Outcomes of Venous Malformation Sclerotherapy: A Review of Study Methodology and Long-Term Results

Sumera Ali, MD¹ Sally E. Mitchell, MD²

¹Department of Radiology, University of Arkansas for Medical Sciences, Little Rock, Arkansas

²Division of Interventional Radiology, Johns Hopkins Medicine, Baltimore, Maryland

Address for correspondence Sally E. Mitchell, MD, Interventional Radiology Center, Sheikh Zayed Tower, Suite 7203, 1800 Orleans Street, Baltimore, MD 21287 (e-mail: smitch@jhmi.edu).

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Abstract

It is very important that patients seeking sclerotherapy for the treatment of venous malformations are aware of the expected course of the therapy. They should be thoroughly counseled about the complications, the need for multiple sessions of therapy, and also about the expected clinical outcome. The aim of this review is to discuss the long-term outcomes of sclerotherapy for the treatment of venous malformation. Many studies have discussed their individual center's experiences and short-midterm results, but there is a relative paucity of data on long-term outcomes. We have reviewed the literature and also shared our experience of a large cohort of patients ($n = 116$) with a relatively longer follow-up period of more than 1 year. Venous malformations are very complex lesions and their treatment is quite variable depending on its extent and complexity. As a result, outcome studies vary considerably in the choice of sclerosant, study methodology, outcome assessment (clinical vs. imaging), and grading scales. This review also highlights this extreme heterogeneity in the literature of the sclerotherapy outcome and summarizes a few national and international studies for comparison.

Keywords

- venous malformation
- sclerotherapy
- interventional radiology

Objectives: Upon completion of this article, the reader will be able to identify the outcomes of sclerotherapy including the initial success rate, recurrence, and long-term outcomes; describe the heterogeneity in the literature regarding study methodology, outcome assessment (clinical vs. imaging), and grading scales to study clinical outcomes of sclerotherapy; and identify the various sclerosants available to treat venous malformation and the factors that govern their uses.

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Venous malformation (VM) is a type of low-flow malformation as classified by the International Society for the Study of Vascular Anomalies. VMs are complex lesions, which can be sporadic, familial, or can occur as a part of syndromes. They occur as a result of defect in vasculogenesis, related to germ line TIE2 mutations in the inherited form and somatic TIE2 mutations in half of sporadic VMs.¹ Mutations in TIE2 cause uncoupling of the endothelial cells and pericytes, altering its development during vasculogenesis. Somatic mutations in PIK3CA are also causative for VMs.²

Unlike infantile hemangiomas, VMs do not regress in childhood and continue to expand and become symptomatic later in life. There are several inciting factors that cause the VMs to enlarge and become symptomatic. Some of the known risk factors include age, gender, pregnancy, and pubertal spurt which are known to cause progression of VMs.

Management of Venous Malformation

Sclerotherapy is the mainstay of treatment and has gained popularity as the first-line treatment for VM. The goal of the therapy should be to control symptoms and improve functional and cosmetic outcomes.

A large group of patients who present to the specialized vascular anomaly centers are usually referred after they have tried all other modes of conservative treatment. Often these patients are frustrated and come seeking a “cure” for these lesions. It is very important that patients understand the expected course of the therapy and have realistic expectations. They should be counseled about the complications, the need for multiple sessions of therapy, and also about the expected clinical outcome. A challenge faced by all interventional radiologists is the lack of literature on the long-term outcomes of sclerotherapy and the recurrence rates of these lesions. Do we treat only to symptom relief? Do we treat until the magnetic resonance imaging (MRI) is clear of VM? Which agent gives us the best long-term outcome with low risk-to-benefit ratio? What is the recurrence rate?

These are difficult questions with limited answers in the literature. In this article, we will review the literature on long-term outcomes of sclerotherapy and also share our experience to help answer some of these questions.

Choice of Sclerosant

There are many sclerosants that are available and their utilization is often institution specific and depends on the comfort level of the treating radiologist. Pure ethanol (100%) is accepted to be the most effective and has the lowest recurrence rate albeit with higher rate of complications.³ The other major group of sclerosant is detergent based and includes polidocanol, sodium morrhuate, sodium tetradecyl sulfate (STS), and ethanolamine oleate. They are considered as milder sclerosants with decreased complication rates. These sclerosants also damage the endothelial cells and cause thrombosis-like ethanol, but the thrombosis occurs at a slower rate and there is a greater probability that the VMs will recanalize.⁴

The other commonly used sclerosant is an antitumor agent (bleomycin). Lack of large randomized control trials limits the accurate evaluation and comparison between various agents. One such limited trial by Zhang et al between ethanol and bleomycin A5 (type of bleomycin used in China) confirmed the higher efficacy of ethanol and lower complication rate with bleomycin A5.³

Often sclerosants are used in combinations depending on the lesion morphology and clinical judgment. Jin et al used a combination of ethanol and bleomycin A5 to treat 200

patients.⁵ They treated the draining vein first with a small dose of ethanol followed by bleomycin injection into the lesion. They found 95% of their patients showing marked improvement.

Another technique used by many authors is to use the ethanol in its gel form, also known as ethylcellulose ethanol.⁶ The idea is to decrease the systemic side effect of ethanol by decreasing its diffusivity in the system. Since the gel is localized to the lesion, it can be used in VMs involving areas with higher risk of side effects such as hand or periorbital regions. Domp Martin et al have shared their experience of treating 44 patients and found it to be as effective as absolute ethanol.⁷ This agent is not available in the United States.

Often the detergent sclerosants are mixed with air and used as foam. The rationale is that foam increases the contact surface area with the endothelium. A prospective randomized study was performed to compare the sclerosant 1% polidocanol with 10% ethanolamine oleate in the form of either liquid or foam. They used smaller doses with foam and found better rates of total disappearance with foam form of therapy.⁸

Clinical versus Imaging Outcomes

Clinical parameter utilized to measure outcome after sclerotherapy is imperative for both the individual patient and for research purposes. Unfortunately, there is no uniformity to define a “successful” sclerotherapy outcome in the literature.

Most authors agree that clinical outcome based on patients’ symptoms should be the endpoint, but it can be subjective. Majority of studies in the literature studying the clinical outcome have used varying methodologies and grading scales to assess the outcome and this makes comparison between studies very difficult.

The methods of studying the clinical outcome have also been variable. Some studies have used physician panels and looked at the clinic follow-up notes and pre- and posttreatment photographs.⁵ We did a similar outcome analysis by looking at patients’ medical records, where patients were routinely asked to mark their symptoms on an objective scale at every clinic visit.⁹ Comparing their symptoms on the pre- and posttreatment scales, we were able to determine their degree of improvement and categorized it as significant, moderate, mild, and no improvement. One advantage of using this methodology was a decrease in recall bias, although it came with a challenge of missing and incomplete information.

Many studies have sent out questionnaires to their patients weeks to months after the treatment has been concluded. This is an effective way to be more uniform and objective in gathering information, but comes with the limitation of recall bias. van der Linden et al sent out a questionnaire to all the patients asking about improvement of individual symptoms, including pain, swelling, functional limitation, and cosmetics on a spectrum of four categories from complete relief to worsening.¹⁰

MRI is frequently used as an objective substitute in evaluating response to treatment. Posttreatment MRI is better utilized in delineating residual malformation for treatment planning and has also been shown to help predict treatment

outcome.¹¹ However, there are no standardized methods of measuring the size of the VM on MRI. Both two-dimensional and two-dimensional volumetric analyses have been performed using STIR, postcontrast, and dynamic imaging. A comprehensive study by Caty et al showed that volumetric analysis is more sensitive in detecting the treatment response as compared with diameter measurements alone.¹²

Some authors including our group have used simplified volumetric analysis by calculating the volume using ellipsoid volume ($4/3\pi abc$, where *a*, *b*, and *c* are the height, width, and length of the lesion, respectively).^{9,10} This is really an estimation, as most of the lesions are not ellipsoid. Some lesions are infiltrating and do not respect tissue boundaries, and in those cases it is difficult to estimate the treatment response. The best way in such cases is to look at only the treated areas.

Another important fact to consider when assessing outcome is that imaging and clinical outcomes may not be concordant. Spence et al studied and compared both the subjective clinical and objective MR outcomes after treating facial VM with bleomycin.¹³ They reported that subjective clinical improvement is not always associated with visual size reduction on MR imaging. Subjective clinical improvement may be possible with minimal fibrosis and small reductions in size. Tan et al studied 72 patients and reported that reduction in size on MR did not necessarily correlate with improvement in symptoms and vice versa.¹⁴

Long-Term Outcomes

VMs have a tendency to recanalize, especially if they have been treated with milder sclerosants. It has also been observed that diffuse VMs tend to recur more often. It is, therefore, very important that patients who are treated with sclerotherapy have a long-term follow-up. Unfortunately, currently there is very limited literature on the long-term follow-up of these lesions after sclerotherapy. Some of the studies that have followed up patients for a longer period of time are summarized in ►Table 1 for comparison.

Many patients who present to large vascular anomaly centers often have been previously treated by surgery or sclerotherapy and present with recurrence of their lesions. In the study by Jin et al, 64 out of 196 responders were previously treated outside.⁵ In our study, we also found that 38% of the patients were previously treated.⁹ This shows that although the short- to mid-term outcomes are promising, there is more work needed to determine the long-term outcomes of sclerotherapy. Unfortunately, this is a challenge faced by all the physicians involved in care, as these patients may be lost to follow-up.

To our knowledge, the national study with the longest follow-up after sclerotherapy of vascular malformations with a good size cohort is by van der Linden et al.¹⁰ They used a combination of treatments, most of which included ethanol with (7/66 patients) or without (34/66 patients) other agents such as Histoacryl and polidocanol. They followed up 66 patients for a mean follow-up time of 39 months (median, 30 months; range, 6–147 months). They showed that clinical success, partial or complete, is

expected in 58% of the patients irrespective of the size or classification of vascular malformation. Another interesting finding from their results was that the patients who had complete initial response, that is, disappearance of all symptoms at 3 months, did not have recurrence later, while those with partial initial response had recurrences. This shows that complete response at short-term follow-up may be predictive of decreased or no recurrence in the long term. Using the Kaplan–Meier analysis, they further showed that the clinical success, whether partial or complete, remained relatively stable over a 5-year follow-up period.

Tan et al shared their experience of treating 72 VM patients with STS sclerotherapy.¹⁴ Their patients had a mean follow-up of 41 months (range, 21–84 months). In their study, they reported 13 patients, who initially reported clinical improvement and had subsequent symptomatic recurrence. The mean time to recurrence was 23 months (range, 7–37 months). This recurrence could be secondary to the use of STS, which is gentler than ethanol.

On the other hand, Lee et al showed no recurrence in 87 patients treated with ethanol with a mean follow-up period of 24.7 months.¹⁵ This again could be secondary to the use of ethanol and aggressive approach in treating the lesions.

Another large international series of 201 patients from China by Jin et al followed up patients for a mean time of 29 months (range of 12–65 months).⁵ Only patients with a minimum follow-up of 1 year were included in the study. The lesions were treated with ethanol and/or bleomycin. The outcomes were assessed by two methods: first by a panel of physicians who used photographs and follow-up clinical evaluation and later a questionnaire was sent out to the patients to assess the outcome on the same 5-point scale. They reported complete response or “cure” in 27.9% of patients (56/196) and near normal in 20.9% of patients (42/196), while 48.7% showed some improvement.

In our study,⁸ we followed up 116 patients from their last procedure and our median follow-up time was 2.5 months (range, 4 weeks to 4 years). We observed an overall significant improvement in 37 patients (32%), moderate improvement in 31 (27%), mild improvement in 20 (17%), no improvement in 21 (18%), and worse than before in 7 (6%) patients. A similar trend was seen in the individual symptoms of pain, swelling, functional impairment, and bleeding outcome. We further explored the clinical improvement for patients with at least 3 months, 6 months, and 1 year of follow-up. Although the number of patients dropped over time, we observed a similar trend in the improvement scale (►Table 2).

Conclusion

Limited literature is available describing the long-term outcomes of treating VMs with sclerotherapy. Even when the literature is available, there is great variability in the methods of measuring outcome. Some authors have used clinical parameters, while others have combined clinical and imaging outcomes. The discordance between the clinical and imaging outcomes has also been reported.

Table 1 A summary of few selected outcome studies of sclerotherapies for treating venous malformations demonstrate extreme heterogeneity in the choice of sclerosant, methodology of follow up, outcome assessment and the grading scale utilized

Study	Total Patients	Types of lesions	Study Period	Range of sessions	Sclerosants	Follow-up Period	Outcome assessment	Grading scale	Results
Ali 2016	116	VM (112) LVM (4)	Jan 2005–July 2011	1 to 21	100% Ethanol (72%) <100% Ethanol (8%) Others (20%)	Median: 2.5 months Range: 4 weeks to 4 years	Clinical assessment by consensus of an interventional radiology team.	5-point scale from significant, moderate, mild, no improvement and worse than before.	76% showed some improvement: Significant - 32%, Moderate - 27%, Mild 17%, No improvement - 18%, Worse than before - 6%
Linden 2009	66	Low flow (55) High flow (11)	Sept 1995–July 2006	1 to 8	Ethanol (51%) Ethanol in combination (11%) Others (38%)	Mean: 39 months Median: 30 months Range: 6–147 months	Clinical assessment by patient questionnaire regarding effectiveness and satisfaction	4-point scale from complete, partial, no improvement and worse than before.	For low flow: 56% showed clinical success at 3 months 39% clinical success at 5 years by Kaplan-Meier 51% satisfied with treatment
Woo-Sung Yun 2009 (Korea)	158	VMs (122), LVM (16), Other low flow (20)	Jan 1995–Jun 2008	Median: 3	100% Ethanol (85%) <100% Ethanol (15%)	Not specified	Combination of post procedure imaging (MRI and/or WBPPS) and patient self-assessment questionnaires	Graded as good and "no-good". A "good response" was defined as ≥ 1 improvement on the self-assessment with $>30\%$ decrease in maximal diameter of VM on MRI or $>50\%$ decrease in abnormal blood pool ratio on WBPPS.	Overall: 16% had a good response Questionnaire: Symptomatic, functional, and cosmetic improvement was 28%, 27%, and 34% Imaging: 27% had marked improvement
Jin 2008 (China)	201	VM	Jan 2002–July 2006	1 to 8	Combination of ethanol (to sclerose the draining vein) and bleomycin A5 (for the lesion)	Mean: 29 months Range: 12–65 months	Combination of clinical assessment by team of plastic surgeons and patient self-assessment questionnaires	5-point scale from cured, near normal, marked, minor improvement and no change/worst	Cure 28%, Nearly normal - 21%, Marked improvement - 31%, Minor improvement 18% and No change or worse 2%
Tan 2007 (Canada)	72	VM	Jul 1997–Jul 2004	1 to 13	Sodium tetradecyl sulfate	Mean: 41 months Range: 21–84 months	Combination of clinical assessment by multidisciplinary team and imaging	4-point scale from asymptomatic, good, improved, no change or worse	Questionnaire: Asymptomatic - 15%, good - 28%, improved - 24%, unchanged - 28%, and worsened - 5%. Imaging size: decrease - 54%, unchanged - 31%, and increase 14%

CVM, Capillary venous malformation; LVM, Lymphovenous malformation; VM, Venous malformation.

Table 2 Clinical improvement of the patients with venous malformation treated with percutaneous sclerotherapy from January 2005 to July 2011

	Significant Improvement ¹	Moderate Improvement ²	Mild Improvement ³	No Improvement ⁴	Worse Than Before ⁵
Overall Outcome (<i>n</i> = 116)	37 (31.9%)	31 (26.7%)	20 (17.2%)	21 (18.1%)	7 (6.0%)
Pain Outcome (<i>n</i> = 104)	41 (35.4%)	20 (17.2%)	15 (12.9%)	20 (17.2%)	8 (7.7%)
Swelling Outcome (<i>n</i> = 104)	26 (25.0%)	30 (28.8%)	21 (20.2%)	21 (20.2%)	6 (5.8%)
Functional Outcome (<i>n</i> = 51)	11 (21.6%)	12 (23.5%)	5 (9.8%)	19 (37.3%)	4 (7.8%)
Bleeding Outcome (<i>n</i> = 10)	4 (40.0%)	2 (20.0%)	1 (10.0%)	1 (10.0%)	2 (10.0%)
Overall Outcome at Follow-Up Intervals*					
≥ 1 months (<i>n</i> = 116)	37 (31.9%)	31 (26.7%)	20 (17.2%)	21 (18.1%)	7 (6.1%)
≥ 3 months (<i>n</i> = 54)	18 (33.3%)	11 (20.4%)	9 (16.7%)	13 (24.1%)	3 (5.6%)
≥ 6 months (<i>n</i> = 30)	9 (30.0%)	6 (20.0%)	6 (20.0%)	7 (23.3%)	2 (6.7%)
≥ 1 year (<i>n</i> = 18)	6 (33.3%)	4 (22.2%)	3 (16.7%)	5 (27.8%)	0 (0.0%)

*Durations from the last procedure to the last available follow-up visit.

¹Significant improvement - No persistent pain or swelling; reduction in pain scale of ≥ 5 points; return of good level of functioning; minimal symptoms remain; represents a very substantial change from the baseline.

²Moderate improvement - notably better with significant reduction of pain (reduction in pain scale of 3–4 points) and swelling symptoms; increase in the level of functioning but some symptoms remain.

³Mild improvement - slightly better with little or no clinically meaningful reduction of symptoms; reduction in pain scale of 1–2 points; represents very little change from baseline symptoms.

⁴No change - symptoms remain essentially unchanged as compared with the baseline.

⁵Worse than before - clinically significant increase in symptoms and diminished functioning.

What we have learned from the review of limited long-term outcome data and our experience is that the short-term outcomes (months) remain relatively stable over time (1–5 years). If there is a complete symptomatic treatment initially at short-term assessment, it is less likely that the treated lesion will recur later. Also, the recurrence of lesions is lower when treated with ethanol albeit with higher complications.

Recommendation

We recommend that complex lesions such as VMs should be treated at specialized centers for a comprehensive and holistic care. Every vascular anomaly center should be encouraged to maintain a database of their patients and record the treatment sessions and their outcomes on a regular basis. Every attempt should be made to be as objective and consistent in data collection as possible. It is very important for a center to assess itself periodically for the success rate, complications, and long-term outcomes and compare its temporal trends. It would be beneficial for the physician community if a consensus can be reached as to how to assess the outcome. That way comparisons among centers and long-term outcomes of sclerotherapy would be easier to assess.

References

- Limaye N, Wouters V, Uebelhoefer M, et al. Somatic mutations in angiopoietin receptor gene TEK cause solitary and multiple sporadic venous malformations. *Nat Genet* 2009;41(01):118–124
- Castillo SD, Tzouanacou E, Zaw-Thin M, et al. Somatic activating mutations in *Pik3ca* cause sporadic venous malformations in mice and humans. *Sci Transl Med* 2016;8(332):332ra43
- Zhang J, Li HB, Zhou SY, et al. Comparison between absolute ethanol and bleomycin for the treatment of venous malformation in children. *Exp Ther Med* 2013;6(02):305–309
- Burrows PE, Mason KP. Percutaneous treatment of low flow vascular malformations. *J Vasc Interv Radiol* 2004;15(05):431–445
- Jin Y, Lin X, Li W, Hu X, Ma G, Wang W. Sclerotherapy after embolization of draining vein: a safe treatment method for venous malformations. *J Vasc Surg* 2008;47(06):1292–1299
- Schumacher M, Dupuy P, Bartoli JM, et al. Treatment of venous malformations: first experience with a new sclerosing agent—a multicenter study. *Eur J Radiol* 2011;80(03):e366–e372
- Domp Martin A, Blaizot X, Theron J, et al. Radio-opaque ethylcellulose-ethanol is a safe and efficient sclerosing agent for venous malformations. *Eur Radiol* 2011;21(12):2647–2656
- Yamaki T, Nozaki M, Sakurai H, Takeuchi M, Soejima K, Kono T. Prospective randomized efficacy of ultrasound-guided foam sclerotherapy compared with ultrasound-guided liquid sclerotherapy in the treatment of symptomatic venous malformations. *J Vasc Surg* 2008;47(03):578–584
- Ali S, Weiss CR, Sinha A, Eng J, Mitchell SE. The treatment of venous malformations with percutaneous sclerotherapy at a single academic medical center. *Phlebology* 2016;31(09):603–609
- van der Linden E, Pattynama PM, Heeres BC, de Jong SC, Hop WC, Kroft LJ. Long-term patient satisfaction after percutaneous treatment of peripheral vascular malformations. *Radiology* 2009;251(03):926–932
- Goyal M, Causer PA, Armstrong D. Venous vascular malformations in pediatric patients: comparison of results of alcohol sclerotherapy

- with proposed MR imaging classification. *Radiology* 2002;223(03):639–644
- 12 Caty V, Kauffmann C, Dubois J, et al. Clinical validation of semi-automated software for volumetric and dynamic contrast enhancement analysis of soft tissue venous malformations on magnetic resonance imaging examination. *Eur Radiol* 2014;24(02):542–551
 - 13 Spence J, Krings T, terBrugge KG, da Costa LB, Agid R. Percutaneous sclerotherapy for facial venous malformations: subjective clinical and objective MR imaging follow-up results. *AJNR Am J Neuroradiol* 2010;31(05):955–960
 - 14 Tan KT, Kirby J, Rajan DK, Hayeems E, Beecroft JR, Simons ME. Percutaneous sodium tetradecyl sulfate sclerotherapy for peripheral venous vascular malformations: a single-center experience. *J Vasc Interv Radiol* 2007;18(03):343–351
 - 15 Lee BB, Do YS, Byun HS, Choo IW, Kim DI, Huh SH. Advanced management of venous malformation with ethanol sclerotherapy: mid-term results. *J Vasc Surg* 2003;37(03):533–538