Efficacy and safety of polidocanol in the treatment of varicose veins of lower extremities

A protocol for systematic review and meta-analysis

Nan Li, MM†, Junhai Li, MB, Mei Huang, MB, Xiujun Zhang, MB

Abstract

Background: The varicose veins of the lower extremities showed earthworm-like dilatation and venous protrusion of the lower extremities. Polidocanol foam sclerotherapy, as a minimally invasive treatment with rapid recovery, less trauma and not easy to relapse, has achieved good results in clinical, but it is lack of evidence-based medicine. The purpose of this study is to evaluate the efficacy and safety of polidocanol in the treatment of varicose veins of the lower extremities by meta-analysis.

Method: Chinese National Knowledge Infrastructure, Wanfang Database, Chinese Scientific Journals Database, China Biology Medicine disc, PubMed, EMBASE database, Web of Science, and Cochrane Library will be used as search sources to conduct for randomized controlled trials of polidocanol in the treatment of varicose veins of lower extremities. The search time is set from the establishment of the database in December 2020 in this study. Two researchers independently extract, delete files, extract data and evaluate the quality. Revman software version 5.3 will be used for statistical analysis of data.

Result: In this study, the efficacy and safety of polidocanol in the treatment of varicose veins of the lower extremities will be evaluated in terms of total effective rate, incidence of complications and recurrence rate.

Conclusion: This study will provide reliable evidence-based evidence for the clinical application of polidocanol in the treatment of varicose veins of lower extremities.

Ethics and dissemination: Private information from individuals will not be published. This systematic review also does not involve endangering participant rights. Ethical approval will not be required. The results may be published in a peer-reviewed journal or disseminated at relevant conferences.

OSF Registration number: DOI 10.17605/OSF.IO/AUR4X.

Abbreviations: CBM = China biology medicine disc, CI = confidence interval, MD = mean difference, RR = risk ratio, VIP = Chinese scientific journals database.

Keywords: meta-analysis, polidocanol, RCTs, varicose vein of lower limb

1. Introduction

Varicose veins of lower extremities are a common vascular surgical disease. It is usually characterized by the heaviness, pulsation and pain of the lower extremities, which can be observed. Lower limb swelling, venous dilatation, late pigmentation, fatty skin sclerosis and ulcers and other symptoms.[1] It affects more than 20% of the population in developed countries.[2] Its treatment brings serious economic pressure. Due to the lack of understanding of this disease, Chinese patients only receive treatment when they develop into severe venous disease, while Europe and the United States tend to be hospitalized early to prevent serious complications.[3] Varicose veins of lower extremities are mainly caused by valvaral insufficiency, weak vein wall and increased pressure of superficial vein.[4] Muscle pump plays a certain role in it. When muscle pump failure is caused by sedentary, neuromuscular degenerative diseases and obesity, it will aggravate venous stagnation and increase venous pressure.[5]

The treatment of varicose veins of the lower extremities includes conservative treatment, open surgery and minimally invasive treatment.[6] Conservative treatment includes taking blood-activating drugs, air pressure therapy, wearing medical elastic socks, raising the affected limbs, changing bad living habits, and so on. These treatments can temporarily relieve the symptoms of patients, but cannot solve the fundamental problem.[7] Open surgery includes high ligation and venous exfoliation, which are mostly used for the treatment of trunk veins such as great saphenous vein. However, this treatment will
make patients feel huge pain and residual surgical scars, as well as higher treatment costs and longer hospital stay. Minimally invasive surgery includes intracaval radiofrequency ablation, laser ablation and sclerotherapy. In the late 1980s, the introduction of ultrasound technology brought sclerotherapy into people's field of vision. Because of its accuracy and safety, it has been popularized. Singh et al. show that foam sclerotherapy has less side effects and good contact with the blood vessel wall, so it is the first choice for treatment. Oliveira et al. show that foam sclerotherapy reduces the use of anesthesia and shortens the time of hospitalization and bed rest after treatment.

At present, there are a number of randomized controlled studies. The results show that polidocanol in the treatment of varicose veins of the lower extremities can significantly relieve symptoms and improve the appearance of legs, eliminate venous reflux and reduce vein diameter, and the operation method is simple and quick, the postoperative recovery is fast, and the adverse events are mild and short-lived. However, there are differences in the research scheme and curative effect of each clinical trial, which leads to uneven results. Therefore, this study plans to systematically evaluate the efficacy and safety of polidocanol in the treatment of varicose veins of the lower extremities, and to provide reliable evidence-based basis for the clinical application of polidocanol in the treatment of varicose veins of lower extremities.

2. Methods

2.1. Protocol register

This study protocol of systematic review and meta-analysis has been drafted under the guidance of the preferred reporting items for systematic reviews and meta-analyses protocols (PRISMA-P). And, it has been registered on open science framework (OSF) (Registration number: DOI 10.17605/OSF.IO/AUR4X).

2.2. Ethics

Since all the data used in this study have been published, there is no need to collect personal information, so the approval of the Ethics Committee is not required. In addition, all data will be anonymously analyzed during the review process.

2.3. Eligibility criteria

2.3.1. Types of studies. Randomized controlled trials of polidocanol in the treatment of polidocanol in the treatment of lower extremities will be included. The literature language is limited to Chinese and English. There is no special requirement that it is single-blind or double-blind.

2.3.2. Research objects. Patients are diagnosed with varicose veins of the lower extremities. The nationality, race, sex and severity of the patients included in the study are not limited, and the incidence of unilateral or bilateral lower extremities will not be limited.

2.3.3. Interventions. The intervention measures of the treatment group are polidocanol or polidocanol combined treatment, and the control group is other treatment methods, the specific treatment will not be limited.

2.3.4. Outcome indicators. Main outcome: Total effective rate: (markedly effective number + effective number) / total (markedly effective CEAP grade rises ≥ grade, clinical symptoms are significantly improved; effective CEAP grade is unchanged. Clinical symptoms were significantly improved.)

Secondary outcome:
(1) incidence of operative complications (subcutaneous congestion, sensory numbness, subcutaneous fat liquefaction infection, skin burn, phlebitis, etc),
(2) intraoperative bleeding volume;
(3) recurrence rate.

2.4. Exclusion criteria

(1) Republished literature.
(2) There is no control group in the original literature.
(3) The outcome index does not meet the requirements.
(4) The data of the article are incomplete, so contact the literature which is still not available to the author.

2.5. Search strategy

Chinese databases (CNKI, Wanfang, Chinese Scientific Journals Database, China Biomedical Database) and English databases (PubMed, EMBASE, Web of science, Cochrane Library) will be searched by computer. The search time is set from the establishment of the database to December 2020 in this study, and all the domestic and foreign literature on the treatment of varicose veins of lower extremities will be collected. Chinese search words are “polidocanol,” “laurothamnogol,” “varicose veins of lower extremities” and so on. English search words are “polidocanol”, “lauromacrogol,” “varicose vein” and so on. Take PubMed as an example, the retrieval strategy is shown in Table 1.

2.6. Data screening and extraction

All the documents are included in EndnoteX9 software. After excluding duplicate documents, the 2-person independent extraction method will be used. According to the above-mentioned inclusion and exclusion criteria, documents that are inconsistent with the research theme will be excluded after reading the title and abstract of the document and carefully reading the full text. Cross-check, and resolve the differences through consensus after discussion. The data extracted include:
the name of the first author, the year of publication, the number of cases in each group, intervention and control measures, outcome indicators, and so on. The screening process is shown in Figure 1.

2.7. Literature quality evaluation

The Cochrane Collaboration network tool will be used to evaluate the quality of the included research. The 2 researchers independently evaluate the literature according to 6 aspects: selection bias, implementation bias, measurement bias, follow-up bias, reporting bias and other biases. The evaluation results can be divided into 3 situations: low risk, high risk and unclear. Cross-check and agree with the third party in case of inconsistency.

2.8. Statistical analysis

2.8.1. Data analysis and processing. Revman software version 5.3 will be used for statistical analysis of data. The $\chi^2$ test will be used for heterogeneity among studies. If $I^2 \leq 50\%$, $P \geq .1$, the heterogeneity results are not statistically significant, and meta-analysis uses a fixed effect model; if $I^2 > 50\%$, $P < .1$, indicating that there is heterogeneity, then look for the causes of heterogeneity, and if possible, conduct a subgroup analysis of heterogeneity factors. If there is only statistical heterogeneity among the studies, but no clinical heterogeneity or no clinical significance, the random effect model is used. The risk ratio statistical analysis will be used for the classified data, and mean difference will be used for the continuous variables, and the 95% confidence interval will be calculated for all the analyses. If the number of studies included is more than 10, a funnel chart is drawn and publication bias is analyzed.

2.8.2. Dealing with missing data. If there are missing data in the article, contact the author by phone or email and complete the data before analysis. If the author cannot be contacted, or if the author has lost the relevant data, no meta-analysis will be performed.
2.8.3. Subgroup analysis. Subgroup analysis will be performed according to CEAP stages of C2, C3, C4, C5 and C6; subgroup analysis will be performed according to the number of varicose limbs in unilateral group and bilateral group; subgroup analysis will be carried out according to the course of treatment.

2.8.4. Sensitivity analysis. Select another research index and change different analysis models to test the stability of the research results.

2.8.5. Assessment of reporting biases. The funnel chart is used to detect the publication offset of each of the above indicators. Publication bias was detected according to whether both sides of the funnel chart are symmetrical.

2.8.6. Evidence quality evaluation. The GRADE scale is used to evaluate the quality of evidence. It includes 5 aspects: bias risk, consistency, directness, accuracy and publication bias. The quality of the evidence will be classified as high, medium, low and very low.

3. Discussion

The symptoms of varicose veins in the lower extremities range from mild symptoms such as fatigue, heaviness, itching, leg restlessness, to severe diseases such as edema, skin fat sclerosis and ulcers, which seriously affect people’s quality of life. Some studies have shown that varicose veins have a substantial effect on the function and psychology of patients.[17] More than 1/3 people said their work was affected, and more than half said their standing or sitting activities was affected. In addition, physical function and psychological effects of people with higher-than-average symptoms were more obvious. The anatomical and pathophysiological causes of clinical lesions are fluidity venous hypertension caused by venous valve reflux, venous flow obstruction or both.[18] Pathophysiological characteristics of cell level are hypoxia, imbalance of apoptosis and changes of extracellular matrix.[19] Not only is the quality of life affected, the presence of varicose veins also increases the risk of superficial venous thrombosis and venous thrombembolism disease.[20]

Polidocanol sclerotherapy is injected into the varicose vein to damage the vein endothelium, and then falls off to form thrombus, resulting in vein wall hypoxia secondary inflammation, granulation tissue formed by fibrosis growth, varicose vein closure, and finally the formation of fiber cord, to achieve the purpose of treatment.[21] And polidocanol belongs to ether compounds, which has anesthetic effect to a certain extent and can reduce the pain response of the body.[22] Although sclerotherapy was originally liquid sclerotherapy. It gradually evolved into foam sclerotherapy. Because the liquid mixes with the blood quickly, the preparation is diluted, inactivated and passivated. Compared with liquid preparation, foam preparation can avoid mixing with intravascular blood and dislocation with target vessels. [23] Foam hardener refers to the gas-liquid equilibrium preparation made by fully mixing liquid polidocanol with a certain proportion of air or carbon dioxide.[24] Wan Xia et al reported that the therapeutic effect of polycinnamyl alcohol foam sclerotherapy was not inferior to that of intravascular electrocoagulation and routine excision, and reduced the recurrence rate.[25–26] However, there are also some complications in the course of treatment, such as pigmentation, pain at the injection site, superficial thrombo- phlebitis, local induration of injection, transient dry cough and so on.[27] The European Association for foam Sclerosing Therapy recommends that the safe dosage of foaming sclerosing agent is 6 to 8mL, and the conventional dosage is 40mL within.[28] Serious adverse reactions can be avoided by controlling the dosage.

We hope to conduct a meta-analysis of the existing randomized controlled trials of polidocanol in the treatment of varicose veins of lower extremities, objectively evaluate its safety and efficacy, and provide reliable evidence-based basis for clinical application. However, due to the lack of a large number of books and high-quality randomized controls, the follow-up time is generally short. The therapeutic effect of polidocanol on Varicose veins of lower extremities still needs to further expand the sample size, improve the research quality, prolong the follow-up time and so on. Due to the limitation of language ability, we only search English and Chinese literature and may ignore studies or reports in other languages.

Author contributions

Data collection: Nan Li and Junhai Li.
Funding support: Xiujun Zhang.
Resources: Junhai Li and Mei Huang.
Software operating: Mei Huang and Xiujun Zhang.
Supervision: Mei Huang.
Writing – original draft: Nan Li and Junhai Li.
Writing – review & editing: Nan Li and Xiujun Zhang.

References

[1] Hua WR, Yi MQ, et al. Causes of recurrent lower limb varicose veins after surgical interventions in 141 limbs—Five-year retrospective analysis of two centers. Vascular 2017;25(3):263-65.
[2] Shadrina AS, Smetanina MA, et al. Polymorphism of matrix metalloproteinases Genes MMP1, MMP2, MMP3, and MMP7 and the risk of varicose veins of lower extremities. Bulletin of Experimental Biology and Medicine 2017;163:650–4.
[3] Wang J-C, Li Y, et al. A comparison of concomitant tributary laser ablation and foam sclerotherapy in patients undergoing truncal endovenous laser ablation for lower limb varicose veins. Vascular and Interventional Radiology 2018;29:781–9.
[4] Liu Z-X, Guo P-M, Zhang, et al. Efficacy of endovenous laser treatment combined with sclerosing foam in treating varicose veins of the lower extremities. Advances in Therapy 2019.
[5] Attaran R. Latest innovations in the treatment of venous disease. Journal of Clinical Medicine 2018;7(7).
[6] Lwaetemz, serupj, lawaetab, etal. comparision of endovenous ablation techniques,foam sclerotherapy and surgical stripping for great saphenous varicose veins:extended 5 year follow up of a rct[J]. angiol, 2017, 36(3): 281–288.
[7] Tasse J, Scotland G, Brittenden J, et al. Cost-effectiveness of ultrasound-guided foam sclerotherapy, endove-nous laser ablation or surgery as treatment for pri-marly varicose veins from the randomized CLASTrial. Br J Surg 2014;101:1532–40.
[8] Star P, Connor DE, Parsi K. Novel developments in foam sclerotherapy: focus on varithena® (polidocanol endovenous microfoam) in the management of varicose veins. Phlebology 2017;33:150–62.
[9] Maurya K, Singh S, V, et al. Outcome of ultrasound guided foam sclerotherapy treatment for varicose veins: procedure is standard and need no further study. Vascular and Endovascular Surgery 2015;5:96–100.
[10] de Oliveira RG, Morais Filho, et al. Foam sclerotherapy for lower-limb varicose veins: impact on saphenous vein diameter. Radiology Brasileira 2018;53:371–5.
[11] Gibson K, Kabnick L. A multicenter, randomized, placebo-controlled study to evaluate the efficacy and safety of Varithena® (polidocanol endovenous microfoam 1%) for symptomatic, visible varicose veins with saphenofemoral junction incompetence. Phlebology 2016;32:185–93.
[12] Vasquez M, Gasparis AP. A multicenter, randomized, placebo-controlled trial of endovenous thermal ablation with or without polidocanol endovenous microfoam treatment in patients with great saphenous vein

4
incompetence and visible varicosities. Phlebology: The Journal of Venous Disease 2016;32:272–81.

[13] Min Dai, Xinglong Yang, Qiang Liu. Application of lauromacrogol in varicose veins. Journal of Molecular Imaging 2016;39:144–6.

[14] Juan Chen, Yunhong Yang, Bing Fan, et al. Effect contrast of foam sclerotherapy of lauromacrogol and high ligation of great saphenous vein for varicose vein of lower extremity. China Medical Herald 2015;12:78–84.

[15] Gangyi Lin, Xianyuan Ma, Zongyang Cai. Clinical efficacy and safety of DSA-guided polidocanol foam sclerotherapy for the treatment of mild to moderate varicose veins of lower extremity. Clinical Medical & Engineering 2019;26:1647–8.

[16] Kundu S, Lure F, Millward SF, et al. Recommended reporting standards for endovenous ablation for the treatment of venous insufficiency: joint statement of the American Venous Forum and the Society of Interventional Radiology. J Vasc Interv Radiol 2009;20(7 Suppl):S417–424.

[17] Mallick R, Lal BK, Daugherty C. Relationship between patient-reported symptoms, limitations in daily activities, and psychological impact in varicose veins. Journal of Vascular Surgery: Venous and Lymphatic Disorders 2017;5:224–37.

[18] Youn YJ, Lee J. Chronic venous insufficiency and varicose veins of the lower extremities. The Korean Journal of Internal Medicine 2019;34:269–83.

[19] Jacobs BN, Andraska EA, Obi AT, et al. Pathophysiology of varicose veins. Journal of Vascular Surgery: Venous and Lymphatic Disorders 2017;5:460–7.

[20] Pannucci CJ, Shanks A, Moore M, et al. Identifying patients at high risk for venous thromboembolism requiring treatment after outpatient surgery. Ann Surg 2012;255:1093–9.

[21] Fengying Wu. Observation on the efficacy of foam sclerosing agent polycinnamol injection in the treatment of varicose veins of lower extremities. China Reflexology 2019;21:133–4.

[22] Chen Luo, Jun Zhou. Application status and research progress of polycinnamol sclerotherapy. Bachu Medical Journal 2020;3:114–7.

[23] Connor DE, Cooley-Andrade O, Goh WX, et al. Detergent sclerosants are deactivated and consumed by circulating blood cells. Eur J Vasc Endovasc Surg 2015;49:426–31.

[24] Guangqi Chang, Junhui Chen, et al. Expert Consensus on Lauromacrogol Injection in the Treatment of Microcirculation of Varicose Vein of Lower Limb. Journal of Vascular and Endovascular Surgery 2020;6:377–81.

[25] Xia Wan. Comparison of intracavitary electrocoagulation and polycinnamyl alcohol foam sclerosing in the treatment of varicose veins of lower extremities. Contemporary Medicine Forum 2018;16:74–5.

[26] Li Wang, Feng Dai. Comparison of ultrasound-guided polidocanol foam sclerosing agent and conventional peeling in the treatment of varicose great saphenous vein. Henan Medical Research 2019;28:1027–8.

[27] Frullini A, Da Pozzo E, Felice F, et al. Prevention of excessive endothelin-1 release in sclerotherapy: in vitro and in vivo studies. Dermatol Surg 2014;40:769–75.

[28] Xue-gang Wang, Dou Bai. Treatment of varicosis of great saphenous vein by high ligation combined with foam sclerotherapy injection. Practical Journal of Clinical Medicine 2015;12:103–4.