (DCV) e o principal motivo de procura por atendimento médico, sendo a insuficiência da veia safena magna (VSM) a causa mais importante para a incidência de sintomas de dor venosa e progressão da doença[4-6].

A Escleroterapia com Espuma Eco-Guiada (EEE) é uma técnica terapêutica que oferece um tratamento minimamente invasivo, rápido, de baixo custo, exclusivamente ambulatorial, e que pode ser realizada dentro da rotina diária dos pacientes[7-9]. Dependendo do volume e concentração de esclerosante empregados pelo cirurgião vascular, a EEE é capaz de oferecer um tratamento efetivo, com resultados equivalentes a outras técnicas como a termoablação ou a cirurgia convencional em diferentes tipos de veias varicosas, como em varizes primárias, recidivadas, tortuosas, safenas insuficientes, tributárias, veias recorrentes pós cirurgias, laser ou radiofrequência[10-12].

Atualmente várias diretrizes defendem a termoablação endovenosa, seja com uso do *endolaser* (EL) ou da radiofrequência (RF), como tratamento de primeira opção seguido por EEE e a safenectomia convencional como alternativas de segunda linha para tratar a doença axial, sendo a EEE ainda a primeira escolha no tratamento das veias varicosas[11-13].

Contudo, ainda são escassas as publicações científicas que estudam os efeitos de diferentes concentrações do esclerosante para o tratamento da VSM, conferindo à técnica da EEE certo grau de empirismo e baseando seus resultados predominantemente na experiência do profissional. Esta ausência de parâmetros objetivos oferece algumas dificuldades, principalmente no tratamento das veias de maior calibre e na qualidade dos resultados estéticos da técnica[15-18].

Com o avanço das novas técnicas no tratamento da doença venosa crônica (DVC), em especial da veia safena magna (VSM), os três trabalhos desenvolvidos exploraram abordagens

inovadoras para melhorar a eficácia e a segurança desses procedimentos, enfrentando desafios conhecidos e buscando soluções.

No primeiro estudo, foi investigada a combinação de diferentes métodos em um único tempo cirúrgico, visando otimizar o tratamento da VSM e reduzir custos e tempo de recuperação. Os resultados positivos, mesmo em pacientes com veias safenas calibrosas, incentivaram uma abordagem mais flexível no tratamento. Este estudo, portanto, concentra-se na termoablação axial por radiofrequência associada a espuma densa, avaliando sua segurança, resultados clínicos e impacto na qualidade de vida.

O segundo trabalho aborda a prevalência da dor nos membros inferiores como queixa predominante na DVC, destacando a importância da insuficiência da VSM nesse quadro. Comparando diferentes intervenções, focou-se na eficácia da escleroterapia com espuma guiada por ultrassom (EEE) para controlar a dor venosa, demonstrando resultados comparáveis às abordagens cirúrgicas convencionais.

Por fim, o terceiro trabalho abordou uma lacuna importante na literatura, explorando os efeitos de diferentes concentrações de esclerosante na escleroterapia com espuma densa para tratamento da VSM. Reconhecendo a falta de parâmetros objetivos nesse campo, o estudo visa reduzir o empirismo associado a essa técnica e melhorar os resultados, especialmente em veias de maior calibre e em termos estéticos.

Esses trabalhos refletem o estado da arte no tratamento da DVC e da VSM, destacando a necessidade contínua de inovação para superar limitações e melhorar os resultados clínicos e estéticos para os pacientes.

1 **OBJETIVO**

1.1 **Objetivo Geral**

Esta tese se propõe a avaliar a segurança e eficácia da combinação de endotermoablação por radiofrequência da veia safena magna com refluxo e dilatação, associada à escleroterapia com espuma densa guiada por ultrassonografia das veias varicosas em regime ambulatorial, assim como a taxa de oclusão da veia safena magna por ultrassonografia Doppler pós-operatória. Além disso, busca-se mensurar a relação com o controle da dor venosa nos membros utilizando a escala visual analógica (EVA) e avaliar o impacto das diferentes concentrações de espuma de polidocanol (POL) no tratamento com escleroterapia guiada por ultrassonografia da veia safena magna com diâmetro maior ou igual a 6 mm.

1.2 **Objetivos Específicos**

Os objetivos específicos são:

a) Avaliar os desfechos de taxa de oclusão, eventos adversos e o impacto na qualidade de vida após a termoablação por radiofrequência (RF) associada a escleroterapia por espuma densa (EEE) guiada por ultrassonografia, simultânea, em regime ambulatorial, para o tratamento respectivo do refluxo na veia safena magna (VSM) associado a varicosidades. (APÊNDICE A)
b) Mensurar a relação com controle da dor venosa nos membros, acessada pela escala visual analógica (EVA) e o tratamento com EEE para VSM insuficiente. (APÊNDICE B)

c) Avaliar o impacto das diferentes concentrações de espuma de polidocanol (POL) no tratamento com escleroterapia guiada por ultrassonografia da veia safena magna com diâmetro maior ou igual a 6 mm. (APÊNDICE C)

2 **METODOLOGIA**

Os aspectos referentes à descrição metodológica, à análise de dados, às questões éticas, os resultados da análise de dados e discussão encontram-se nos artigos anexos publicados nas revistas científicas *Vascular Health And Risk Management* e no *International College of Angiology*, e submetido à revista científica Jornal Vascular Brasileiro.

3 **DISCUSSÃO**

A eficácia dos tratamentos com espuma densa vem sendo demonstrada nos últimos anos através da prática clínica e nos estudos publicados. Seu resultado no tratamento da VSM cada vez mais tem colocado de lado a cirurgia convencional em nosso meio na busca de uma abordagem ambulatorial e menos invasiva[19-21].

O tratamento com espuma densa é considerado prático, de baixo custo e efetivo quando comparado com o procedimento cirúrgico convencional, apesar de seus resultados no longo prazo serem inferiores nos estudos randomizados quanto à durabilidade em vista dos tratamentos com *endolaser* e radiofrequência[22-24].

No estudo que empregou o uso da Radiofrequência (RF) em conjunto com a administração de espuma densa, a inexistência de eventos adversos graves, juntamente com a observação de eventos adversos leves semelhantes e resultados comparáveis em ambos os conjuntos tratados, sugere que a intervenção ambulatorial combinada pode ser considerada viável, segura e factível para uma ampla gama de diâmetros da veia safena magna (VSM). A possibilidade de oferecer um tratamento seguro e menos invasivo, mesmo para pacientes altamente sintomáticos com veias de maiores dimensões, com ou sem úlcera aberta, representa uma informação de significativo impacto prático no planejamento terapêutico para esses pacientes [11,25].

O tratamento combinado atingiu parâmetros indicativos de resultados significativamente superiores ou comparáveis em ambos os conjuntos analisados, resultando em uma melhoria na qualidade de vida até o terceiro ano no subconjunto com maiores diâmetros da VSM, reforçando a importância do tratamento da doença axial com varicosidades, apesar das condições anatômicas desfavoráveis ao sucesso esperado. O elevado índice de cicatrização da úlcera, com resultados equivalentes entre os conjuntos, reitera a relevância desta estratégia[11].

Entretanto, a relação entre a redução na taxa de oclusão da VSM e a manutenção do fechamento da úlcera não é clara e demanda uma investigação mais aprofundada no futuro.

Dentro do período de três anos, a amostra total e ambos os subconjuntos exibiram melhorias equivalentes nos questionários de qualidade de vida (EVA, VCSS e AVVQ), juntamente com uma oclusão axial satisfatória e um fechamento duradouro da úlcera[26,27].

No 2º estudo, ao avaliarmos a utilização da Escala Visual Analógica (EVA) para mensurar a dor associada à DVC observamos que diversos estudos têm empregado esse instrumento para comparar a intensidade da dor antes e depois de procedimentos como ablação térmica, cirurgia e escleroterapia com espuma. A avaliação objetiva da dor é crucial, proporcionando uma base sólida para a compreensão dos resultados das intervenções[5-7].

A literatura destaca diversas abordagens para o tratamento da VSM na DVC, e embora a cirurgia convencional demonstre resultados excelentes em termos de tratamento, estudos recentes indicam que abordagens menos invasivas, como a ablação térmica e o uso de espuma densa de polidocanol, oferecem vantagens, como menor tempo de ausência ao trabalho e controle eficaz da dor. Comparando os diferentes métodos de tratamento, observamos que apesar da escleroterapia com espuma apresentar taxas de oclusão inferiores a médio e longo prazo em comparação com ablação com laser e radiofrequência, mesmo pacientes com fechamento incompleto da veia safena relataram melhora total dos sintomas, indicando que a eficácia do tratamento vai além da simples oclusão anatômica. Esse achado é consistente com estudos anteriores que sugerem que a redução do refluxo axial pode explicar os benefícios clínicos, independentemente do padrão de oclusão da safena[11,28,29].

A avaliação objetiva da dor, utilizando instrumentos como a EVA, oferece uma dimensão tangível dos resultados das intervenções e auxilia na compreensão ampla do controle de sintomas. Esta prática pode ser facilmente incorporada na prática clínica diária, proporcionando uma base sólida para a tomada de decisões clínicas e contribuindo para o aprimoramento contínuo das estratégias terapêuticas para pacientes com DVC[27,29,30].

Observamos ainda que a complexidade da DVC requer uma abordagem multifacetada, considerando não apenas as características anatômicas, mas também fatores individuais como gênero, idade e classificação clínica. A avaliação precisa e personalizada dos sintomas, é fundamental para direcionar estratégias terapêuticas eficazes e melhorar a qualidade de vida dos pacientes[31].

No último trabalho apresentado, destacamos que apesar da utilização cada vez mais popular da técnica, ainda não existem protocolos de aplicação da EEE bem definidos quanto ao volume, concentração, número de sessões entre outros parâmetros de tratamento.

Embora estudos randomizados indiquem uma menor durabilidade nos resultados da espuma de POL em comparação com técnicas termoablativas, como o laser e a radiofrequência, a espuma

é considerada segura, de baixo custo e eficaz em resultados imediatos, além de proporcionar melhoria a longo prazo na qualidade de vida dos pacientes. A ausência de protocolos estabelecidos para a aplicação da espuma, incluindo volume, concentração e número de sessões, tem sido uma lacuna na prática clínica, sendo as diretrizes atuais limitadas em fornecer orientações específicas[32,33].

Os resultados apresentados no estudo demonstram eficácia em todas as concentrações testadas, alinhando-se com descobertas prévias. A análise global revelou reduções estatisticamente significativas na Escala Visual Analógica (EVA) e no *Venous Clinical Severity Score* (VCSS), indicando melhora clínica consistente com outros estudos e prática clínica com espuma de POL[26].

A segurança da escleroterapia com espuma guiada por ultrassonografia (EEE) foi corroborada pelos resultados do estudo, refletindo a raridade de complicações graves já observadas em revisões anteriores[34]. Entretanto, o número de sessões necessárias para obter resultados satisfatórios variou significativamente com a concentração de POL utilizada. A concentração de 1% exigiu mais sessões em comparação com a de 3%, uma diferença estatisticamente significativa (p=0,015), enquanto as concentrações de 2% e 3% mostraram resultados clínicos semelhantes.

A incidência de pigmentação cutânea, uma preocupação conhecida com a espuma de POL, foi mais acentuada com a concentração de 1%, especialmente em veias mais calibrosas, revelando uma tendência estatística (p=0,075). No entanto, a dificuldade em quantificar a pigmentação cutânea e a limitação na análise estatística dificultam conclusões definitivas. A comparação com a literatura existente revela uma ampla variação na incidência de pigmentação cutânea associada à espuma de POL, evidenciando a complexidade da avaliação dessa complicação[35].

O 3º estudo aponta ainda, a concentração de 2% como uma opção favorável, oferecendo resultados clínicos sólidos, menor número de sessões necessárias e baixa incidência de pigmentação cutânea. Apesar da eficácia similar entre as concentrações de 2% e 3%, a escolha entre elas pode depender de considerações clínicas individuais e reconhece a importância da experiência clínica na tomada de decisões personalizadas.

Limitações incluem a falta de avaliação a longo prazo das taxas de recanalização e a dificuldade em estabelecer relações conclusivas entre pigmentação cutânea, número de sessões e outras variáveis. A necessidade de futuras investigações se faz evidente para aprimorar a compreensão e aplicação da EEE na prática clínica, promovendo uma abordagem mais embasada e menos empírica no tratamento da DVC.

CONCLUSÃO

A presente tese oferece uma abordagem abrangente sobre o tratamento da insuficiência da veia safena magna (VSM) e da doença venosa crônica (DVC), explorando o método da escleroterapia com espuma densa eco-guiada isoladamente ou em associação com outras técnicas de trataemento da veia safena magna insuficiente.

Os resultados destacam a eficácia da técnica como alternativa à cirurgia convencional, especialmente em busca de abordagens ambulatoriais menos invasivas. A combinação de radiofrequência (RF) com espuma densa se mostra uma intervenção ambulatorial segura e viável, oferecendo benefícios notáveis para pacientes com grandes diâmetros da VSM, inclusive aqueles com úlceras abertas. O tratamento combinado demonstrou resultados superiores ou comparáveis, melhorando a qualidade de vida, a oclusão axial e o fechamento duradouro de úlceras até o terceiro ano de acompanhamento.

A avaliação da dor, fundamental na compreensão dos resultados das intervenções, destaca a importância de considerar fatores individuais, como sexo, idade e classes CEAP, para um planejamento terapêutico personalizado.

Destacamos a falta de protocolos bem definidos na prática clínica da EEE, mas apesar das limitações, os resultados indicam a eficácia global da EEE, observamos a concentração de 2% como uma opção favorável em termos de eficácia clínica, menor número de sessões necessárias e baixa incidência de pigmentação cutânea.

Em síntese, esta tese contribui para a compreensão da DVC e VSM, oferecendo insights valiosos para aprimorar a prática clínica e promover estratégias terapêuticas mais eficientes e personalizadas. Contudo, reconhecemos a necessidade de pesquisas futuras para aprofundar a compreensão a longo prazo, validar protocolos de aplicação e explorar ainda mais as complexidades da EEE na busca de abordagens mais embasadas e menos empíricas no tratamento dessas condições.

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APÊNDICE A – Artigo 1: Radiofrequency Ablation for Axial Reflux associated with Foam Sclerotherapy for Varicosities in One-step Approach: A Prospective Cohort Study Comprising Large Diameters Saphenous Veins

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ORIGINAL RESEARCH

Radiofrequency Ablation for Axial Reflux Associated with Foam Sclerotherapy for Varicosities in One-Step Approach: A Prospective Cohort Study Comprising Large Diameters Saphenous Veins

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Objective: This study assessed the outcomes and impact on the quality of life following one-step outpatient radiofrequency ablation (RFA) and ultrasound guided foam sclerotherapy (USGFS) for large reflux with varicosities in the great saphenous vein (GSV).

Design: Prospective, single-centre, analytical cohort.

Materials and Methods: Thirty symptomatic patients having reflux in the GSV and varicosities (CEAP C3 to C6) were treated with RFA and USGFS simultaneously, in a single-step procedure, from March 2016 to December 2016. They were followed up at 1 week, 6 months, 1 and 3 years. Clinical outcomes, changes in the Quality of Life (QOL) questionnaires SF-36™, VCSS and AVVQ, evolutive vein occlusion rates were assessed by duplex ultrasound, and ulcer closure was checked.

Results: The sample was divided into two groups: (Group 1) GSV diameter ≥13.0 mm (median 19.0 [14–24]), 17 subjects, and (Group 2) GSV diameter ≤12.9 mm (median 10.3 [10–12]), 16 subjects. No major adverse event was observed, and the postoperative minor adverse event rates were similar between the two groups. A significant improvement was observed in VCSS and AVVQ from the preoperative levels to the sixth month and the third-year follow-up. Twelve of 13 ulcers had healed at 1 year and remained closed until 3 years. The entire sample had a significant increase in all short form 36 domains, except for mental health in the Group 2 (GSV ≥ 13.0 mm). Overall first week occlusion rate for the whole sample was 90.9% and 69.7% at the 3-year follow-up. No difference in occlusion rate was observed between the two groups at any time.

Conclusion: Exclusively outpatient combined techniques were safe and feasible in this study with no major adverse events, despite the large diameters of the GSV or ulcer presence. Within 3 years, both diameter groups showed equivalent improvement in all QOL parameters, satisfactory axial occlusion, and maintained ulcer closure.

Keywords: saphenous vein, varicose veins, varicose ulcer, quality of life, catheter ablation, sclerotherapy

Introduction

Worldwide reports of prevalence estimates that Chronic Venous Disease (CVD) varies from <1–73% and Chronic Venous Insufficiency (CVI) from <1%–40%.[1]

In the early twentieth century, Professor William Babcock developed High Ligation and Stripping (HL/S) of Great Saphenous Vein (GSV) technique,[2] which was widely used to treat axial reflux with marked improvement in the quality of life.[3,4]

Received: 31 March 2021
Accepted: 2 June 2021
Published: 2 July 2021

Vascular Health and Risk Management

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Received: 31 March 2021
Accepted: 2 June 2021
Published: 2 July 2021

Currently, treatment for varicose veins has undergone significant changes following the introduction of new, less invasive techniques with better clinical results.[5,6] Several guidelines advocate endovenous thermal ablation, with laser or radiofrequency as the first-line treatment, followed by Ultrasound Guided Foam Sclerotherapy (USGFS) and HL/S as the third option to treat the axial disease, and USGFS as the first option for treating varicose veins.[7–11]

In cases that require treatment of both, GSV reflux and varicosities, many surgeons postpone the USGFS as the second step, to be performed weeks after the main axial thermal ablation surgery.[12,13] This traditional approach requires more resources, repeated medical visits, and more time.[14]

A combined procedure with Radiofrequency Ablation (RFA) and USGFS, is safe and successful and can become an important treatment option.[15,16] However, there are limited data on the efficacy and safety of this combined procedure in patients with large GSV diameters.

The study aims to evaluate the safety, clinical outcomes, impact on the quality of life, rate of ulcer closure, and the rate of occlusion of GSV following radiofrequency ablation associated with USGFS, to treat varicosities in a one-step outpatient basis approach in a cohort of patients with different GSV diameters.

Materials and Methods

Study Overview

Approval of this prospective non-randomized cohort study was granted by the Pedro Ernesto University Hospital Research Ethics Committee, and was conducted in accordance with the Declaration of Helsinki. (CAEE: 16437219.1.0000.5259). The Brazilian Health System supported the viability of the research. The same team of experienced surgeons performed all procedures at the university's ambulatory surgery centre. The physicians involved in direct patient care managed data entry. The authors take responsibility for adherence to the protocol, reported data, and the analyses.

Patients

A cohort of 30 subjects who required treatment for varicose veins, were sequentially recruited from March to November 2016, during consultation at the university's vascular surgery clinic in Rio de Janeiro.

Inclusion criteria were age between 18 and 65 years, ASA physical status 1 or 2,[17] the presence of primary symptomatic varicose veins greater than 3 mm in diameter,[9] Clinical Etiologic Anatomic Pathophysiologic (CEAP) class 3 or higher,[18] GSV diameter in the mid-thigh at least 6 mm, from intima to intima, away from focal dilatation, with reflux greater than 0.5 seconds measured by Doppler ultrasonography in the standing position after calf compression/release, and willingness to provide written informed consent.

Exclusion criteria were a history of peripheral arterial disease, ankle brachial pressure index below 0.9, pregnancy, a history of thrombophilia, previous deep vein thrombosis, pulmonary embolism, thrombophlebitis of the GSV, current cancer, immobility, absolute contraindications to the use of foam[19] or tortuosity rendering the GSV unsuitable for catheter progression.

Participants matching the inclusion criteria were concurrently referred for the first consultation, the baseline data collection, QOL questionnaire filling and duplex analysis.

Assessments

At the time of inclusion in the study as well as at each follow-up assessment, patients' clinical history was collected, and they were submitted to physical exam and duplex ultrasonography. Data about the CEAP clinical class, the Visual Analogue Scale (VAS) score evaluated for pain after venous physical or chemical ablation,[20] the Venous Clinical Severity Score (VCSS)[21] and the Aberdeen Varicose Veins Questionnaire (AVVQ)[22] were also documented. The Medical Outcome Study Short Form 36 (SF-36™)[23] was administered during the first examination (preoperative) and six months after the intervention. The patients were followed up on the 7th day, six months, one, two and three years after the procedure.

An occluded or absent GSV was defined as technical success. If a segment length greater than 10 cm with flow or reflux was seen in a previously occluded GSV, it was defined as axial vein recanalisation.[5]

Study Treatment

The RFA was performed using the ClosureFast™ (Medtronic, San Jose, CA, USA) catheter according to the described technique.[24] A point just below the knee was preferred for cannulation; however, a distal segment of reflux in GSV in the thigh was also acceptable. After advancing the catheter tip until 2 cm below the saphenofemoral junction, the Cold Tumescent Anaesthesia (CTA),[25] a formula derived from Klein's Solution[26]

containing epinephrine, lidocaine, and saline, was injected manually in the saphenous compartment at a rate of 10 mL/cm through a 22 G x 88 mm needle. All steps were performed under ultrasound guidance.

Each patient underwent two cycles of ablation at 120º C for 20 seconds in the first segment of the GSV and one cycle per segment until the last segment in the thigh during the withdrawal of the catheter.

Next, USGFS of the varicosities was performed under 26 G needle (Descarpack, São Paulo, Brazil) spot anaesthesia to minimise puncture discomfort. The foam was prepared according to the Tessari's technique[27] in a ratio of 2-mL polidocanol (Polidocanol; Victa Manipulation Laboratory; São Paulo; Brazil) to 4-mL air, in which 1.5 to 3.0% polidocanol concentration was used according to the size of the varicosities. The estimate cylinder volume was used to guide the solution administration and no more than 10 mL was injected per session.[19] A butterfly needle 23 G (Descarpack, São Paulo, Brazil) was used to inject the foam into the varicosities under Duplex ultrasound guidance and control. Varicose vein entry spot far from the saphenous confluence was preferred to avoid the polidocanol chemical effect in GSV. Direct injection into the saphenous trunk was not part of the protocol.

Light compression sterile bandage was applied with 48h programmed removal after the procedure. General postoperative self-care orientation and a direct contact to anticipate the first assessment, to inform an adverse event or to report unstoppable pain was provided. Both RFA and USGFS procedure were done entirely on an outpatient basis and in a single-step approach.

Groups According to the GSV Calibre

The patients were split into two groups according to the greatest GSV truncal Calibre and the total treated limbs group median diameter was used as the cut-off point. They were compared for adverse events, postoperative pain, quality of life questionnaires, ulcer closure, and venous occlusion rates. The objective of splitting the groups was to maximise the analyses of possible outcomes for GSV with extra-large diameters.

Statistical Analysis

Descriptive analysis shows measures of central tendency and range for the numeric data or frequency and percentage for the categorical variables. Some numeric variables did not exhibit a Gaussian distribution; hence, they were expressed as median and interquartile range (IQR). To assess the normality of data distribution to the 5% level, we used histogram's graphical analysis and the Shapiro Wilk's test. All reported P values are 2-sided, and $P < 0.05$ was considered to infer statistical significance.

Baseline variables between the groups were compared using independent samples *t*-test or Mann–Whitney *U*-test for numeric measures and chi-square test (χ^2) or Fisher's exact test for categorical variables. The latter tests were also used to analyse differences in the occurrence of postoperative adverse events.

For longitudinal analysis of VCSS, AVVQ, VAS, and SF-36, the Mann–Whitney *U*-test was used for comparison between the groups. To evaluate the evolution of VCSS, AVVQ, and VAS through time, we used the Friedman's ANOVA test.[28] Nemenyi's test was performed to analyse differences in the three variables of postoperative assessments.[29] To analyse the short form 36 scores, we used the Wilcoxon signed-rank test. For increasing the statistical power and consistency of the results, data of three VCSS and AVVQ assessments were analysed, namely, preoperative, six months and 3-year postoperative. The VAS and occlusion rate were assessed on the 7th day, six months, and 3-year postoperative. Short form 36 was assessed preoperatively and at six months postoperatively compared. Postoperative adverse events were evaluated at each follow-up.

To evaluate GSV occlusion rate alterations over time, we used repeated measures of categorical data ANOVA according to The CATMOD Procedure of SAS™ software.[30] Corrected McNemar test was used to identify differences between the groups at specific time points.

The data analysis for this paper was performed using SPSS, Version 26.0 and SAS™ software, Version 6.11 (SAS Institute Inc., Cary, NC, USA).

Results

In the total sample of 30 participants, 33 treated limbs were split into two groups: (1) those with GSV diameter of 13.0 mm or more (median 19.0 [14–24]) with 17 subjects, and (2) those with maximum diameter up to 12.9 mm (median 10.3 [10–12]), with 16 subjects. Due to the small number of bilaterally treated limbs, no impact was observed on analysis using treated legs instead of treated patient.

Baseline Variables

The descriptive baseline variables were compared between the groups. Except for a higher proportion of subjects with a family history of CVD in the GSV ≤ 12.9 mm group (p <

Table 1 Baseline Characteristics of the Included Participants in a Total of Treated Limbs and Divided According to the Great Saphenous Vein Diameter Range

Characteristics	Total (n = 33)	GSV ≥ 13.0 mm (n = 17)	GSV ≤ 12.9 mm (n = 16)	p value*
Female sex	21	12	9	0.39
Age – y	51.4 ± 10.2	54.2 ± 6.7	48.3 ± 12.4	0.10
Ethnicity				
Caucasian	17	9	8	0.99
Mixed	8	4	4	
Afro-Latin Americans	8	4	4	
Obesity†	6	5	1	0.10
CVD family history	22	14	8	**< 0.05**
Smoking	5	2	3	0.47
OHC/Replacement Therapy	5	4	1	0.26
Previous thrombophlebitis	7	5	2	0.22
CEAP - clinical class				
CEAP - C3	7	2	5	>0.05
CEAP - C4 (a/b)	9	3	6	
CEAP - C5	4	4	0	
CEAP - C6 (Active Ulcer)	13	8	5	0.35
Perforator vein reflux	6	5	1	0.10
Truncal GSV diameter – mm	13.2 (10–19)	19 (14–24)	10.3 (10–12)	#
Treated limb				
Left Inferior Leg	20	9	11	0.35
Surgical Time – min	36 (30–45)	36 (30–40)	37.5 (31–45)	0.44

Notes: Data are presented as number (n), mean ± standard deviation (SD) or median (Interquartile range [IQR] Q1–Q3). †Obesity was defined as body mass index ≥ 30.0; #Not applicable. *p value between GSV diameter range groups. Any statistically significant p value (<0.05) had bold written.

Abbreviations: GSV, great saphenous vein; y, years; CVD, Chronic Venous Disease; OHC, Oral Hormone Contraceptive; CEAP, Comprehensive Classification System for Chronic Venous Disorders; C, Clinical Class; mm, millimetre; min, minutes.

0.05), there were no other differences in the homogeneity (Table 1) between the groups.

Adverse Events and Other Complications

In the immediate postoperative period, there were no cases of malaise, flush, allergy, neck constriction, cough, chest or neurological symptoms. One patient complained of transient pain, which resolved without medications. No contact for anticipates the scheduled assessment, to inform unstoppable pain or impaired walking abilities occurred within the first postoperative week.

On the seventh postoperative day (D7), 4/33 limbs developed symptomatic superficial varicosities thrombophlebitis and required non-steroidal anti-inflammatory drugs (NSAIDs) without coagulum drainage (GSV ≥ 13.0 mm: 3/4; GSV ≤ 12.9 mm: 1/4 [$p = 0.32$]). Symptoms were absent at 6-month follow-up (D180).

Thigh bruising on the medial side was present on D7 in 13/33 limbs (GSV ≥ 13.0 mm: 4/13; GSV ≤ 12.9 mm: 9/13 [$p = 0.06$]) and was absent at D180. Hyperpigmentation was seen on D180 in 14/33 limbs (GSV ≥ 13.0 mm: 8/14; GSV ≤ 12.9 mm: 6/14 [$p = 0.58$]) and at 3 years in 9/33 limbs (GSV ≥ 13.0 mm: 5/9; GSV ≤ 12.9 mm: 4/9 [$p = 0.54$]). Clinical residual or recurrent varicose veins were seen on D7 in 14/33 (GSV ≥ 13.0 mm: 6/14; GSV ≤ 12.9 mm: 8/14 [$p = 0.39$]), on D180 in 21/33 (GSV ≥

Table 2 Venous Clinical Severity Score and Aberdeen Varicose Veins Questionnaire Preoperative and Postoperative Values in a Total of Treated Limbs and Divided According to the Great Saphenous Vein Diameter Range

Variable	Total (n = 33)		GSV ≥ 13.0 mm (n = 17)		GSV ≤ 12.9 mm (n = 16)		p value*
	Median	IQR	Median	IQR	Median	IQR	
VCSS - preoperative	8.0	6–19	12.0	8–18	5.5	4–19	**< 0.05**
VCSS - six months	4.0	2–7	5.0	4–8	2.5	1–7	0.06
VCSS - 3-year	6.0	3–8	8.0	5–10	4.0	3–8	0.07
p value †	**< 0.05 [a, b, c]**		**< 0.05 [a, b]**		**< 0.05 [a, b]**		
AVVQ - preoperative	25.1	15–40	33.7	22–43	24.5	11–35	0.08
AVVQ - six months	9.1	6–15	11.6	6–15	8.0	6–10	0.18
AVVQ - 3-year	7.0	4–12	11.0	6–16	4.4	3–10	**< 0.05**
p value†	**< 0.05 [a, b]**		**< 0.05 [a, b]**		**< 0.05 [a, b]**		

Notes: Data are presented as number (n) and median (Interquartile Range [IQR] Q1–Q3). Analytical pairs = [a]preoperative and six months, [b]preoperative and 3 years [c]six months and 3 years. *p value comparison between groups with Mann–Whitney's *U*-test. †p value comparison between pairs with Friedman test, followed by Nemenyi's test to observe which of them differed significantly. Any statistically significant *p* value (<0.05) had bold written.

Abbreviations: GSV, great saphenous vein; mm, millimetre; VCSS, Venous Clinical Severity Score; AVVQ, Aberdeen Varicose Veins Questionnaire.

13.0 mm: 11/21; GSV ≤ 12.9 mm: 10/21 [$p = 0.90$]) and at 3 years in 25/33 limbs (GSV ≥ 13.0 mm: 14/25; GSV ≤ 12.9 mm: 11/25 [$p = 0.31$]).

There were no other adverse events such as oedema, skin burns, endothermal heat induced thrombosis (EHIT), deep vein thrombosis, pulmonary embolism, or death during the follow-up period.

The rate of postoperative adverse events between the two groups was similar.

VCSS, AVVQ, VAS, Ulcer Closure and Short Form 36

Table 2 presents the comparisons between the groups for each postoperative assessment and for each of them in the following time pairs: (a) preoperative and D180, (b) preoperative and 3 years and (c) D180 and 3 years. VAS had three analytical pairs, (a) D7 and D180, (b) D7 and 3 years and (c) D180 and 3 years. Short form 36 had one analytical pair: preoperative and D180 and is presented in Table 3.

The total sample had median VAS scores as follows: D7 (2[0 4.5]); D180 and 3-year (0[0 0]). The GSV ≥ 13.0 mm group had median VAS scores as: D7 (2[0 5.0]); D180 and 3 years (0[0 0]). The GSV ≤ 12.9 mm group had median VAS scores as: D7 (0[0 2.8]); D180 (0[0 0.8]) and 3 years (0[0 0]). No significant reduction from D7 scores to D180 was observed and the VAS scores did not differ significantly between the groups at any assessment.

A significant improvement was seen in VCSS and AVVQ from preoperative to D180 and preoperative to 3 years, for the entire sample and in each group.

Except for significant worsening in VCSS in the total sample, no other differences were observed from D180 to 3-year postoperative assessments.

AVVQ measures at 3 years were higher in the GSV ≥13.0 mm group compared to the GSV ≤ 12.9 mm group.

In the D180 assessment, 11/13 ulcers had healed, which increased to 12/13 at one year assessment. There was no difference in the rate of ulcer closure or time to heal between the groups ($p = 0.42$).

There was a significant improvement in all short form 36 domains from preoperative to D180 in the total sample and in the GSV ≥13.0 mm group, except for the mental health domain in the latter. The GSV ≤ 12.9 mm group had a statistically significant improvement in Physical Functioning, Role Physical, Role Emotional, Vitality and Health Change. The GSV ≥13.0 mm group had higher Health Change values than the GSV ≤ 12.9 mm group.

Great Saphenous Vein Occlusion

The rate of GSV occlusion at D7 postoperative assessment was 30/33 in the entire sample (Table 4). No difference in occlusion rate was observed between the two groups on follow-up assessments. Within each group, no difference was observed when pairs in time were compared, except

Table 3 Short Form 36 Preoperative and Postoperative Values in a Total of Treated Limbs and Divided According to the Great Saphenous Vein Diameter Range

Short Form 36 Domain	Total (n = 33)		GSV ≥ 13.0 mm (n = 17)		GSV ≤ 12.9 mm (n = 16)		p value*
	Median	IQR	Median	IQR	Median	IQR	
Physical Functioning –preoperative	75	65–92.5	70	60–85	87.5	66–99	**< 0.05**
Physical Functioning – six months	100	95–100	95	95–100	100	95–100	0.58
p value †	**< 0.05**		**< 0.05**		**< 0.05**		
Role-Physical – preoperative	75	0–100	25	0–100	100	56–100	**< 0.05**
Role-Physical – six months	100	100–100	100	100–100	100	100–100	0.64
p value †	**< 0.05**		**< 0.05**		**< 0.05**		
Role-Emotional – preoperative	100	33–100	100	33–100	100	42–100	0.88
Role-Emotional – six months	100	100–100	100	100–100	100	100–100	0.64
p value †	**< 0.05**		**< 0.05**		**< 0.05**		
Vitality – preoperative	70	65–85	65	57.5–75	77.5	66.3–92.5	**< 0.05**
Vitality – six months	95	83–100	90	78–100	95	86–95	0.82
p value †	**< 0.05**		**< 0.05**		**< 0.05**		
Mental Health – preoperative	80	80–90	80	78–90	82	80–90	0.81
Mental Health – six months	92	84–100	92	80–100	94	82–100	0.96
p value †	**< 0.05**		0.06		0.06		
Social Functioning – preoperative	87.5	63–100	75	56–100	87.5	66–100	0.46
Social Functioning – six months	100	88–100	100	88–100	100	91–100	0.87
p value †	**< 0.05**		**< 0.05**		0.13		
Bodily Pain – preoperative	57.5	45–78	57.5	45–66	73.8	48–98	**< 0.05**
Bodily Pain – six months	90	67.5–100	90	68.8–95	95	51–100	0.59
p value †	**< 0.05**		**< 0.05**		0.23		
General Health – preoperative	65	60–72.5	65	50–70	65	60–75	0.44
General Health – six months	75	65–82.5	75	62.5–82.5	75	66–84	0.80
p value †	**< 0.05**		**< 0.05**		0.14		
Health Change – preoperative	50	25–50	50	25–50	50	31–50	0.97
Health Change – six months	100	75–100	100	75–100	75	50–100	**< 0.05**
p value †	**< 0.05**		**< 0.05**		**< 0.05**		

Notes: Data are presented as number (n) and median (Interquartile Range [IQR] Q1–Q3). Analytical pair = preoperative and six months. *p value comparison between groups was made with Mann–Whitney's *U*-test. †p value Wilcoxon signed-rank test was used to make comparisons between pairs. Any statistically significant p value (<0.05) had bold written.

Abbreviations: GSV, great saphenous vein; mm, millimetre.

for the total sample itself, which presented a significant decrease in the rate of occlusion from D7 postoperative to 3-year postoperative ($p < 0.05$). One case of axial occlusion failure required additional USGFS session after one month and two cases with clinical recurrence were seen at one year postoperative assessment.

Table 4 Postoperative Occlusion Rates in a Total of Treated Limbs and Divided According to the Great Saphenous Vein Diameter Range

Postoperative Assessment – Occlusion Rate	Total (n = 33)		GSV ≥ 13.0 mm (n = 17)		GSV ≤ 12.9 mm (n = 16)		p value*
	n	%	n	%	n	%	
7th day	30	90.9	16	94.1	14	87.5	0.48
Six months	26	78.8	13	76.5	13	81.3	0.54
3 years	23	69.7	12	70.6	11	68.8	0.60
p value †	**< 0.05 ***		0.12		0.25		

Notes: Data are presented as frequency (n) and percentage (%). Analytical pair = (a) D7 postoperative and 3 years. *p value comparison between groups with Fisher's exact test. †p value comparison between pairs with ANOVA according to The CATMOD Procedure of SAS software, followed by corrected McNemar test to identify differences in pairs at specific time points. Any statistically significant p value (<0.05) had bold written.
Abbreviations: GSV, great saphenous vein; mm, millimetre.

Among the seven patients with an initial axial well-succeed ablative treatment in the 7th day, followed by GSV occlusion failure at six months or three-year postoperative assessments, three experienced important proximal stump reflux increases, defining occlusion failure. No additional significant proximal stump reflux length increase was observed in the total group of patients.

Six cases of perforator veins with reflux were treated with no ultrasonographical recurrence until the third year of follow-up.

Discussion

The uncommonly wide diameters observed in this study could be accounted to the tertiary centre profile and treatment delay, allowing disease's progression and venous enlargement.[31] Such measures are unfrequently seen in developed countries, as observed in a recognised observational cohort study conducted in the United Kingdom, with a maximum referred venous diameter of 9.2 mm.[32]

The rate of thrombophlebitis on the seventh day postoperative could be associated with inflammation related to the polidocanol sclerotherapy technique.[5,33] All four cases of thrombophlebitis in the study had an extra clinical assessment at one month and were asymptomatic for this adverse event. Bruising was not an element of concern among participants, but highly observed in some until the end of the first month.

Almost half of the legs treated were of Mixed or Afro-Latin American individuals, a known risk factor for hyperpigmentation, contributing to the higher observed in the study. Series with higher rates of Caucasian individuals usually presents a lower hyperpigmentation incidence range of 10–30% and diminish over time.[34] The GSV diameter cannot be considered a risk factor since no statistical difference was seen; however, more information is required about the incidence in these individuals.

Residual or recurrent varicose veins were cumulatively seen in 76% of the limbs, probably due to the limited amount of foam up to 10 mL injected per session.[19] It is supported by an initial rate of 42% residual varicose veins in the D7 postoperative assessment. In the absence or improvement of remaining symptoms, conservative treatment was followed. Despite the discrepant diameter measures seen, there was no difference in the recurrence rate between the groups.

A recently published systematic review with meta-analysis including 6915 limbs treated in single or in multiple stages showed no difference in the safety profile.[35] In this study, the absence of major adverse events, equivalent minor adverse events and outcomes in both groups suggests that the ambulatory combined intervention could be feasible and safe for several GSV diameters. The feasibility of offering a safe and less invasive treatment, even for highly symptomatic patients with wider GSV, with or without open ulcer, is a considerable achievement.

Preoperatory QOL comparison findings converge with a recent systematic review observation, where truncal venous diameter is not directly linked to AVVQ and short form 36 clinical scales. Otherwise, a VCSS worst median was observed in the broader GSV group, following the same study conclusions.[36]

We observed a substantial early postoperative improvement in the Quality of Life (QOL) questionnaires, AVVQ, VCSS and short form 36 in the overall sample and in both groups, reinforcing previous reports about the potential for marked improvement after axial treatment.[37] The low total sample VCSS score was not maintained from six months

to three years, perhaps due to increasing recurrence of reflux and varicose veins. A valid strategy to prevent the scale downsize could be sclerotherapy of all remaining varicosities despite satisfactory clinical achievements.

Both, AVVQ and short form 36, showed significantly better or comparable results in both groups indicating the feasibility of combined treatment even for broad GSV diameters. The relatively greater improvement of quality of life until the third year in the subgroup with more severe disease, reinforces the relevance of treating axial disease with varicosities despite the anatomical odds against expected success. The high rate of ulcer healing, with equivalent results between the groups reaffirms this strategy.

The axial recanalisation can reach rates greater than 30% in a GSV treated with a thermal ablation technique.[38] This study observed significant GSV occlusion rates reduction in the total sample and a statistical tendency of axial reflux recurrence inside the groups. However, no difference appeared between the groups rate comparisons.

One limb with an ulcer in the GSV ≥13.0 mm group, in which the reflux persisted since the D7 assessment, did not heal. Nevertheless, all other leg ulcers healed in the first year and remained closed until the third year assessment. The correlation between reduction in GSV occlusion rate and maintained ulcer closure is unclear and needs further research.[39] Initial truncal reflux treatment might be necessary to achieve sustained healing over time in this group.

The statistical comparison between the groups has a limited strength due to the small sample size and the study design; nevertheless it indicates that large GSV diameters are not an absolute limitation for low adverse events, perform a secure treatment, achieve greater improvements in QOL, and comparable rates of ulcer closure.

In this study, the outpatient combined technique was safe and feasible in this population with no major adverse events, despite the large diameters of GSV and a considerable proportion of leg ulcers. Within the third year, the total sample and both saphenous vein diameter range subgroups showed equivalent improvement in VAS, VCSS, and AVVQ quality of life questionnaires, satisfactory axial occlusion, and maintained ulcer closure.

Acknowledgments

The authors thank their colleagues in the Teaching and Health Care Unit of Vascular and Endovascular Surgery for all diligent work done throughout the time of the study.

Disclosure

The authors reported no conflicts of interest for this work.

This research did not receive any specific grant from funding agencies in the public, commercial, or not for profit sectors.

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APÊNDICE B – Artigo 2: Impact of Ultrasound Guided Foam Sclerotherapy for Pain Control in Patients with Chronic Venous Disease and Great Saphenous Vein Reflux

Article published online: 2022-11-11

172 Original Article

Impact of Ultrasound-Guided Foam Sclerotherapy for Pain Control in Patients with Chronic Venous Disease and Great Saphenous Vein Reflux

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Int J Angiol 2023;32:172–178.

Abstract

Chronic venous disease (CVD) associated with great saphenous vein (GSV) reflux has a higher prevalence of pain in the lower limbs. This study evaluates the impact of ultrasound-guided foam sclerotherapy (UGFS) for GSV and symptom control, accessed by the visual analogue scale (VAS). Patients with CVD who underwent GSV-UGFS were included in this retrospective cohort (417 limbs). The pain was measured before and after the treatment. The scale alteration was assessed as a function of age, sex, Clinical Etiologic Anatomic Pathophysiologic (CEAP) classes, total of sclerotherapy sessions, GSV occlusion patterns, and ulcer healing. Majority of patients were female (59.2%), and the mean age was 56 ± 11.5 years. In the total sample, 78.2% of the GSVs were fully occluded, 19.7% had partial occlusion, 2.2% remained open, and 3.2 ± 1.9 (median $= 3.0$) sessions were performed. The reduction of symptoms occurred in 88.3% of participants (VAS drop median = 4.8). Patients younger than 50 years and females had the greatest VAS decreases. When comparing the outcomes of complete occlusion versus partial occlusion, there was no significant difference in VAS pain reduction ($p = 0.14$). The comparison between CEAP clinical classes also did not show statistically significant differences in delta VAS ($p = 0.71$). GSV-UGFS was effective for pain control. However, this improvement does not appear to be related to the pattern of occlusion, indicating that in the short term, the outcomes of total and partial occlusion suggest successful management of symptoms. Other aspects such as gender, age, pretreatment pain intensity, and CEAP classes seem to play a role in the clinical outcome.

Keywords

- sclerotherapy
- saphenous vein
- venous insufficiency
- chronic venous disease polidocanol
- vascular surgery ambulatory
- ulcer

Pain in the lower limbs is the most frequent complaint in chronic venous disease (CVD) and the main reason for seeking medical care. A general prevalence of 60 to 77% was reported in a study enrolling approximately 100,000 individuals.[1] Great saphenous vein (GSV) insufficiency figures prominently contribute to venous pain symptoms incidence and disease progression.[2]

When comparing the different interventions for treating CVD, ultrasound-guided foam sclerotherapy (UGFS) was demonstrated to be as effective as high ligation and stripping surgery and GSV's endovenous ablation with regarding pain control.[3]

However, it has already been suggested that the saphenous vein's pattern of lumen occlusion is not the sole responsible for the clinical improvement in these patients, despite the lack of studies in the literature directly accessing this association.[4]

This study evaluates the impact of UGFS treatment for insufficient GSV, its's occlusion outcomes, and the relation to

article published online
November 11, 2022

DOI https://doi.org/10.1055/s-0042-1758384.
ISSN 1061-1711.

Article published online: 2022-11-11

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Int J Angiol 2023;32:172–178.

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article published online
November 11, 2022

DOI https://doi.org/10.1055/s-0042-1758384.
ISSN 1061-1711.

limb venous pain control, accessed by the visual analogue scale (VAS).

Materials and Methods

Study Overview

This retrospective cohort single-center study was approved by the Pedro Ernesto University Hospital Research Ethics Committee, Rio de Janeiro, Brazil, and was conducted in accordance with the Declaration of Helsinki. The Brazilian Public Health System supports the viability of this research. The same team of experienced vascular surgeons performed all procedures at the university's ambulatory. The authors take responsibility for adherence to the protocol, reported data, and the analyses.

Patients

The review and data extraction were made over charts of patients with symptomatic CVD who required UGFS treatment from May 2017 to February 2019, consecutively attended at the university's vascular surgery ambulatory.

Inclusion criteria for initial treatment were age between 18 and 85 years, ASA physical status 1, 2, or 3,[5] Clinical Etiologic Anatomic Pathophysiologic (CEAP) class 2 or higher,[6] GSV diameter of least 6 mm in the midthigh, from intima to intima, away from focal dilatation, with reflux greater than 0.5 seconds measured by Doppler ultrasonography in the standing position after calf compression/release, and willingness to provide written informed consent.

Exclusion criteria for initial treatment were an ankle brachial pressure index below 0.9, pregnancy, breastfeeding, previous pulmonary embolism, current cancer, immobility, and absolute contraindications to the use of foam.[7]

Participants who matched the criteria were referred for the initial treatment. The availability of chart data was the inclusion criterion for this study.

Assessments

At the time of inclusion for treatment, as at each follow-up assessment and discharge, the patient clinical history, CEAP clinical class, and the VAS data were collected and then submitted for physical examination and ulcer dressing exchange, if applicable. According to the individualized treatment plan, a sclerotherapy session and the control duplex ultrasonography were performed.

Every participant had a pretreatment venous mapping, done by a specialized sonographer's physician team, repeated before ambulatory discharge. A total occluded GSV lumen was defined as an occlusion pattern. If a segment length greater than 10 cm with flow or reflux was seen, it was defined as partial occlusion. The absence of segment obliteration was defined as no occlusion.

VAS score ranged from zero to ten, according to the patients' known pain reference, graphically and numerically expressed in a standardized tool. The VAS score improvement was calculated by subtracting the discharge assessment score from the entry score. An improvement cut-off value of 80% was adopted to assure that every participant in this group had a discharge VAS score in the mild pain stratus. Negative values were considered in the improvement <80% group for analysis.

Ambulatory Ultrasound-Guided Foam Sclerotherapy of the Great Saphenous Vein

The foam was prepared according to Tessari's technique[8] in a ratio of 1-mL polidocanol (Polidocanol; Victa Manipulation Laboratory; São Paulo; Brazil) to 4-mL air, in which 1.0 to 3.0% polidocanol concentration was used according to the size of the varicosities. A limit of 10 mL was injected in each session.[7]

A straight or a butterfly needle 23 G (Descarpack, São Paulo, Brazil) was used to inject the foam into the GSV under Duplex ultrasound guidance and control. Saphenous transducer compression, leg elevation, or milking moves were not applied.

The general self-care orientation, contact to anticipate the first assessment, to inform an adverse event and immediate ambulation followed the procedure. An inelastic compression bandage under the knee was used for all participants. The postprocedure ambulatory assessment was scheduled for 2 to 4 weeks.

Variables Subgroups

The patients were split into stratus subgroups according to sex, age, total number of sclerotherapy sessions, CEAP clinical class, limb side, GSV occlusion pattern, ulcer healing status, and pretreatment VAS measures. The groups were compared with revealed significant discrepancies in the VAS score to analyze the chances of a variable to be implicated in improvements greater than 80% in VAS. The objective of splitting age, total number of sclerotherapy sessions, GSV occlusion pattern, and ulcer healing status groups into stratus subgroups according to median and quartiles was to maximize the analyses of possible outcomes.

Statistical Analysis

Descriptive analysis shows measures of central tendency and range for the numeric data or frequency and percentage for the categorical variables. Despite the size of the total sample, numeric variables did not exhibit a Gaussian distribution; hence, they were expressed as median and interquartile range.

To assess the normality of data distribution to the 5% level, we used histogram's graphical analysis and Kolmogorov-Smirnov's test. All reported p-values are two-sided, and $p < 0.05$ was considered to infer statistical significance.

The association between delta VAS scores and the numeric variables was done using independent Spearman's correlation coefficient. The Mann–Whitney U-test was used for categorical variables with two subgroups and the Kruskal–Wallis One-Way ANOVA for variables with three or more subgroups, followed by the Dunn multiple comparison test to reveal differences among the subgroups in both cases.

Binary logistic regression was used to predict variables implicated in the odds of an unsatisfactory improvement after sclerotherapy treatment. The 80% cut-off value was

used to grant only mild pain cases in the satisfactory improvement group.

The data analysis for this paper was performed using SPSS, Version 26.0.

Results

A total sample of 417 treated limbs were retrospectively included and analyzed in this study. ►**Tables 1** and **2** present the descriptive baseline characteristics of the included participants in a total of treated limbs, VAS scores, and treatment outcomes.

Pain improvement after treatment occurred in 370 (88.3%) cases. In 43 (10.3%) patients, the pain remained unaltered and worsening was seen in six cases (1.4%). Among participants who experienced pain reduction, a delta VAS score median of 4.8 points was observed.

A significantly higher delta VAS was observed in female participants, in the subgroup ≤50 years compared with the >60 years subgroup and in the subgroup with less than three sclerotherapy sessions. When comparing the CEAP clinical classification subgroups, the C3 and C6 subgroups had a higher delta VAS than the C2 subgroup. No difference in delta VAS was observed among the subgroups concerning GSV occlusive outcomes, ulcer grade of healing, and other variables considered for this study (►**Table 3**).

Table 1 Baseline characteristics of the included participants in a total of treated limbs and subgroups

Characteristics	Total | $n = 417$ (100)
Female sex—*n*	247 (59.2)
Age—years	56 (49–64)
Age groups—*n*	
≤50	127 (30.5)
51 to 60	134 (32.1)
>60	156 (37.4)
Total of assessments—*n*	4 (4–6)
Total of sessions—*n*	3 (2–4)
Total session groups—*n*	
≤3	292 (70.0)
CEAP clinical class—*n*	
CEAP—C2	137 (32.9)
CEAP—C3	122 (29.3)
CEAP—C4 (a/b)	65 (15.6)
CEAP—C5	47 (11.3)
CEAP—C6 (active ulcer)	46 (11.0)
Treated limb—*n*	
Right inferior leg	217 (52.0)

Abbreviations: C, Clinical Class; CEAP, Comprehensive Classification System for Chronic Venous Disorders.
Note: Data are presented as total number (*n*) and percentage or median and interquartile range [IQR (Q1–Q3)].

Table 2 VAS score, VAS improvement, GSV occlusion pattern, and ulcer healing subgroups

Characteristics	Total | $n = 417$ (100)
VAS score	
Pretreatment	7 (4–9)
Posttreatment	1 (0–2)
Delta (pre minus post)	5 (3–7)
VAS improvement range	
≥80%	257 (61.6)
<80%	160 (38.4)
GSV occlusion	
Total	326 (78.2)
Partial	82 (19.7)
No occlusion	9 (2.2)
Ulcer healing	
Total	21 (45.6)
Partial	23 (50.0)
No healing	2 (4.3)

Abbreviations: GSV, great saphenous vein; VAS, visual analogue scale.
Note: Data are presented as total number (*n*) and percentage or median and interquartile range (Q1–Q3).

Clinical CEAP C6 classification included participants having an entry VAS score significantly higher compared with patients with CEAP 2 or 4.

The binary logistic regression suggested the female sex and higher initial VAS scores as significantly predictors of unsatisfactory improvement or VAS count reduction equal to or inferior to 80%. The CEAP clinical class 6 and an open GSV after treatment presented a tendency of poor symptom improvement, with no statistical significance in this study. No significance was observed among the other variables considered in this study (►**Table 4**).

Discussion

Several studies have used VAS to measure the pain associated with CVD, especially with the aim of comparing this symptom before and after various types of procedures such as thermal ablation, surgery, and foam sclerotherapy.[3,9–12]

Different approaches to treating GSV have been described in the literature. Although conventional surgery has excellent occlusion results, a Cochrane review observed that USGFS has equivalent clinicians accessed recurrence and symptom-related recurrence. Average outcomes have recently been demonstrated for surgery, in terms of pain-level control and postprocedure complications, in addition to having a longer work absence time compared with radiofrequency, laser, or UGFS ablation.[13]

Foam sclerotherapy demonstrates lower rates of GSV occlusion after treatment and a higher frequency of recanalization in the medium and long term compared with surgical or the higher-grade recommended, endothermal ablation

Table 3 Delta VAS according to clinical and treatment variables subgroups

Subgroup	*n*	Median	IQR	*p*-Value[a]
Sex				
Female	247	5	3–8	**<0.0001**
Male	170	4	1–7	
Age groups				
≤50	127	5	3–8	**0.033**
51 to 60	134	5	3–7	
>60	156	4	2–7	
Total session groups				
≤3	292	5	3–7	**0.027**
>3	125	4	2–7	
CEAP clinical class				
CEAP—C2	137	4	2–7	**0.030**
CEAP—C3	122	6	3–7	
CEAP—C4 (a/b)	65	5	2–7	
CEAP—C5	47	5	3–7	
CEAP—C6 (active ulcer)	46	5.5	3.8–7	
Treated limb				
Right Inferior Leg	217	5	3–7	0.21
Left Inferior Leg	200	5	3–7	
GSV occlusion				
Complete	326	5	3–7	0.14
Partial	82	5	2–7	
No occlusion	9	4	0–6	
Ulcer healing				
Complete	21	5	1.8–7.3	0.60
Partial	23	5	3–6	

Abbreviations: ANOVA, analysis of variance; CEAP, Comprehensive Classification System for Chronic Venous Disorders; C, Clinical Class; GSV, great saphenous vein.

Note: Data are presented as total number (*n*), median, and interquartile range (Q1–Q3).

[a]*p*-Value. The Mann–Whitney U-test was used for categorical variables with two subgroups and the Kruskal–Wallis one-way ANOVA for variables with three or more subgroups, followed by Dunn's multiple comparison test to reveal differences among the subgroups in both cases. Any statistically significant *p*-value (<0.05) is given in bold.

methods. In some series, rates of merely 50% occlusion using foam were achieved in the 5-year follow-up, against 90 to 95% in the surgical or endothermal groups. However, the technique is as effective as other techniques in ensuring the improvement of pain and other symptoms of venous disease.[3,14]

In this cohort, the higher VAS values observed before treatment could explain the wider variation in the female score. Despite the greater amplitude of pain score reduction, females did not present the best clinical improvement, since women have the greatest drops in VAS, but men achieved the best results at the end of treatment. This behavior of sex relation to pain is not fully understood, but it is widely described in the literature.[15–17] Females are more sensitive to pain stimuli compared with males and the difference in pain perception between them is associated with possible biological aspects.[16]

Patients over 60 years of age had a lower reduction in pain symptoms after foam sessions compared with the group up to 50 years of age. Age is an established factor in reducing pain sensitivity and maybe the fact that explains this difference.[18–20] It has been speculated that the aging process causes sensory loss to pain or an increase in pain tolerance to chronic pain stimulus.[21]

A randomized single-center study compared the results of anatomic occlusion, rate of complications, and quality of life in patients with GSV insufficiency allocated in three branches, treated with laser ablation, radiofrequency, and UGFS.[22] After 1 year, the rate of anatomical occlusion in the UGFS group was lower than that in the other two groups. However, approximately half of the patients with incomplete saphenous vein closure reported complete improvement in symptoms.

Table 4 VAS improvement range according to clinical and treatment variables subgroups

	Improvement <80%		Improvement ≥80%				
Subgroup	***n***	**%**	***n***	**%**	**OR**	**CI 95%**	***p*-value[c]**
Sex							
Female	106	66.3	141	54.9	1.61	1.07–2.43	**0.022**
Male	54	33.8	116	45.1	ref.		[a]
Age—years							
Median (Q1–Q3)	56 (50–64)		57 (47–64)		1.00	0.99–1.02	0.58
Age groups							
≤50	45	28.1	82	31.9	ref.		[a]
51 to 60	56	35.0	78	30.4	1.31	0.79–2.16	0.29
>60	59	36.9	97	37.7	1.11	0.68–1.80	0.68
Total session groups							
≤3	116	72.5	176	68.5	ref.		
>3	44	27,5	81	31.5	0.82	0.53–1.27	0.38
CEAP clinical class							
CEAP—C2	55	34.4	82	31.9	ref.		[a]
CEAP—C3	41	25.6	81	31.5	0.75	0.45–1.25	0.28
CEAP—C4 (a/b)	21	13.1	44	17.1	0.71	0.38–1.33	0.28
CEAP—C5	17	10.6	30	11.7	0.84	0.43–1.68	0.63
CEAP—C6 (active ulcer)	26	16.3	20	7.8	1.94	0.99–3.81	0.054
Treated limb							
Right inferior Leg	90	56.3	127	49.4	ref.		[a]
Left inferior Leg	70	43.8	130	50.6	0.76	0.51–1.13	0.17
GSV occlusion							
Complete	122	76.3	204	79.4	ref.		
Partial	32	20.0	50	19.5	1.07	0.65–1.76	0.79
No occlusion	6	3.8	3	1.2	3.34	0.82–13.6	0.092
Ulcer healing							
Complete	10	37.0	11	57.9	ref.		
Partial	15	55.6	8	42.1	2.55	0.78–8.36	0.12
No healing	2	7.4	0	0.0	[b]	0.00–	0.99
Pretreatment VAS							
Median (Q1–Q3)	8 (5–9)		6 (3–9)		1.17	1.99–1.25	**<0.0001**

Abbreviations: C, Clinical Class; CEAP, Comprehensive Classification System for Chronic Venous Disorders; GSV, great saphenous vein; ref., reference; VAS, visual analogue scale.

Note: Data are presented as total number (*n*) and percentage or median and Interquartile range (Q1–Q3), odds ratio (OR), and confidence interval (CI).

[a]Not applicable.

[b]Mathematically not applicable.

[c]*p*-Value. OR and a respective CI 95% for a <80% improvement, according to the individual binary logistic regression. Any statistically significant *p*-value (<0.05) is given in bold.

Williamson et al found an occlusion rate of 70% in foam-treated patients. The authors suggest that the reduction in axial reflux is a possible explanation for why individuals with partially occluded saphenous veins also achieved a complete reduction in symptoms.[4,23] These findings were observed in this study, since both groups obtained the same clinical benefits, regardless of whether the result of saphenous occlusion pattern was complete or partial.

The observed pretreatment VAS score increasing values, as a function of the CEAP clinical classes, suggests a representation of the CVD phases. However, it is impossible

to differentiate them only by this parameter, due to the superposition of the means and medians observed, except for the C4, which presents an alternate behavior in this series.

Numerous authors have investigated the relationship between CEAP clinical classes and pain symptoms, observing that this relationship has been a controversial spot.[24–27] The C2 subgroup benefited the least after the foam treatment, with the mildest lowering in the VAS score. The fact that his subgroup has a more incipient clinical picture, compared with the other patients evaluated in this study, suggests the clinical result presented. The C6 subgroup with high pre-treatment scores probably justified the logistic regression that identifies the C6 class as an impediment to a greater than 80% reduction in pain score after foam treatment.

Venous pain is a frequent symptom that is highly correlated with the quality of life of patients with CVD. Due to the multiplicity of associated factors, the absence of a direct relationship between pain intensity and anatomical dysfunction in vascular ultrasound examination, and the biopsychological and sociocultural aspects, the expression of this common symptom presents differences that are still not well understood.[2]

The objective assessment of pain with quick instruments and simple to use, such as the VAS, can be easily incorporated into daily clinical practice and offer us a palpable dimension of the results of the interventions, effectively helping the specialist in a broader understanding of the symptom control and in decision-making.

Conclusion

This study reinforces the effectiveness of UGFS in pain management for symptomatic patients at all stages of CVD and GSV insufficiency, being a valuable strategy to carry treatment in which endothermal ablation is not possible. The clinical improvement does not seem to be necessarily related to the complete or partial patterns of occlusion in the axial vein. Other aspects such as gender, age, pretreatment pain intensity, and CEAP classes seem to play a significant role in the clinical outcome of the treatment and can be considered to make an individualized therapy plan and discuss patient's expectations.

Note
This study was accepted for oral abstract presentation at XIX World Congress of Phlebology – 2022 (UIP) Istanbul, Turkey.

Conflict of Interest
None declared.

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APÊNDICE C – Estudo clínico randomizado do impacto da escleroterapia com espuma ecoguiada da veia safena magna com diferentes concentrações de polidocanol

ESTUDO CLÍNICO RANDOMIZADO DO IMPACTO DA ESCLEROTERAPIA COM ESPUMA ECOGUIADA DA VEIA SAFENA MAGNA COM DIFERENTES CONCENTRAÇÕES DE POLIDOCANOL

RANDOMIZED CLINICAL TRIAL OF THE IMPACT OF SCLEROTHERAPY ON ULTRASOUND-GUIDED FOAM OF THE GREAT SAPHENOUS VEIN WITH DIFFERENT POLIDOCANOL CONCENTRATIONS

RESUMO

Contexto: A insuficiência da veia safena magna (VSM) está entre as principais causas para os sintomas da doença venosa crônica dos membros inferiores. Dependendo do volume e concentração do esclerosante utilizado, a Escleroterapia com Espuma Guiada por Ultrassonografia é capaz de oferecer melhora da qualidade de vida equivalente a outras técnicas. As publicações que estudam os efeitos de diferentes concentrações do esclerosante para o tratamento da VSM são escassas, conferindo certo grau de empirismo à técnica.

Objetivos: Avaliar o impacto das diferentes concentrações de espuma de polidocanol (POL) no tratamento da VSM ≥ 6 mm.

Métodos: É um estudo randomizado, com alocação para tratamento em três grupos. Grupo A (POL 1%), Grupo B (POL 2%) ou Grupo C (POL 3%). O resultado do tratamento foi avaliado segundo o grau de pigmentação, taxa de oclusão, Escala Visual Analógica (EVA) e *Venous Clinical Severity Score* (VCSS). A escleroterapia foi realizada com 8 ml de solução por sessão, limitado a cinco sessões.

Resultados: Foram incluídos 169 membros, CEAP 2 a 5, média de 54,5 (± 12,9) anos, 64,3% sexo feminino. O número de sessões necessárias foi em média 1,9 (Grupo A), 1,6 (Grupo B) e 1,4 (Grupo C), $p = 0,048$. 149 apresentaram oclusão, 18 oclusão parcial e

duas falhas de tratamento, sem diferença entre os grupos e com melhora equivalente de EVA e VCSS. Houve tendência do Grupo A apresentar grande pigmentação.

Conclusões: As três concentrações foram eficazes, entretanto a de 1% requereu mais sessões e apresentou tendência a maior pigmentação.

PALAVRAS-CHAVE: escleroterapia; veia safena; insuficiência venosa; varizes; polidocanol; procedimentos cirúrgicos vasculares.

ABSTRACT

Background: Insufficiency of the great saphenous vein (GSV) is one of the main causes of symptoms of chronic venous disease of the lower limbs. Depending on the volume and concentration of the sclerosant used, ultrasound-guided foam sclerotherapy is capable of offering an improvement in quality of life equivalent to other techniques. Publications that study the effects of different concentrations of sclerosant for treating GSV are scarce, giving a certain degree of empiricism to the technique.

Objectives: To evaluate the impact of different concentrations of polidocanol foam (POL) for treating GSV ≥ 6 mm.

Methods: This was a randomised study with treatment allocation in three groups. Group A (POL 1%), Group B (POL 2%), or Group C (POL 3%). Treatment results were evaluated according to the degree of pigmentation, occlusion rate, Visual Analogue Scale (VAS), and Venous Clinical Severity Score (VCSS). Sclerotherapy was performed with 8 ml of solution per session, limited to five sessions.

Results: 169 limbs were included, CEAP 2 to 5, average 54.5 (± 12.9) years, 64.3% female. The number of sessions required was on average 1.9 (Group A), 1.6 (Group B), and 1.4 (Group C), p = 0.048. A total of 149 patients presented with occlusion, 18 with partial occlusion, and two with treatment failures, with no difference between the groups and with equivalent improvement in VAS and VCSS. There was a tendency for Group A to exhibit high pigmentation.

Conclusions: The three concentrations were effective; however, 1% required more sessions and tended to cause greater pigmentation.

KEYWORDS: sclerotherapy; saphenous vein; venous insufficiency; varicose veins; polidocanol; vascular surgical procedure.

INTRODUÇÃO

A insuficiência da veia safena magna (VSM) está entre as principais causas para os sintomas da doença venosa crônica (DVC) dos membros inferiores.[1,2]

A Escleroterapia com Espuma Guiada por Ultrassonografia (EEGUS) é uma técnica terapêutica que oferece um tratamento minimamente invasivo, rápido, de baixo custo, exclusivamente ambulatorial, sem impacto na rotina diária dos pacientes. Dependendo do volume e concentração do esclerosante utilizado, a EEGUS é capaz de oferecer um tratamento eficaz, com resultados imediatos equivalentes a outras técnicas como a termoablação ou cirurgia convencional da VSM insuficiente.[3,4]

No entanto, ainda são escassas as publicações científicas que estudam os efeitos de diferentes concentrações do esclerosante para o tratamento da VSM, conferindo à técnica da EEGUS certo grau de empirismo e baseando seus resultados predominantemente na experiência do profissional.[5] Esta ausência de parâmetros objetivos oferece algumas dificuldades, principalmente no tratamento das veias de maior calibre e na qualidade dos resultados estéticos da técnica.[6]

O objetivo desse estudo foi avaliar o impacto das diferentes concentrações de espuma de polidocanol (POL) no tratamento com escleroterapia guiada por ultrassonografia da veia safena magna com diâmetro maior ou igual a 6 mm.

MÉTODOS

Esse é um estudo randomizado, unicêntrico e prospectivo para avaliar o impacto da utilização de diferentes concentrações de POL na oclusão da VSM e no resultado clínico do tratamento com EEGUS em pacientes com DVC.

Os pacientes foram selecionados consecutivamente de acordo com os critérios de inclusão e exclusão estabelecidos para o estudo (Tabela 1). Cada membro inferior a

ser tratado foi alocado de forma aleatória em um dos três grupos de tratamento, Grupo A (POL 1%), Grupo B (POL 2%) ou Grupo C (POL 3%), de acordo com a concentração da solução de polidocanol utilizada na EEGUS (Tabela 2). A randomização foi realizada com o aplicativo para Iphone/Ipad *Randomizer for Clinical Trial Unlimited Version* (*Medsharing Solution e-CRF, Fontenay-sous-Bois, FR*). Todos os pacientes foram submetidos a exames clínicos, ultrassonográficos, e à aplicação dos escores clínicos Escala Visual Analógica (EVA) para quantificar a queixa de dor venosa no membro e *Venous Clinical Severity Score* (VCSS) para mensurar a gravidade clínica da DVC antes e após o tratamento com EEGUS.[2,7,8]

O calibre da VSM foi medido pelo mesmo examinador através da ultrassonografia Doppler, com o paciente em posição ortostática no corte transversal em dois segmentos: cinco centímetros abaixo da junção safeno-femoral (JSF) e na linha do joelho (linha J). O diâmetro aceito para inclusão no estudo foi igual ou superior a 6 mm em ambas as medidas em um segmento com extensão de pelo menos 20 centímetros de comprimento.

O tratamento foi realizado com um volume de injeção de solução de POL de no máximo 8 ml por sessão, conforme estabelecido em algumas diretrizes de tratamento, e um limite de cinco sessões com o intervalo entre as sessões de 15±2 dias.[4] A espuma de POL foi administrada diretamente na VSM ou através de uma veia tributária conforme a técnica de Tessari, utilizando a diluição padrão de 1 ml do esclerosante para 4 ml de ar ambiente em concentração que variou de acordo com o grupo de randomização.

A oclusão foi definida como obliteração anatômica completa da VSM pela ultrassonografia Doppler (USD) e o sucesso técnico do tratamento foi considerado quando a VSM estava completamente ocluída ou tornou-se competente ao final da

terapia (ausência de refluxo no decúbito dorsal maior que 1 segundo no modo *Power Doppler*), conforme publicações anteriores sobre a padronização dos resultados.[9–11]

A presença de pigmentação após a escleroterapia foi registrada no momento da alta ambulatorial. Para efeitos de classificação foi categorizada como Grau I (ausência de pigmentação ou pigmentação com extensão menor do que 10 cm no trajeto da VSM) ou Grau II (igual ou maior do que 10 cm de extensão).

Para a análise estatística a comparação das variáveis basais entre os grupos de randomização foi analisada pelo ANOVA de um fator (*one-way*) ou de Kruskal-Wallis (não paramétrico) para dados numéricos, e pelo teste de qui-quadrado ou teste exato de Fisher para dados categóricos. A variação do pré para pós-tratamento foi avaliada pelo teste de Wilcoxon no interior de cada grupo e a diferença entre os grupos foi analisada pelo ANOVA de Kruskal-Wallis. A normalidade na distribuição dos dados foi avaliada pelo teste de Shapiro-Wilk. O critério de determinação de significância adotado foi o nível de 5%. A análise estatística foi processada pelo software SPSS versão 26.

O estudo foi aprovado pelo Comitê de Ética em Pesquisa a que se vinculam os autores (CAAE: 16427719.6.0000.5259 / Número do Parecer: 3.550.511). Não há conflito de interesse a ser declarado.

RESULTADOS

Entre maio de 2019 e maio de 2021, 169 membros (143 pacientes) foram incluídos para tratamento com EEGUS. A média de idade dos participantes foi de 54,5 (± 12,9) anos, variando de 21 a 83 anos, sendo 92 (64,3%) do sexo feminino. Os pacientes tratados foram classificados como C2 (n=46), C3 (n=53), C4 (n=30) e C5 (n=14) com referência à classificação clínica da CEAP. A VSM apresentava diâmetro proximal de 0,92 cm e diâmetro distal de 0,77 cm, em média, antes do tratamento. Os

grupos selecionados foram homogêneos em relação aos dados basais avaliados (Tabela 3).

O número de sessões necessárias para completar o tratamento entre os diferentes grupos foi registrado, sendo em média 1,9 sessões no Grupo A, 1,6 sessões no Grupo B e 1,4 sessões no Grupo C. Houve diferença significativa entre os grupos A e C, quanto ao número de sessões ($p = 0,048$).

Dos 169 membros tratados, 149 apresentaram oclusão completa da VSM, 18 tiveram oclusão parcial da VSM, mas com abolição completa do refluxo, e dois membros permaneceram com a VSM totalmente aberta e com refluxo, sendo considerados falência do tratamento. Não houve diferença estatística quanto à oclusão da VSM após tratamento com EEGUS quando comparamos os três grupos. A proporção de VSM aberta não diferiu significativamente entre os três grupos ($p = 0,78$), mas os 2 casos em que o refluxo persistiu após 5 sessões de tratamento ocorreram no Grupo A (Tabela 4).

A análise dos escores clínicos antes e após a conclusão do tratamento mostrou uma redução absoluta de 65% na escala de dor da EVA e de 48% no VCSS quando considerados todos os grupos tratados (Tabela 5). No entanto, não houve diferença estatisticamente significativa dos resultados clínicos entre os três grupos de tratamento quando utilizamos estes escores (Figuras 1 e 2).

Em relação ao desfecho pigmentação, houve 10 casos de pigmentação Grau II (grande pigmentação) ao longo do trajeto da veia safena magna, sendo 7 casos no Grupo A (11,9%), 1 caso no Grupo B (1,8%) e 2 casos no Grupo C (3,7%). A análise estatística não foi conclusiva, mas sugeriu uma tendência ($p = 0,075$) do grupo com concentrações de POL a 1% ter maior frequência de grande pigmentação, com 11,9% dos casos, quando comparados ao Grupo B e ao Grupo C com 1,8% e 3,7% dos casos

respectivamente. Uma análise do subgrupo dos casos de VSM com calibre acima de 0,8 cm de diâmetro (n=113) também identificou maior frequência de pigmentação no grupo A (4 casos) quando comparados aos grupos B e C (nenhum caso registrado), indicando que pelo menos em VSM de grande calibre essa diferença foi estatisticamente significativa, com *p=0,033* (Tabela 6). Com exceção da presença de pigmentação cutânea, não houve complicações nos procedimentos realizados.

DISCUSSÃO

A eficácia dos tratamentos com espuma de POL já foi demonstrada através da prática clínica e de estudos publicados nos últimos anos.[12,13] Com relação à intervenção da VSM, os cirurgiões vasculares têm deixado cada vez mais de lado a técnica cirúrgica convencional na busca por uma abordagem ambulatorial e menos invasiva.[14]

Embora os resultados do tratamento com espuma de POL sejam inferiores em estudos randomizados quanto à sua durabilidade frente ao uso das técnicas termoablativas, a EEGUS é considerada segura, de baixo custo e eficiente em seus resultados imediatos e na melhora da qualidade de vida dos pacientes no longo prazo.[15,16]

Apesar do uso cada vez mais popular da espuma, ainda não existem protocolos de aplicação bem estabelecidos quanto ao volume, concentração, número de sessões, entre outros parâmetros de tratamento. Diretrizes publicadas recentemente apenas oferecem orientações gerais sobre estes aspectos da técnica.[4] A concentração do fármaco, a técnica de injeção e produção de espuma, e outras variáveis anatômicas como o diâmetro e profundidade das veias, ainda não foram exaustivamente explorados para garantir, com sólidas evidências científicas, a máxima padronização possível e eficácia do método.[5]

Neste estudo, nosso objetivo foi estudar diferentes concentrações de POL para oclusão da VSM insuficiente através da EEGUS, e, avaliar o seu impacto nas taxas de oclusão venosa, nos resultados clínicos imediatos e no número de sessões necessárias às quais o paciente deve ser submetido para seu tratamento.

Considerando o limite estabelecido de cinco sessões para o tratamento, observamos que todas as concentrações utilizadas foram eficazes no fechamento da VSM. Esses achados estão de acordo com os resultados de outros autores.[17–19] A análise dos grupos apontou para redução estatisticamente significativa da EVA e do VCSS após os tratamentos, sem diferença entre os grupos. Ao avaliar os pacientes incluídos no estudo, houve melhora de 65% na escala de dor (EVA) e de 48% no VCSS, consistente com o encontrado na prática clínica e em estudos com espuma POL.[2,20,21]

Artigos de revisão demonstraram a segurança e eficácia da técnica de escleroterapia com espuma guiada por USD e a raridade de efeitos colaterais, seja utilizada como terapia única ou associada a outras técnicas.[22–24] Em nosso estudo não foi diferente, com ausência de complicações graves.

Contudo, para atingir os mesmos resultados satisfatórios, foi necessário realizar mais sessões de tratamento quando utilizamos o POL na concentração a 1% (Grupo A) em comparação ao Grupo C (3%), com diferença estatisticamente significativa ($p=0,015$). Quando a concentração utilizada foi a de POL 3%, 66,7% dos casos necessitaram apenas de uma única sessão, enquanto no Grupo A (1%), em 59,3% dos tratamentos foram necessárias duas ou mais sessões. Em outros estudos publicados comparando concentrações de 1% e 3% não houve diferença nos resultados de oclusão da VSM com a espuma de POL.[17–19] Tanto no artigo publicado por Blaise *et al*. quanto na publicação de Hamel-Denos *et al*., o diâmetro das veias tratadas foi limitado a 8 mm, e pode ter influenciado nos resultados apresentados. No presente estudo foram tratadas

veias safenas com diâmetro de até 2,4 cm, portanto, é intuitivo que houvesse necessidade de mais injeções de espuma. Entretanto, não houve diferença estatística na comparação entre os Grupos B (POL 2%) e C (POL 3%) quanto ao número de sessões necessárias, ou seja, as duas concentrações obtiveram resultados clínicos similares.

Por fim, observamos a maioria dos casos de grande pigmentação ao longo do trajeto da veia safena magna no Grupo A (POL 1%). A análise estatística não foi conclusiva, mas sugeriu uma tendência do subgrupo com concentração de POL 1% a apresentar mais pigmentação ($p=0,075$). Quando analisamos um subgrupo de casos com VSM de grande calibre, esta diferença tornou-se mais evidente, com diferença estatística significativa ($p=0,033$).

A pigmentação após o tratamento com espuma POL sempre foi vista como uma das fragilidades desta técnica. A incidência de hiperpigmentação é muito variada na literatura médica e depende do modelo de avaliação e do tipo de vaso tratado. Uma meta-análise recente apresentou uma superposição de resultados. A incidência de pigmentação de troncos venosos encontrada ficou entre 7% e 45,8% para POL a 1% (líquido ou espuma), entre 16% e 17% para POL a 2% (espuma) e entre 7,4% e 32,5% para concentrações de POL a 3% (líquido ou espuma).[25]

Estes resultados conflitantes estão relacionados a metodologias de estudo diversas, diferentes vieses de seleção não analisados, mas sobretudo pela dificuldade de aplicação de um método objetivo para quantificar o grau de pigmentação cutânea.[26] Esta dificuldade está presente neste estudo, onde nos limitamos a mensurar a extensão das manchas cutâneas e dividir apenas em dois grupos para facilitar a análise estatística.

De modo geral, a hiperpigmentação parece estar associada a concentrações maiores do POL e ser mais comum em veias epifasciais. Por outro lado, não há tanta certeza com relação a outros fatores como a compressão pós-procedimento e volume de

esclerosante.[25] Também não há informações sobre o efeito do número de sessões sobre o risco de dano à pele. É plausível que a maior frequência de pigmentação cutânea encontrada no Grupo A (1%) possa estar associada ao maior número de sessões realizadas com essa concentração de esclerosante, gerando uma resposta inflamatória continuada nesses pacientes durante o tratamento mais prolongado, especialmente com intervalos de tempo menores entre as sessões.

Considerando os resultados que encontramos, a concentração de POL 2% parece ser a melhor opção entre as concentrações analisadas, devido à associação de bom resultado clínico, menor número de sessões e baixa incidência de pigmentação cutânea pós-tratamento, ainda que na prática, os resultados com o POL em concentrações de 2% e 3% tenham sido similares.

Por outro lado, a concentração de POL 1%, embora tenha obtido resultados clínicos de oclusão da VSM e redução dos escores de dor e severidade clínica similares aos outros dois grupos, foi associada a um maior número de sessões e maior frequência de pigmentação cutânea, sobretudo em VSM mais calibrosas. Portanto não parece ser uma boa alternativa no tratamento de VSM insuficientes maiores que 8 mm de diâmetro nos participantes desse estudo.

Este trabalho não pretende definir uma concentração ideal para o tratamento com espuma densa da VSM insuficiente. A boa técnica sempre vai exigir o criterioso julgamento por parte do médico assistente na análise dos parâmetros individuais e na definição da melhor estratégia de intervenção, aspectos que dependem sobretudo de experiência do profissional. Esperamos, contudo que os nossos dados forneçam subsídios para o melhor entendimento do impacto das diferentes concentrações de POL na EEGUS para o tratamento da DVC, sempre em busca de melhores resultados.

O presente estudo tem algumas limitações. Considerando que os dados apresentados se referem aos resultados imediatos do tratamento com espuma, não foi possível avaliar as taxas de recanalização da VSM após um seguimento de tempo maior. É provável que a concentração do POL esteja diretamente relacionada ao resultado da ablação no longo prazo. Tampouco é possível fazer afirmações categóricas sobre a hipótese levantada de que a pigmentação cutânea esteja de fato relacionada ao maior número de sessões necessárias para o tratamento com espuma, levando-se em conta que outras variáveis podem coexistir como a coloração cutânea, a profundidade do vaso na pele, o que torna necessários outros estudos para elucidar esses e outros aspectos da técnica em busca de mais qualidade e menos empirismo na utilização da EEGUS.

CONCLUSÃO

Este estudo demonstrou que as concentrações de espuma utilizadas de POL a 1%, 2% e 3% foram eficazes no tratamento da insuficiência da veia safena magna e obtiveram resultados semelhantes na melhora dos escores de dor venosa (EVA) e de severidade clínica (VCSS). No entanto, a concentração de 1% de POL esteve associada a um maior número de sessões e sugere uma tendência a pigmentação mais frequente, pelo menos em VSM de maior calibre.

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TABELA 1. Critérios de inclusão e exclusão dos participantes do estudo.

Critérios de Inclusão	Critérios de Exclusão
• idade superior a 18 anos; • apresentar DVC com classificação clínica CEAP C2, C3, C4, C5 ou C6; • apresentar insuficiência safena magna proximal multissegmentar ou difusa com diâmetro maior ou igual a 6 mm em segmento superior a 20 cm de comprimento; • assinar o termo de consentimento livre e esclarecido.	• trombose venosa profunda aguda, trombose venosa profunda crônica sem recanalização, doença varicosa não associada à insuficiência da veia safena magna; • pacientes que já foram submetidos a cirurgia prévia de varizes das veias safenas; • pacientes com diagnóstico de trombofilia; • neoplasia ativa ou câncer em tratamento, doenças pulmonares; • doença arterial periférica com índice tornozelo-braço inferior a 0,8.

Nota: DVC: doença venosa crônica.

TABELA 2. Grupos de randomização para tratamento de acordo com a concentração de polidocanol (n=169).

Grupo A – 59 membros tratados com espuma de polidocanol a 1%
Grupo B – 56 membros tratados com espuma de polidocanol a 2%
Grupo C – 54 membros tratados com espuma de polidocanol a 3%

TABELA 3. Características dos grupos de randomização (n=169).

Variável	Grupo A (1%)		Grupo B (2%)		Grupo C (3%)		*p valor*
Sexo – n (%)							
Masculino	17	28,8	23	41,1	22	40,7	0,29
Feminino	42	71,2	33	58,9	32	59,3	
Idade (anos)	55,3 ± 11,5		54,6 ± 13,9		53,6 ± 13,2		0,79
EVA	8	5–9	7,5	5–8	8	5–9	0,95
VCSS	6	5–11	7	5–9	6	5–10	0,97
Membro Tratado – n (%)							
MID	26	44,1	24	42,9	28	51,9	0,59
MIE	33	55,9	32	57,1	26	48,1	
Diâmetro da VSM (cm)							
Safena Proximal	0,83	0,72–1,03	0,85	1,72–1,00	0,82	0,72–1,04	0,92
Safena Distal	0,76	0,62–0,90	0,75	0,60–0,94	0,74	0,64–1,00	0,80
VSM > 8mm – n (%)							
Sim	40	67,8	36	64,3	37	68,5	0,87
Não	19	32,2	20	35,7	17	31,5	
Total de sessões – n (%)							
1	24	40,7	33	58,9	36	66,7	
2	25	42,4	15	26,8	15	27,8	***0,048***
3 a 5	10	16,9	8	14,3	3	5,6	

Nota: EVA: Escala Visual Analógica; VCSS: *Venous Clinical Severity Score*; MID: membro inferior direito; MIE: membro inferior esquerdo; VSM: veia safena magna; n: membros incluídos; %: percentual dentro do grupo; cm: centímetros; mm: milímetros. *p valor* significativo se < 0,05.

TABELA 4. Desfecho pós-tratamento segundo o grupo de randomização (n=169).

Variável	Grupo A (1%)		Grupo B (2%)		Grupo C (3%)		*p valor*
Oclusão da VSM – n (%)							
aberta	6	10,2	5	8,9	7	13,0	0,78
ocluída	53	89,8	51	91,1	47	87,0	
Pigmentação – n (%)							
Grau I	52	88,1	55	98,2	52	96,3	*0,075*
Grau II	7	11,9	1	1,8	2	3,7	

Nota: VSM: veia safena magna; n: membros incluídos; %: percentual dentro do grupo; p valor significativo se < 0,05.

TABELA 5. Escores clínicos pré e pós-tratamento conforme o grupo de randomização (n=169).

Variável	Pré-tratamento		Pós-tratamento		Diferença (Pós-Pré)		*p valor**	*p valor*†
	Mediana	IIQ	Mediana	IIQ	Mediana	IIQ		
EVA								
Grupo A (1%)	8	5–9	1	0–5	-4	-7– -2	<0,000 1	0,75
Grupo B (2%)	7,5	5–8	1	0–5	-5	-7,8– -2	<0,000 1	
Grupo C (3%)	8	5–9	0,5	0–5	-4	-8 – -1,8	<0,000 1	
VCSS								
Grupo A (1%)	6	5–11	3	2–5	-3	-6– -2	<0,000 1	0,80
Grupo B (2%)	7	5–9	3	2,3–5	-3	-5– -2,3	<0,000 1	
Grupo C (3%)	6	5–10	4	2–5,3	-3	-5– -2	<0,000 1	

Nota: EVA: Escala Visual Analógica; VCSS: *Venous Clinical Severity Score*. *Teste dos postos sinalizados de Wilcoxon para comparação entre pré e pós cirurgia no interior de cada grupo. †ANOVA de Kruskal-Wallis para comparação do delta (pós-pré) entre os grupos; *p valor** – valor individual de cada grupo; *p valor*† – p de comparação entre os grupos. Os dados numéricos foram expressos pela mediana e intervalo interquartílico. p valor significativo se < 0,05.

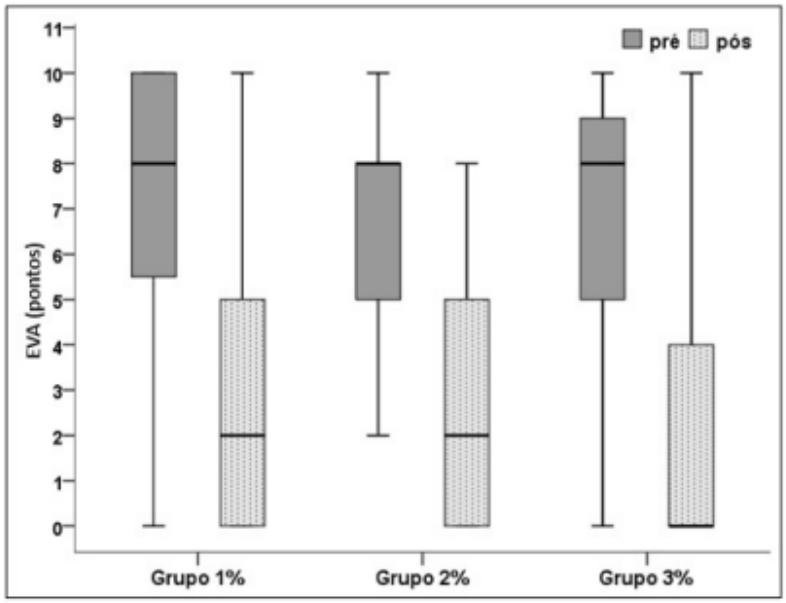
TABELA 6. Desfechos pós-tratamento em análise do subgrupo de veias safenas magnas de grande calibre (maiores que 8mm de diâmetro) conforme os grupos de randomização (n=113).

Variável	Grupo A (1%)		Grupo B (2%)		Grupo C (3%)		*p valor*
Oclusão da VSM – n (%)							
aberta	5	12,3	2	5,6	4	10,8	0,62
ocluída	35	87,5	34	94,4	33	89,2	
Pigmentação – n (%)							
Grau I	36	90,0	36	100	37	100	***0,033***
Grau II	4	10,0	0	0	0	0	

Nota: VSM: veia safena magna; n: membros incluídos; %: percentual dentro do grupo; p valor significativo se < 0,05.

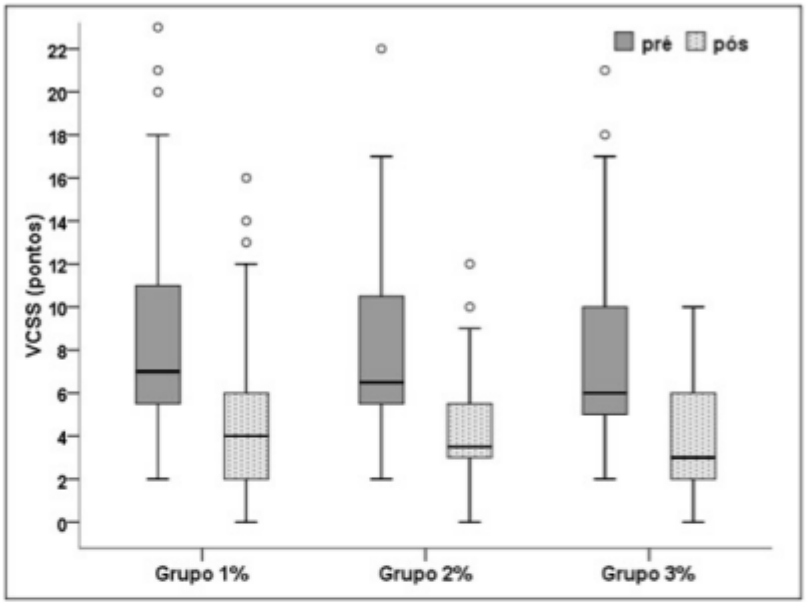
FIGURA 1. Resultados pré e pós-tratamento da Escala Visual Analógica para dor venosa conforme os grupos de randomização.

FIGURA 2. Resultados pré e pós-tratamento do *Venous Clinical Severity Score* conforme os grupos de randomização.



Resultados pré e pós-tratamento da Escala Visual Analógica para dor venosa conforme os grupos de randomização.

111x85mm (120 x 120 DPI)



Resultados pré e pós-tratamento do Venous Clinical Severity Score conforme os grupos de randomização.

114x85mm (120 x 120 DPI)

ANEXO A – Escala Visual Analógica (EVA) / *Visual Analogue Scale* (VAS)

HAWKER, G. A. et al. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36). **Arthritis care & research**, v. 63 Suppl 1, n. SUPPL. 11, p. S240-52, nov. 2011.

ANEXO B - Escore de Severidade Clínica Venosa / *Venous Clinical Severity Score* (VCSS)

Parâmetro	Ausente (0)	Leve (1)	Moderado (2)	Severo (3)
Dor ou outro desconforto ligado a doença venosa	Não	Ocasional	Sintomas Diários, interferindo, mas não impedindo as atividades rotineiras	Sintomas diários limitando a maioria das atividades rotineiras
Veias varicosas	Não	Poucas, dispersas, inclui a coroa flebectásica	Limitadas a panturrilha ou coxa	Envolvendo panturrilha e coxa
Edema de origem venosa	Não	Limitado ao pé e tornozelo	Acima do tornozelo mas abaixo do joelho	Até o joelho ou acima
Hiperpigmentação	Não	Limitada a área perimaleolar	Difusa e até o terço inferior da perna	Distribuição ampla (acima do terço inferior da perna)
Inflamação	Não	Limitada a área perimaleolar	Difusa e até o terço inferior da perna	Distribuição ampla (acima do terço inferior da perna)
Endurecimento	Não	Limitada a área perimaleolar	até o terço inferior da perna	Acima do terço distal da perna
Número de úlceras abertas	Não	1	2	>2
Duração da úlcera	Não	<3 meses	>3meses mas <1 ano	>1 ano
Tamanho da úlcera	Não	<2cm	2 a 6 cm	>6 cm
Terapia de compressão	Não utilizada	Uso intermitente	Uso na maioria dos dias	Uso diário

BACON, J. **Adaptação Transcultural do Revised Venous Clinical Severity Score para o Português do Brasil e Aplicabilidade na Atenção Primária**. [s.l.] Universidade do Vale do Sapucaí, 2017.

ANEXO C – Comprovante de submissão do artigo “Estudo clínico randomizado do impacto da escleroterapia com espuma ecoguiada da veia safena magna com diferentes concentrações de polidocanol”

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Estudo Clínico Randomizado do Impacto da Escleroterapia com Espuma Ecoguiada da Veia Safena Magna com Diferentes Concentrações de Polidocanol

Journal:	*Jornal Vascular Brasileiro*
Manuscript ID	JVB-2024-0036
Manuscript Type:	Original Article
Keyword--Select your keywords from the list available here.:	escleroterapia, veia safena, insuficiência venosa, varizes, polidocanol, procedimentos cirúrgicos vasculares

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