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Effectiveness of Sclerotherapy, Surgery, and Laser Therapy in Patients With Venous Malformations: A Systematic Review

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Abstract
Purpose Because the best possible treatment for venous malformations is unclear, this study systematically reviews the available literature regarding the effectiveness of different treatment options for the patient group. Venous malformations result from incorrect development of the veins during embryogenesis and are present at birth. Venous malformations may exhibit symptoms, such as pain, swelling, and inflammation of the vessel.
Materials and Methods A systematic literature search in PubMed and Embase was performed. Data regarding the design, participants, intervention and, treatment outcome (success and complications) were extracted. The validity of the studies was assessed with the Cochrane Collaboration's risk of bias tool.
Results Thirty-five studies were identified studying the effectiveness of eight treatments: sclerotherapy/embolization with ethanol, gelified ethanol, bleomycin, polidocanol, sodium tetradecyl sulfate (STS), Ethibloc, surgery, and laser therapy. All of the included studies have a high or unclear risk of bias. The average biased reported success rates for ethanol, gelified ethanol, bleomycin, polidocanol, STS, Ethibloc, surgery, and laser therapy were 74, 89, 88, 90, 86, 65, 90, and 94 %, respectively.
Conclusion Until more valid evidence is available, the choice for treatment remains a shared decision between the patient and a multidisciplinary treatment group. From a cost perspective, sclerotherapy with STS or polidocanol should be the treatment of choice.

Keywords Venous malformation · Systematic review · Sclerotherapy · Laser

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Introduction

Venous malformations (VMs) are the most common vascular malformations and are a result of errors in vascular morphogenesis. A VM is present at birth, although symptoms may arise in later life and will never regress [1–5]. VMs may be present in the head and, neck area (40 %), limbs (40 %) and trunk (20 %) [3, 6, 7]. Symptoms vary and include cosmetic complaints localized intravascular coagulopathy, pain, swelling, and functional limitations [4, 5, 7, 8]. In some patients, symptoms may be mild necessitating no or only conservative measures. Patients with severe symptoms may require an active and more aggressive approach.

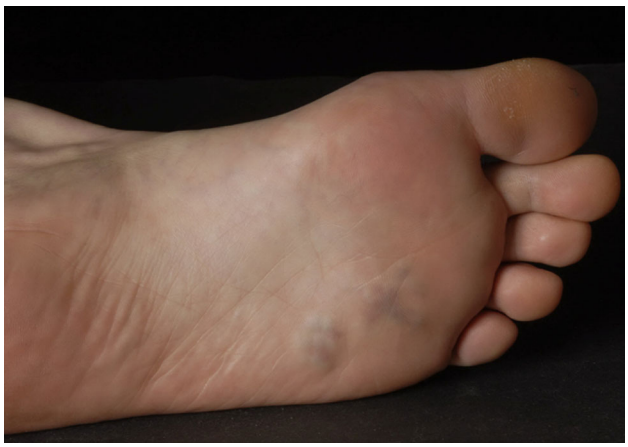

Fig. 1 A 39-year-old female with a VM characterized by a livid, compressible swelling, 1.5 × 4 cm in diameter, on the plantar side of the left foot

A typical case of VM is presented in Figs. 1 and 2. These figures concern a 39-year-old woman with congenital bluish swelling on the bottom of her left foot (Fig. 1). Her family history was negative for glomuvenous malformation. The lesions could typically be emptied when she raised the leg. During puberty and pregnancy, her symptoms increased. She had swelling and pain both spontaneously and during walking. Laboratory investigations showed normal d-dimer levels. Ultrasound (US) and magnetic resonance imaging (MRI) investigations were performed (Fig. 2). The VM appeared to be small (15.4 × 31.5 mm) and superficial. Therefore, treatment was started by sclerotherapy with polidocanol (Aethoxysklerol, 2 %, Sigma Tau, Utrecht, The Netherlands) under US guidance without anaesthesia. Three sessions were performed with an interval of 6 weeks between each session. This had only a temporary effect. At the moment, the patient is considering alcohol embolization with general anaesthesia.

Most studies have focused on the technical and short-term results of treatment and indicate that VMs are difficult to treat and that most patients require multiple consecutive therapeutic sessions before clinical effect is reached. Furthermore, the effectiveness of these treatments remains uncertain, and practice is experience-rather than evidence-based. Some clinicians prefer surgery, whereas others prefer sclerotherapy or laser treatment. A systematic review regarding the evidence of the different treatment options for VMs has not yet been performed. This study therefore provides a comprehensive systematic review of the available literature regarding the effectiveness of the different treatment options for patients with a VM.

Materials and Methods

Search Strategy

We systematically searched the bibliographical databases PubMed (1966 to April 2012) and Embase (1988 to April 2012) using the following terms—"VM", "treatment," "sclerotherapy," "ethanol," "polidocanol," "aetoxisclerol," "bleomycin," "pingyangmycin," "Ethibloc," "sodium tetradecyl sulphate," "laser," and "surgery"—as well as their synonyms to identify papers on the treatment of VMs. The different search strategies can be found in Appendix. In addition, we performed a reference and related article search.

Study Selection

We first selected articles by screening titles and abstracts resulting from the search without blinding to authorship or journal. Potentially relevant studies were retrieved, and the full text was analysed. Inclusion was based on treatment strategy and effect measurement. Studies were excluded if they used more than one therapy at the same time.

Data Extraction

Information was gathered from each study on design, participants, intervention, and treatment outcome. For the

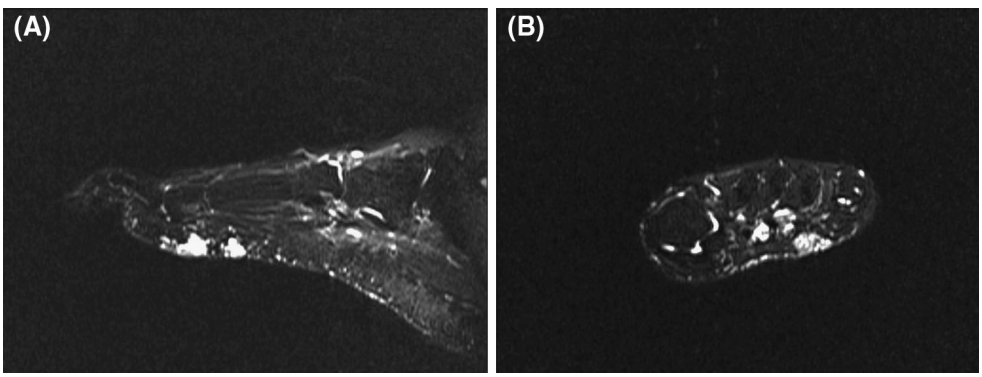

Fig. 2 MRI pictures (T2 weighted and fat-suppressed) of the left foot of the patient in Fig. 1. **A** Transversal and **B** sagittal images, in which the white discolorations show the superficial VM on the plantar side of the foot

latter, we noted information on both success and complication rates. Because the number of included patients varied in the different studies, we used the weighted average of data.

Assessment of Risk of Bias in Included Studies

It is important to assess risk of bias in all studies in a review irrespective of anticipated variability in either the results or the validity of the included studies. For instance, the results may be consistent among studies but all of the studies may be flawed. In this case, the review's conclusions should not be as strong as if a series of rigorous studies yielded consistent results about an intervention's effect. Bias refers to systematic error, meaning that multiple replications of the same study would reach the wrong answer on average [9].

Two authors (A. K., M. R.) independently assessed the quality of all included studies using the Cochrane Collaboration tool for assessing risk of bias [9]. In this tool, six specific domains are addressed, i.e., sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and "other biases." Selection bias refers to systematic differences between baseline characteristics of the groups being compared. Performance bias refers to systematic differences between groups in the care provided or to exposure to factors other than the interventions of interest. Detection bias refers to systematic differences between groups in how outcomes are determined. Attrition bias refers to systematic differences between groups in withdrawals from a study. Reporting bias refers to systematic differences between reported and unreported findings. In addition other sources of bias are relevant only in certain circumstances e.g., contamination. By answering prespecified questions, we reported the execution of the study and judged the risk of bias for each domain. The outcome for each domain was either yes (high risk), no (low risk), or unclear. We resolved disagreement by discussion (A. K., M. R.).

Results

Literature search shows that therapeutic interventions for VM include the following: surgery, sclerotherapy, laser therapy, compression, and pain management [5, 8, 10–16]. For the first three interventions, evidence regarding effectiveness was sought.

Sclerotherapy

We performed a literature search to study the currently available evidence regarding the effectiveness of all five commonly used forms of sclerotherapy: ethanol, bleomycin, polidocanol, sodium tetradecyl sulfate (STS), and Ethibloc.

Ethanol

Our search identified 72 unique articles. After screening titles and abstracts, we excluded 55 nonrelevant articles because they did not study the effectiveness of ethanol. Two articles on gelified ethanol (radio-opaque ethylcellulose-ethanol) were set aside because we believe this is a different treatment because it diffuses differently due to its different viscosity [17]. The results of this gelified ethanol are described later in the text.

The 15 remaining articles were retrieved in full text for formal review. After independent review, 13 articles met the inclusion criteria and were eligible for further analysis [18–30]. The other two papers were excluded because they reported on vascular instead of VMs ($n = 1$) or described a single case ($n = 1$). Figure 3 shows the results of the quality assessment according to the Cochrane Collaboration risk of bias tool for intervention studies. In general, the methodological quality of all 13 included studies was poor since none of them comprises a randomized placebo controlled trial, i.e. adequate sequence generation, allocation concealment, and blinding of participants was lacking in all studies. The outcome assessment was not described well enough to assure the unpredictability of the measurements. Furthermore, the risk of incomplete outcome data and selective reporting appears to be high but could not be determined from the papers themselves. The characteristics of the studies are listed in Table 1. All studies are retrospective or prospective case series. The weighted average success rate of the 13 included studies is 74 % (range 27–100 %) (see also Fig. 4).

Gelified Ethanol

Radio-opaque ethylcellulose-ethanol (gelified ethanol), which has a different viscosity compared with liquid ethanol, was assessed separately. We argue that smaller quantities of ethanol might be used, which will increase safety. We found two studies of the same group, both published in 2011, but one of them appeared to be a conference abstract and could not be retrieved [17]. The methodological quality of this study was poor to moderate because adequate sequence generation, allocation concealment, and blinding of participants was lacking. The success rate for this study was 89 % (Fig. 4).

Bleomycin

Our search identified 15 unique articles for bleomycin A5 (pingyangmycin). After screening titles and abstracts, we

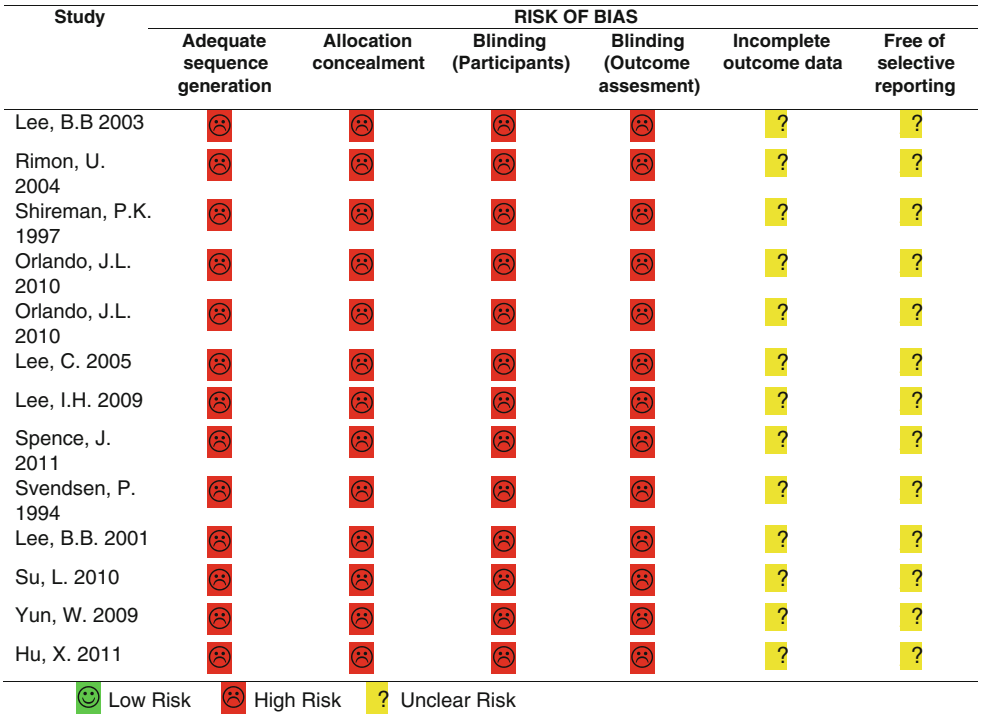

Fig. 3 Flow chart ethanol. Risk of bias for all ethanol studies, which is typical for all comparisons, i.e., all comparisons had a high risk of bias first *four columns* and an unclear risk of bias for the last *two columns*

excluded eight nonrelevant articles that did not study the effectiveness of Bleomycin. The seven remaining articles were retrieved in full text for formal review. After independent review, five articles met the inclusion criteria and were eligible for further analysis [27, 31–34]. The other two papers were excluded because they both used a combination of sclerosants so the individual effect of bleomycin could not be studied. The methodological quality of all five included papers was low because none of them comprised a randomised placebo controlled trial, i.e., adequate sequence generation, allocation concealment, and blinding of participants was lacking in all studies. The outcome assessment was not performed in such a way that the unpredictability of the following assignments could be assured. The five included papers did not clearly describe incomplete outcome data, and selective reporting could not be precluded. Table 2 lists an overview of the characteristics of the five included studies. Four studies are retrospective case series, and one is a prospective case series. The weighted average success rate for five included studies on bleomycin is 88 % (range 55–96 %) (see also Fig. 4) (Table 2).

Polidocanol

We identified 29 articles, of which five remained after screening titles and abstracts. After independent review, four articles met the inclusion criteria and were eligible for further analysis [35–38]. The other article was excluded because it reported on capillary malformation instead of VM. Again, none of the included studies comprised a randomised placebo controlled trial resulting in a poor methodological quality of the studies, i.e., adequate sequence generation, allocation concealment, and blinding of participants was lacking. Outcome assessment, incomplete outcome data, and selective reporting could not be assessed due to the poor reporting of the papers. All studies were retrospective case series (see also Table 3). The weighted average success rate of all four studies was 90 % with a minimum of 82 % and a maximum of 96 % (see also Fig. 4).

Sodium Tetradecyl Sulfate (STS)

Seventeen unique articles were retrieved with our literature search. After screening titles and abstracts, we excluded 13 nonrelevant articles. The four remaining articles were retrieved in full text for formal review. After independent review, two articles met the inclusion criteria and were eligible for further analysis [39, 40]. The other two papers were excluded because they both used a combination of sclerosants so the individual effect of STS could not be studied. Because both studies were prospective case series, adequate sequence generation, allocation concealment, and blinding of participants were not performed, resulting in an overall low quality. The characteristics of the two included studies are listed in Table 4. The average success of STS therapy is 86 % with a range from 85 to 87 % (Fig. 4).

Table 1 Characteristics of the 13 included ethanol studies

Investigator	Year	Design	No. of participants	Intervention	Outcome	Notes
Lee et al. [19]	2003	Retrospective case series	87	Ethanol sclerotherapy	Clinical improvement in 95.4 %; minor/major acute complications in 27.9 % (7 with chronic complications)	
Rimon et al. [25]	2004	Prospective (?) case series	21	Ethanol sclerotherapy	Success (partial or complete symptomatic relief) in 76.2 %; complications: 2 major, 3 minor	
Shireman et al. [26]	1997	Prospective case series	12	Direct injection with ethanol	Ethanol effective; no complications in ±50 % (skin ulceration)	No effect size given
Orlando et al. [23, 24]	2010	Prospective case series	39	Outpatient percutaneous treatment using pure ethanol at low doses with the patient under local anaesthesia	Symptoms disappeared in 14 patients (35.9 %) and improved in 24 (61.5 %) (total 97.4 %); lesion size decreased to zero in 6 patients (15.4 %) and decreased (no volume differences mentioned) in 32 (82 %) (total 97.4 %); no complications in 32 patients (82 %), whereas 3 presented local paresthesia (7.7 %), 2 superficial thrombophlebitis (5.1 %), 1 skin ulcer (2.6 %), and 1 hyperpigmentation (2.6 %)	
Orlando et al. [23, 24]	2010	Prospective case series	81	Ethanol sclerotherapy	Lesions and symptoms disappeared in 20 patients (24.7 %) or improved in 57 (70.4 %) (total 94.7 %); size decreased to zero in 17 patients (21 %) and decreased in 58 (71.6 %) (total 92.6 %); no complications in 64 (79 %), whereas 11 (13.6 %) presented a small skin ulcer, 3 (3.7 %) hyperpigmentation, and 3 (3.7 %) paresthesia	
Lee and Chen [21]	2005	Retrospective case series	5	Direct percutaneous ethanol instillation	All patients had remission and complete alleviation of symptoms; no major complications	
Lee et al. [22]	2009	Retrospective case series	71	Ethanol sclerotherapy	Outcome: 23/71 (32.4 %) excellent, 37/71 (52.1 %) good, 11/71 (15.5 %) poor; considered effective in 60/71 (84.5 %); complications: 2.3 % (2/87) respiratory difficulty, 1.15 % (1/87) tongue dullness, and 1.15 % (1/87) transient facial nerve palsy	
Spence et al. [27]	2011	Retrospective case series	17 alcohol, 17 bleomycin	Percutaneous treatment with alcohol and bleomycin sclerotherapy	Success rate/experienced clinical improvement with alcohol: 100 %; adverse events 11.8 %; complications 41.2 %	
Svendsen et al. [29]	1994	Retrospective case series	23	Instillation of alcohol	Only alcohol embolisation in 18/23; excellent/good result in 78.3 %	Study design not mentioned
Lee et al. [20]	2001	Prospective case series	30 treated patients; 28 available for follow-up	Absolute ethanol sclerotherapy	Overall improvement in lesions: good/fair response on clinical assessment in 27 (of 28; 96 %); major and minor acute complications in 8 (of 30; 26.7 %) (ischemic bullae, tissue fibrosis, deep venous thrombosis, pulmonary embolism, peripheral nerve palsy, and temporary pulmonary hypertension); 1 case of permanent peroneal nerve palsy	Study design not mentioned
Su et al. [28]	2010	Prospective consecutive case series	60: 48 only alcohol sclerotherapy, 12 previous surgeries or laser therapy	Absolute ethanol sclerotherapy	Complete volume reduction in 68.33 %; 25 % marked response (total 93.33 %); 6.67 % moderate response; 6.67 % ($n = 4$) surgical excision after sclerotherapy; 10 % minor complications; no major complications	

continued

Investigator	Year	Design	No. of participants	Intervention	Outcome	Notes
Yun et al. [30]	2009	Retrospective, cross-sectional study	158	Ethanol sclerotherapy	Marked improvement reported: symptoms in 28 %, function in 27 %, cosmesis in 34 % (see Table 4); whole body blood pool scintigraphy (WBBPS): 20 % marked improvement; local complications: 8 % skin necrosis, 13 % nerve palsy; systemic complications: 1 % transient pulmonary hypertension, 2 % elevated liver enzymes, 1 % cardiac arrhythmia, 8 % hemoglobinuria	
Hu et al. [18]	2011	Retrospective case series	91	Ethanol sclerotherapy	9 facial nerve paralysis (9.9 %), 8 of them recovered (88.9 %)	

Ethibloc

We identified 11 unique articles, of which two appeared to study the effectiveness of Ethibloc. After independent review, one article met the inclusion criteria and was eligible for further analysis [41]. The other article was excluded because a combination of sclerosants was used so the individual effect of Ethibloc could not be studied. Because the included study only comprises a retrospective case series, the overall quality was again very low. Ethibloc was effective in 65 % of the cases (Fig. 4).

Surgery

Our search identified 296 unique articles. After screening titles and abstracts, we excluded 289 nonrelevant articles. The seven remaining articles were retrieved in full text for formal review. After review, one article met the inclusion criteria and was eligible for further analysis [42]. The other six articles were excluded because they reported on vascular instead of VMs ($n = 1$) or because they reported only an individual case ($n = 4$). The remaining study, by Zhong et al. [42], comprises a retrospective case series of 10 patients with a solitary VM in the mid-cheek region. Due to the retrospective design and the lack of randomisation, blinding, and a clear outcome assessment, the overall quality was low. Surgery was effective in 90 % of the patients (see also Fig. 4).

Laser

Our search identified 118 unique articles. After screening titles and abstracts, we excluded 106 nonrelevant articles. The 12 remaining articles were retrieved in full text for formal review. After independent review, four articles met the inclusion criteria and were eligible for further analysis [43–46]. The excluded papers did not report a quantitative effect ($n = 2$) or reported on individual cases ($n = 3$). In all four included studies, intralesional (endovenous) laser treatment was applied [43–46]. Again, due to the lack of randomised placebo controlled trials, the methodological quality was low, i.e., adequate sequence generation, allocation concealment, and blinding of participants was lacking. The risk of incomplete outcome data and selective reporting appears to be high but could not be determined from the papers themselves. Table 5 lists the characteristics of these four included retrospective or prospective case series. The weighted mean average success rate of these four studies is 94 % (range 68–100 %) (see also Fig. 4).

Comparison of Different Treatment Options

Figure 4 shows the weighted average success rates of the different treatment options, which vary from 74 % for

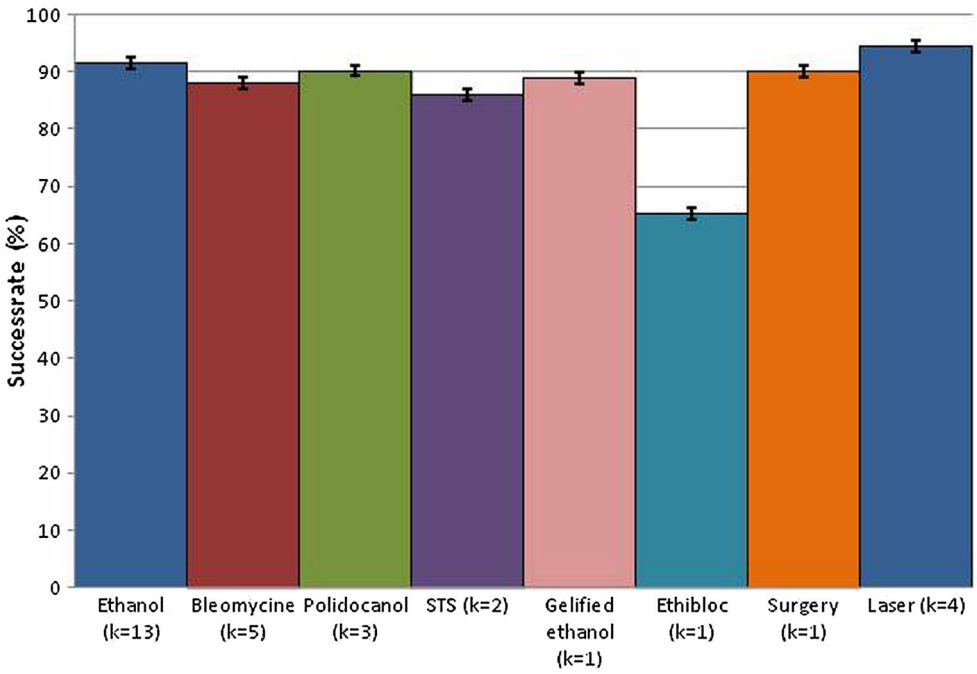

Fig. 4 Comparison of effectiveness between therapies for VM

Table 2 Characteristics of bleomycin

Investigator	Year	Design	Participants	Intervention	Outcome	Notes
Spence et al. [27]	2011	Retrospective case series	17 patients bleomycin, 17 patients alcohol	Percutaneous treatment with alcohol and bleomycin sclerotherapy	Success rate/experienced clinical improvement with bleomycin: 88.2 %; adverse events: 7.9 %; complications: 2.6 %	
Zhi et al. [34]	2008	Prospective case series	82	Intralesional pingyangmycin in the treatment	Regression 76–100 % in 81.7 %; regression 51–75 % in 14.6 % (total 96.3 %); 3 underwent surgery for remaining swelling	Study design not mentioned
Zhao et al. [32]	2004	Retrospective case series	85	Sclerotherapy with use of pingyangmycin and/or sodium morrhuate	Result of pingyangmycin good/ excellent in 89 %, excellent in 71 %; complications: sometimes fever, 1 with ulceration and subsequent scarring	
Li et al. [31]	2010	Retrospective case series	11	Digital subtraction angiography–guided percutaneous sclerotherapy with pingyangmycin and/or absolute ethanol	45.5 % excellent ($n = 5$), 9.1 % good ($n = 1$) (total 54.6 %), 36.4 % fair ($n = 4$), 1 lost to follow-up; complications (all): 5 fever, 1 incomplete facial paralysis (recovered), 1 swelling, 3 ulceration	
Zheng et al. [33]	2009	Retrospective case series	179	Intralesional injection with pingyangmycin	"Cure" in 74.86 %, marked improvement in 11.18 % (total 86.04 %), improvement in 13.96 %; complications in all: 10 < 5 year fever; no allergic shock, pulmonary fibrosis, localized necrosis, nerve damage, scarring, and changes in renal function or cytopenia	Complications are of all VMs Small number of patients also treated with surgery

Table 3 Characteristics of polidocanol

Investigator	Year	Design	Participants	Intervention	Outcome	Notes
Blaise et al. [35]	2011	Retrospective single-centre consecutive case series	24	US-guided sclerotherapy with polidocanol foam	Decreased pain in 23/24, size reduction >50 % in 37.5 %, size reduction <50 % in 58.3 % (total 95.8 %); 2 minor side effects	
Mimura et al. [37]	2003	Retrospective case series	14	Percutaneous sclerotherapy using polidocanol under fluoroscopy guidance	Improvement of symptoms in 93 %; complications: 1 blistering of skin and erythema, 1 decreased blood pressure and bradyarrhythmia, 2 numbness of limbs during treatment; early side effects: 10 swelling, 8 increased pain/signs of pain	
Yamaki et al. [38]	2000	Retrospective case series	28	Colour duplex-guided sclerotherapy with polidocanol	Effective in 82 %, complete disappearance in 54 %, decreased lesion size in 29 %, recanalization within 4 weeks in 18 %; complications: pain in 82 %, swelling in 75 %, hemoglobinuria in 11 %, epidermal necrosis in 3 each	Small number also treated with surgical ligation
Mimura et al. [36]	2009	Retrospective case series	29 (follow-up)	Polidocanol sclerotherapy	26/29 (89.7 %) improved; adverse effects: hypotension and bradycardia; no major complications	

Table 4 Characteristics of the two included studies on STS

Investigator	Year	Design	Participants	Intervention	Outcome	Notes
Khandpur and Sharma [39]	2010	Prospective case series	11	Intralesional sclerotherapy with 3 % sodium tetradecyl sulphate	Resolution of VM in ≥90 %; resolution after mean of four sittings in 84.6 %; complications: cutaneous blistering, erosion, and crusting in 7 (53.8 %), atrophic scarring in 4 (30.7 %)	
O'Donovan et al. [40]	1997	Prospective case series	15	Treatment with percutaneous injection of sodium tetradecyl sulfate	Benefit in 87 %	Complications not separate for VM Small number of patients also treated with surgery

ethanol to 94 % for laser therapy. The major limitation, besides the low methodological quality of the included studies, is that the criteria for success differ between the included studies.

Discussion

This systematic literature review shows that there is a lack of evidence for the effectiveness of different treatments of VM. Studies included in our review are mostly retrospective, and therefore the methodological quality is poor. In daily practice, the size of the VM and the level of infiltration appear to be important parameters. We therefore tried to distinguish between superficial and deep lesions. However, because the reporting in most studies was quite poor, we were not able to distinguish between these types of VM. The reported success rates suggest that all treatments are effective, but due to the methodological limitations a final conclusion cannot be drawn from the available data.

Other articles on the treatment of VM focus on the different therapy options rather than on the effectiveness of those treatments [5, 8, 11, 13, 47, 48]. Only Greene and Alomari [8] mention an effectiveness between 75 and 90 % for sclerotherapy, which is comparable with our results.

The major strength of our study is that it is the first systematic review studying the effectiveness and the validity of the studies on different treatments for VM. However, some potential limitations should also be discussed. First, the risk of bias was high for all studies, so we could not draw reliable conclusions. Confounding by

Table 5 Characteristics of the four included laser studies

Investigator	Year	Design	Participants	Intervention	Outcome	Notes
Poetke et al. [44]	2001	Retrospective case series	176	Interstitial Nd:YAG laser therapy	Results: excellent in 43 %, good in 52 % (total 95 %), failed in 5 %; complications: 14 % temporary paresthesia, 2 dysthesia (perforation of buccal mucosa); no permanent complications or long-term skin problems	
Lu et al. [43]	2011	Retrospective consecutive case series	38	Percutaneous endovenous treatment with US-guided and 810-nm diode laser	Clinical success: decreased swelling in 70 %, cosmetic effect in 67 %; 64 % excellent, 32 % good (total 96 %), 4 % fair; complications: 1 spot skin burn injuries (resolved), 5.48 % parethesia (disappeared), 6 fibrogen level (recovered)	
Sarig et al. [45]	2006	Retrospective case series	56	YAG laser	Success rate: 92.8 % (71.4 % excellent, 21.4 % good); complication rate: 3.57 % (minimal scarring and deformity)	
Sidhu et al. [46]	2005	Retrospective case series	6	US-guided endovenous diode laser	Clinical success rate: pain 100 %, swelling/cosmetic complaints in 63 %; minor complication rate: 11.8 %	

indication appears to be a great problem, i.e., prognostic factors, such as size and level of infiltration, may influence treatment decisions. Only well-designed randomized controlled trials are not affected by confounding by indication; therefore, they are needed to study the real effectiveness of the various treatment options available. Second, many studies focus on the treatment of one particular part of the body. It is possible that the treatment effect differs for distinct parts of the body, which might influence generalizability. However, so far, there is no strong evidence for this. Third, we studied single treatments instead of combinations of treatments. Only seven studies could be identified that reported on the effectiveness of combined treatments, and because they all studied different combinations, they could not be analysed systematically [49–55]. Furthermore, none of these seven studies performed a randomised controlled study, so bias is also a serious problem in these studies.

In daily practice, treatment of a VM is chosen from the experience of (a group of) specialists in consultation with the patient, taking into account the clinical and radiological picture as well as the risks and benefits of the treatment. No standard operating procedures or guidelines are available for this condition. From the present review, we can learn that also in literature, all reported effects appear to be biased. Therefore, this review also cannot provide evidence-based recommendations regarding the treatment of VM.

When taking costs in account, STS or polidocanol would be the treatment of choice because in adult patients, treatment can be administered in an outpatient setting without general anaesthesia. Intralesional bleomycin A5 (pingyangmycin) injection also has low costs, but caution is commonly advised because of pulmonary side effects, in particular pulmonary fibrosis. Therefore, this therapeutic option is usually not the first-choice treatment because repetitive procedures increase the total cumulative dose, thus expanding the risk of side effects. Ethanol embolization is performed with the patient under general anaesthesia. Reported complication rates for ethanol are higher than for other sclerosants, which is a reason to avoid injudicious use of ethanol; only for experienced doctors does the high efficacy outweigh the potential serious adverse events. It unclear to what respect this will be improved by the use of radio-opaque ethylcellulose-ethanol. Surgery requires the operating room (OR), and laser treatment involves up-to-date laser equipment and may also require the OR because of the anaesthesia needed for interstitial/intralesional laser therapy because conventional transcutaneous laser treatment usually does not penetrate sufficiently for the typical bulky VM. The costs of these treatments are ~€500/patient for outpatient administration of STS or polidocanol; ethanol embolization, surgery, and laser treatment involve multiple costs because of general anaesthesia, redemption of laser equipment, and/or hospitalisation.

Future prospective studies, particularly RCTs, should provide evidence for the effectiveness of VM treatment. We suggest initiating a trial that compares ethanol and polidocanol as these sclerosants appear to be used most frequently. Furthermore, in the current era of personalised medicine, we should aim to study which treatment is best for which patients.

Conclusion

There is no reliable evidence regarding the effectiveness of the treatment of VMs. The choice for treatment should remain a shared decision between the patient and the

multidisciplinary treatment group until further evidence is available. From a cost perspective, STS or polidocanol should be the treatment of choice.

Conflict of interest All authors, C.J.M. van der Vleuten, A. Kater, M.H.W.A. Wijnen, L.J. SchultzeKool, M.M. Rovers, declare no conflict of interest.

Appendix: Search Strategy

Ethanol

- Search strategy pubmed: (ethanol[Title/Abstract] AND sclerotherapy[Title/Abstract]) AND (venous[Title/Abstract] AND malformation[Title/Abstract])
- Search strategy pubmed: ((absolute[Title/Abstract] AND ethanol[Title/Abstract]) AND sclerotherapy[Title/Abstract]) AND (venous[Title/Abstract] AND malformation[Title/Abstract])
- Search strategy pubmed: (alcohol[Title/Abstract] AND sclerotherapy[Title/Abstract]) AND (venous[Title/Abstract] AND malformation[Title/Abstract])
- Search strategy pubmed: ((absolute[Title/Abstract] AND alcohol[Title/Abstract]) AND sclerotherapy[Title/Abstract]) AND (venous[Title/Abstract] AND malformation[Title/Abstract])
- Search strategy pubmed: ((“ethanol”[MeSH Terms] OR “ethanol”[All Fields]) AND (“sclerotherapy”[MeSH Terms] OR “sclerotherapy”[All Fields])) AND ((“veins”[MeSH Terms] OR “veins”[All Fields] OR “venous”[All Fields]) AND (“congenital abnormalities”[MeSH Terms] OR (“congenital”[All Fields] AND “abnormalities”[All Fields]) OR “congenital abnormalities”[All Fields] OR “malformation”[All Fields]))
- Search strategy embase: (ethanol and sclerotherapy and venous malformation).ab.
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- Search strategy embase: (absolute ethanol and sclerotherapy and venous malformation).ab.
- Search strategy embase: (absolute alcohol and sclerotherapy and venous malformation).ab.

Bleomycin

- Search strategy pubmed: (bleomycin[Title/Abstract] AND sclerotherapy[Title/Abstract]) AND (venous[Title/Abstract] AND malformation[Title/Abstract])
- Search strategy pubmed: (pingyangmycin[Title/Abstract] AND sclerotherapy[Title/Abstract]) AND (venous[Title/Abstract] AND malformation[Title/Abstract])
- Search strategy pubmed: ((“bleomycin”[MeSH Terms] OR “bleomycin”[All Fields]) AND (“sclerotherapy”[MeSH Terms] OR “sclerotherapy”[All Fields])) AND ((“veins”[MeSH Terms] OR “veins”[All Fields] OR “venous”[All Fields]) AND (“congenital abnormalities”[MeSH Terms] OR (“congenital”[All Fields] AND “abnormalities”[All Fields]) OR “congenital abnormalities”[All Fields] OR “malformation”[All Fields]))
- Search strategy pubmed: ((“bleomycetin”[Supplementary Concept] OR “bleomycetin”[All Fields] OR “pingyangmycin”[All Fields]) AND (“sclerotherapy”[MeSH Terms] OR “sclerotherapy”[All Fields])) AND ((“veins”[MeSH Terms] OR “veins”[All Fields] OR “venous”[All Fields]) AND (“congenital abnormalities”[MeSH Terms] OR (“congenital”[All Fields] AND “abnormalities”[All Fields]) OR “congenital abnormalities”[All Fields] OR “malformation”[All Fields]))
- Search strategy embase: (bleomycine and sclerotherapy and venous malformation).ab.
- Search strategy embase: (pingyangmycine and sclerotherapy and venous malformation).ab.

Polidocanol

- Search strategy pubmed: ((venous[Title/Abstract] AND malformation[Title/Abstract]) AND sclerotherapy[Title/Abstract]) AND polidocanol[Title/Abstract]
- Search strategy pubmed: (aetoxisclerol[Title/Abstract] AND sclerotherapy[Title/Abstract]) AND (venous[Title/Abstract] AND malformation[Title/Abstract])
- Search strategy pubmed: (((aetoxisklerol[Title/Abstract])) AND (sclerotherapy[Title/Abstract])) AND (venous malformation[Title/Abstract])
- Search strategy pubmed: (etoxisclerol[Title/Abstract] AND sclerotherapy[Title/Abstract]) AND (venous[Title/Abstract] AND malformation[Title/Abstract])
- Search strategy pubmed:((“polidocanol”[Supplementary Concept] OR “polidocanol”[All Fields] OR “aetoxisclerol”[All Fields]) AND (“sclerotherapy”[MeSH Terms] OR “sclerotherapy”[All Fields])) AND ((“veins”[MeSH Terms] OR “veins”[All Fields] OR “venous”[All Fields]) AND (“congenital abnormalities”[MeSH Terms] OR (“congenital”[All Fields] AND “abnormalities”[All Fields]) OR “congenital abnormalities”[All Fields] OR “malformation”[All Fields]))
- Search strategy embase: (polidocanol and sclerotherapy and venous malformation).ab.
- Search strategy embase: (aetoxisclerol and sclerotherapy and venous malformation).ab.

- Search strategy embase: (aetoxisklerol and sclerotherapy and venous malformation).ab.
- Search strategy embase: (etoxisclerol and sclerotherapy and venous malformation).ab.

STS

- Search strategy pubmed: ((sodium[Title/Abstract] AND tetradecyl[Title/Abstract] AND sulfate[Title/Abstract]) AND sclerotherapy[Title/Abstract]) AND (venous[Title/Abstract] AND malformation[Title/Abstract])
- Search strategy pubmed: ((“sodium tetradecyl sulphate”[All Fields] OR “sodium tetradecyl sulfate”[MeSH Terms] OR (“sodium”[All Fields] AND “tetradecyl”[All Fields] AND “sulfate”[All Fields]) OR “sodium tetradecyl sulfate”[All Fields]) AND (“sclerotherapy”[MeSH Terms] OR “sclerotherapy”[All Fields])) AND ((“veins”[MeSH Terms] OR “veins”[All Fields] OR “venous”[All Fields]) AND (“congenital abnormalities”[MeSH Terms] OR (“congenital”[All Fields] AND “abnormalities”[All Fields]) OR “congenital abnormalities”[All Fields] OR “malformation”[All Fields]))
- Search strategy pubmed: (sotradecol[Title/Abstract] AND sclerotherapy[Title/Abstract]) AND (venous[Title/Abstract] AND malformation[Title/Abstract])
- Search strategy pubmed: ((sodium[Title/Abstract] AND lauryl[Title/Abstract] AND sulfate[Title/Abstract]) AND sclerotherapy[Title/Abstract]) AND (venous[Title/Abstract] AND malformation[Title/Abstract])
- Search strategy: (sodium tetradecyl sulfate and sclerotherapy and venous malformation).ab
- Search strategy embase: (sotradecol and sclerotherapy and venous malformation).ab.
- Search strategy embase: (sodium lauryl sulfate and sclerotherapy and venous malformation).ab.

Ethibloc

- Search strategy pubmed: (ethibloc[Title/Abstract] AND sclerotherapy[Title/Abstract]) AND (venous[Title/Abstract] AND malformation[Title/Abstract])
- Search strategy pubmed: ((“alcoholic prolamine solution”[Supplementary Concept] OR “alcoholic prolamine solution”[All Fields] OR “ethibloc”[All Fields]) AND (“sclerotherapy”[MeSH Terms] OR “sclerotherapy”[All Fields])) AND ((“veins”[MeSH Terms] OR “veins”[All Fields] OR “venous”[All Fields]) AND (“congenital abnormalities”[MeSH Terms] OR (“congenital”[All Fields] AND “abnormalities”[All Fields]) OR “congenital abnormalities”[All Fields] OR “malformation”[All Fields]))
- Search strategy: (ethibloc and sclerotherapy and venous malformation).ab.

Surgery

- Search strategy pubmed: (surgical[Title/Abstract] AND treatment[Title/Abstract]) AND (venous[Title/Abstract] AND malformation[Title/Abstract])
- Search strategy pubmed: ((surgical[Title/Abstract] AND treatment[Title/Abstract]) AND (vascular[Title/Abstract] AND surgery[Title/Abstract])) AND (venous[Title/Abstract] AND malformation[Title/Abstract])
- Search strategy embase: (surgery and venous malformation).ab.

Laser

- Search strategy pubmed: (((laser[Title/Abstract] AND therapy[Title/Abstract]) AND laser[Title/Abstract]) AND treatment[Title/Abstract]) AND (venous[Title/Abstract] AND malformation[Title/Abstract])
- Search strategy pubmed: ((((“laser therapy, low-level”[MeSH Terms] OR (“laser”[All Fields] AND “therapy”[All Fields] AND “low-level”[All Fields]) OR “low-level laser therapy”[All Fields] OR (“laser”[All Fields] AND “therapy”[All Fields]) OR “laser therapy”[All Fields] OR “laser therapy”[MeSH Terms] OR (“laser”[All Fields] AND “therapy”[All Fields])) AND (“lasers”[MeSH Terms] OR “lasers”[All Fields] OR “laser”[All Fields])) AND (“therapy”[Subheading] OR “therapy”[All Fields] OR “treatment”[All Fields] OR “therapeutics”[MeSH Terms] OR “therapeutics”[All Fields])) AND ((“veins”[MeSH Terms] OR “veins”[All Fields] OR “venous”[All Fields]) AND (“congenital abnormalities”[MeSH Terms] OR (“congenital”[All Fields] AND “abnormalities”[All Fields]) OR “congenital abnormalities”[All Fields] OR “malformation”[All Fields]))

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