



Alcohol embolization versus non-invasive treatment for pain relief in peripheral venous malformations: a comparative study

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Contributions: (I) Conception and design: All authors; (II) Administrative support: A Tuleja, FN Helfenstein, SM Bernhard, I Baumgartner; (III) Provision of study materials or patients: A Tuleja, FN Helfenstein, F Haupt, G Hamvas, SM Bernhard, I Baumgartner; (IV) Collection and assembly of data: A Tuleja, FN Helfenstein, F Haupt, G Hamvas, SM Bernhard, I Baumgartner; (V) Data analysis and interpretation: J Rössler, M Vikkula, FN Helfenstein; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: Pain is one of the most important symptoms affecting quality of life in patients with venous malformations. Alcohol embolization is a common approach among other treatment modalities. However, the benefits and complications of this therapy require rigorous evaluation in the face of emerging alternative treatments. The aim of this study was to evaluate the efficacy of alcohol embolization in pain management compared with non-invasive treatment, and to explore associated complications.

Methods: We performed a retrospective, comparative study at the Vascular Malformation Center, University Hospital of Bern, from 2008 to 2022. Consecutive patients with peripheral venous malformations were included, one group underwent alcohol embolization and the other group received non-invasive treatment including counseling for compression stockings, physical therapy and anticoagulation. Decision to treat was made jointly by the clinician and the patient, after discussing the potential harms and benefits. Pain levels were measured using the 0–10 Numerical Rating Scale on every scheduled visit. Inverse probability of treatment weights were used to adjust for confounders such as severity of malformation indicated by number of tissues affected, localization, presence of hypertrophic tissue, history of thrombophlebitis, age, and level of pain at the initial visit. The primary outcome was change in maximal pain level, and secondary outcomes included changes in mean and minimal pain levels within 1 year of follow-up.

Results: A total of 227 patients were included in the analysis, 86 in the intervention group and 141 in the

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control group. Over the course of one year, both the control and alcohol embolization groups experienced reductions in pain. The control group showed a reduction in maximal pain from 4.42 by 0.95 points, with an additional non-significant reduction of 0.99 points in the alcohol embolization group [estimate: -0.0027 per day, 95% confidence interval (CI): $-0.0061, 0.0007$, $P=0.12$]. However, alcohol embolization led to a more pronounced and significant reduction in mean and minimal pain, with additional reductions of 1.06 (-0.0029 per day, 95% CI: $-0.0055, -0.0003$, $P=0.02$) and 0.69 points per year (-0.0019 per day, 95% CI: $-0.0035, -0.0004$, $P=0.01$), respectively. Seven minor and five major complications occurred in the alcohol embolization group.

Conclusions: Non-invasive treatment helps patients with venous malformations to manage maximal pain effectively. Alcohol embolization results in a faster and more pronounced reduction in mean and minimal pain levels, but we found no statistical evidence of an advantage of alcohol embolization for reducing maximal pain. Treatment efficacy did not appear to be influenced by gender, age, or previous treatment history. To adequately assess the efficacy of new therapies, future trials should include both disease-specific, patient-reported outcome measures and a control group.

Keywords: Pain management; clinical outcome; alcohol embolization; venous malformation

Submitted Oct 15, 2024. Accepted for publication Feb 20, 2025. Published online Jun 26, 2025.

doi: 10.21037/cdt-24-529

View this article at: <https://dx.doi.org/10.21037/cdt-24-529>

Introduction

Venous malformations are the most common vascular malformations characterized by dilated, dysfunctional venous-like vessels. Pain affects at least half of all

patients diagnosed with venous malformations (1-3). The intensity and duration of this pain vary greatly among individuals and can critically impact their quality of life (4-8). Various factors including the malformation's location, affected compartment, extent, and the presence of phleboliths influence the severity of the pain in those patients (4,5,7,9,10). It is widely assumed that once these malformations become symptomatic, the symptoms tend to persist or even worsen over time (10-13). Despite the availability of a variety of therapeutic options, the assessment of their efficacy in terms of pain reduction is infrequent, with therapeutic success often assessed through diverse criteria (14).

The well-recognized technical efficacy of alcohol embolization in treating venous malformations has traditionally been assessed by the reduction in malformation size (15,16). However, in assessing its clinical efficacy, also in face of newer, less invasive alternatives, holistic measures combining pain, functionality, aesthetics and quality of life emerged (6,8,17). While these measures are still undergoing validation, pain—often subjective yet critical to a patient's quality of life—serves as a tangible and understandable metric to evaluate treatment outcomes.

In this study, our aim was to investigate whether alcohol embolization provides superior pain relief compared to non-invasive, supportive treatment, considering the natural course of venous malformations and patients' adaptive

Highlight box

Key findings

- One-year after alcohol embolization, patients experienced faster and more pronounced minimal and mean pain relief compared to non-invasively treated patients, with mean pain decreasing from 3.15 to 1.52 and minimal pain decreasing from 1.152 to 0.545. Both groups experienced similar decreases in maximal pain. Complications occurred in 14% of treated patients.

What is known and what is new?

- Recent meta-analyses have demonstrated the effectiveness of various sclerotherapy agents for venous malformations, with alcohol embolization standing out for its superior visual improvements.
- Our study shows that while alcohol embolization improves appearance, its effect on pain relief is moderate, emphasizing the need for better patient-centered outcome measures and new targeted treatments.

What is the implication, and what should change now?

- To adequately assess the efficacy of new therapies, future trials should include both disease-specific, patient-reported outcome measures and a control group.

responses to pain. Our goal was to elucidate the role of alcohol embolization in pain management, assess its efficacy and complication rate in comparison to non-invasive therapy, and thereby position it among other treatment options. We present this article in accordance with the STROBE reporting checklist (available at <https://cdt.amegroups.com/article/view/10.21037/cdt-24-529/rc>).

Methods

Study design

This is a single-center, retrospective comparative cohort study conducted at the Vascular Malformation Center, Department of Angiology, University Hospital of Bern between January 2008 and December 2022. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study protocol was approved by the Cantonal Ethics Committee Bern, Switzerland, Project “Bernese VAScular COngential Malformation Cohort”, Project-ID 2017-01960. All participants gave informed consent for anonymized data analysis and publication.

Data collection

Data of all consecutive patients diagnosed with vascular malformations were systematically inputted during consultations into a dedicated database. Since 2020, we additionally implemented a check system for reporting and correcting missing inputs through the treating team. A previous publication described the broader population of 457 adolescent and adult patients with vascular malformations from which the participants for this study were derived, including a description of data collection and diagnostic criteria (1).

Study population

Patients diagnosed with extracranial, extraspinal venous malformations aged >14 years were included. We suspected venous malformation if there was a blue or skin-colored swelling or a bluish mucosal lesion present. The lesion typically emptied upon compression and refilled in a dependent position. Patients often reported pain, particularly upon awakening or after exercise, with prolonged pain lasting 1 to 2 weeks in cases of local thrombosis. Additionally, no murmur was detected on

auscultation. To confirm the diagnosis, duplex ultrasound was performed to identify a low-flow phenomenon, and magnetic resonance imaging was utilized to determine the localization and extent of the malformation. During the cohort observation period, participants either underwent at least one alcohol embolization for a symptomatic venous malformation (forming the intervention group) or had never undergone alcohol embolization at our center (forming the control group). For the analysis of the endpoints, intervention group was required to have an initial visit and at least one follow-up visit at 2 weeks, 3, 6, or 12 months. The control group consisted of individuals diagnosed with venous malformations who did not undergo any interventions (neither embolization/sclerotherapy nor surgery) and who had an initial visit and at least one follow-up visit. At each visit, patients were asked to describe their pain using the Numerical Rating Scale (NRS), which ranges from 0 (indicating no pain) to 10 (representing the worst pain imaginable). Patients reported three categories of pain: maximum pain, reflecting the highest level of pain experienced; mean pain, representing the average pain felt; and minimal pain, indicating the lowest level of pain experienced without reference to a specific time frame (18). In addition, history of local thrombosis, oedema, local and gastrointestinal bleeding was documented. Patients underwent regular d-dimer testing.

Intervention group management

Treatment was offered to symptomatic patients or those at risk of complications due to coagulopathy. Treatment method (embolization or surgery) was decided jointly by the patient and physician, with uncertain cases reviewed by our interdisciplinary vascular anomaly board. Patients who underwent surgery or sclerotherapy were excluded from this study. Intervention group patients underwent at least one alcohol embolization under general anesthesia. All procedures were performed by one operator (I.B.). The malformation was localized and punctured under ultrasound, confirmed by phlebography. Fractionated 96% ethanol was injected into the malformation vessels, with doses based on patient weight (max 1 mL/kg) or local skin changes. After each procedure, patients received combined anti-inflammatory and anticoagulant therapy for 10 days (rivaroxaban 10 mg per day). The procedure was repeated based on the operator's decision and/or the results of the 2-week follow-up visit. If no residual flow has been detected as indicated by duplex ultrasound or the patient experienced

a major complication, the treatment was discontinued and the patient was followed up at 3, 6, and 12 months after the last alcohol embolization. Local pain, inflammation, edema, necrosis, nerve damage, hypotension, failed embolization, infection, bleeding, and other related problems were recorded in the complication registry.

Control group management

This group consisted of patients who have been diagnosed with a venous malformation, but did not receive any interventional treatment during the study period. They were advised about appropriate supportive measures such as compression stockings on the extremities, physio- and/or ergotherapy. In addition, on-demand oral anticoagulation therapy with rivaroxaban 10mg per day for 2 weeks was recommended to treat symptoms of localized thrombosis such as swelling and pain (11,19-21). Long-term anticoagulation was recommended only in sporadic cases. We have not regularly recommended anti-inflammatory drugs, as the primary cause of pain was managed with other non-invasive measures. Patients were routinely followed annually, with 5 to 10-year intervals for those with stable and minimal symptoms.

Endpoints and statistical analysis

The primary endpoint was the variation in maximum pain from baseline to focal follow-up visit. Variations in mean and minimal pain between the initial and the same follow-up visit were secondary endpoints. Due to differences in the follow-up schedule in both groups, to minimize missing values we defined the focal follow-up visit as either the visit available at 1 year or the one closest to 1 year but no later than 2 years.

We investigated the effect of alcohol embolization on the variation in pain level (maximal, mean, minimal) from baseline to follow-up using linear mixed-effect models for repeated measures, with the primary or secondary outcome at baseline and follow-up as dependent variables and treatment (alcohol embolization *vs.* noninvasive treatment) and time to follow-up in days (set to 0 for baseline) as explanatory factors. Missing data were handled using a complete case analysis approach. We included the interaction between treatment and time to test for a difference in pain variation through time (difference in slope) between the treatments. To control for the effects of known confounders, due to the observational nature of

the study, we used inverse probability of treatment weights (IPTW). In an observational study, unlike a randomized controlled trial, treatments—intervention *vs.* control—are not randomly assigned, so differences between treatments in outcome variables may be confounded by measured and unmeasured confounders. IPTW is a statistical technique that aims to address causality by removing the effect of measured potential confounders. The general idea behind IPTW is to generate individual surrogate observations, so that confounders are no longer related to the treatment being studied. The aim is to transform the data so that the measured confounders are approximately randomly distributed across the treatments. In short, the first step of IPTW is to calculate the probability of receiving the intervention or control treatment, given an individual's characteristics. Second, weights are calculated for all individuals as the inverse of the probability of receiving their actual treatment (22). A Type III ANOVA test of the interaction treatments x time evaluated whether the change in pain levels over time differed between the two groups (difference in slopes).

IPTW were derived from a logistic model, including treatment as the dependent variable and the following potential confounding factors: severity of malformation indicated by number of tissues affected, presence of hypertrophic tissue (yes/no), history of thrombophlebitis (yes/no), age as a binary variable (≤ 18 ; >18 years old), bleeding (yes/no), level of pain (maximal, mean and minimal) at the initial visit and time until follow-up visit (days). Also, we investigated whether and how gender, age, and history of previous treatment moderated—interacted with—the effect of alcohol embolization on the variation in maximal pain from baseline to follow-up using three separate linear mixed-effect models for repeated measures including the triple interaction between treatment, time and gender, age or history of previous treatment respectively.

For comparisons of patients' baseline characteristics between control patients and patients who underwent alcohol embolization, in accordance with recommendations by the American Statistical Association (23), we do not provide results of statistical tests, because they have little informative value due to multiple testing and subsequent inflation of the type I error. In the report we refer to the mean with standard deviation as “N (SD)” or the median with 25% and 75% bounds as “N [25%, 75%]” but unless otherwise specified, we report on means. All statistical analysis, tables and figures were done with R-Studio 4.2.1 (2022-06-23).

Results

Patient's baseline characteristics at initial visit

Of the total 227 patients included in the descriptive analysis (described in the *Table 1*), we included 113 for the primary endpoint analysis and 63 or 62 for the secondary endpoint analysis due to missing values (*Figure 1*).

Patients who underwent alcohol embolization were younger 25.19 [19.11, 33.89] *vs.* 29.85 [17.71, 45.13] years, than those treated non-invasively, were predominantly women (62%), and had a shorter follow-up time 315.00 [238, 396] *vs.* 372.00 [263, 492] days. The intervention group mostly had malformations in the lower extremity, whereas the control group had a more balanced distribution across the lower and upper extremities, as well as the head and neck regions. Nearly half of the patients in each group had a history of previous treatments. Surgery was the most common, and concerned 29% of patients in the intervention group and 26% in the control group. While surgery and laser therapy had similar patient numbers across groups, embolization pretreatments were more common in the intervention group (23% *vs.* 9% in controls) (*Table 1*).

There were considerable differences in baseline pain levels between the groups, before implementation of IPTW. The intervention group reported higher pain of all types: 5.17 (2.53) *vs.* 4.33 (3.12) for maximum pain, 3.17 (1.84) *vs.* 2.10 (2.41) for mean pain, and 1.12 (1.41) *vs.* 0.9 (1.85) for minimal pain. 34% of patients in the treatment group (N=86) had localized intravascular coagulopathy, compared to 27% of patients in the control group (N=141). Other symptoms like superficial thrombosis, phleb- or lymphedema, and bleeding were comparably rare, seen in only 11% of patients.

Primary endpoint: maximal pain

Complete case set

The complete case set for the primary outcome was smaller due to missing values: 91 patients had missing data for the initial and/or follow-up visit within two years; this left 113 patients (53 treated and 60 controls) for the analysis.

Patients' characteristics

Initial maximum pain scores were 5.17 for the intervention group and 4.33 for the control group. At follow-up visit closest to 1 year, maximal pain scores were 3.26 and 3.05, respectively. Other patients' characteristics are summarized in *Table S1*.

Confounders and probability of treatment

We conducted a logistic regression model to identify factors susceptible to predict the likelihood of a patient to receive the intervention. Although the odds ratio for the variable "maximal pain" was not numerically the largest, it had the strongest statistical evidence of a difference between the two groups (*Table S2*). After applying IPTW to our sample, confounders were equally distributed between the control and the intervention groups, therefore cancelling the imbalance in initial maximal pain level, now being 4.92 for the control and 4.96 for the intervention group (*Table S2*).

Effect of alcohol embolization

A mixed-effect linear model for repeated measures with IPTW showed that maximal pain reduced from initial to follow-up visit in both the control and the intervention groups. Specifically, over the course of one year, the control group experienced a reduction in maximal pain from an initial level of 4.42 by approximately 0.95 points [estimate: -0.0026 per day, 95% confidence interval (CI): -0.0049, -0.0004, *P*=0.02] (*Table 2*). In the alcohol embolization group, pain decreased slightly more, with an additional reduction of approximately 0.99 points per year (interaction estimate: -0.0027 per day, 95% CI: -0.0061, 0.0007, *P*=0.12); however, this difference in pain reduction between the two groups was not statistically significant (*Table S2*, *Figure 2*).

Moderators

Neither gender, age nor history of prior treatments seemed to moderate (interact with) the effect of alcohol embolization (*Table S3*).

Secondary endpoint analysis: mean and minimal pain

Complete case set

Other analyses for mean and minimal pain at the follow-up visit closest to 1 year included 63 and 62 patients, respectively. We applied a consistent statistical approach for the secondary endpoints, focusing on the difference in mean and minimal pain levels as illustrated in *Figures 3,4*.

Effect of alcohol embolization on mean pain

At baseline, treated patients reported a mean pain level of 3.17 and control patients reported 2.10 (*Table S1*). After applying IPTW, the adjusted mean pain scores were 2.76 and 3.11 for the treated and control groups, respectively. Using a mixed-effect linear model for repeated measures

Table 1 Summary of patient characteristics at initial visit stratified by intervention

Characteristic	Overall, n=227	Alcohol embolization, n=86	No alcohol embolization, n=141
Age (years), median [25%, 75%]	27.95 [18.47, 42.06]	25.19 [19.11, 33.89]	29.85 [17.71, 45.13]
Gender (female)	128 (56%)	53 (62%)	75 (53%)
Follow-up visit (days), median [25%, 75%]	361.00 [238.50, 444.00]	315.00 [238.00, 396.00]	372.00 [263.25, 492.50]
Localization			
Head/neck	22 (12%)	0 (0%)	22 (20%)
Lower extremity	88 (46%)	49 (60%)	39 (36%)
Trunk	22 (12%)	7 (8.5%)	15 (14%)
Upper extremity	47 (25%)	21 (26%)	26 (24%)
Multifocal	12 (6.3%)	5 (6.1%)	7 (6.4%)
Extent of malformation number of tissues, mean (SD)	1.60 (0.85)	1.64 (0.80)	1.58 (0.89)
Previous therapy			
Surgery	61 (27%)	25 (29%)	36 (26%)
Laser	5 (2.2%)	1 (1.2%)	4 (2.8%)
Embolization	33 (15%)	20 (23%)	13 (9.2%)
Minimal pain at initial visit			
Median [25%, 75%]	0.00 [0.00, 2.00]	0.50 [0.00, 2.00]	0.00 [0.00, 1.00]
Missing	110	42	68
Average pain at initial visit			
Median [25%, 75%]	2.00 [0.00, 4.00]	4.00 [2.00, 4.00]	2.00 [0.00, 3.75]
Missing	107	40	67
Maximal pain at initial visit			
Median [25%, 75%]	4.00 [2.00, 6.00]	6.00 [3.00, 7.00]	4.00 [2.00, 6.00]
Missing	45	16	29
Presence of other symptoms at the initial visit			
Superficial thrombosis	25 (11%)	9 (10%)	16 (11%)
Phlebolympheidema	17 (7.5%)	5 (5.8%)	12 (8.5%)
Gastrointestinal bleeding	1 (0.4%)	0 (0%)	1 (0.7%)
Bleeding from malformation	5 (2.2%)	1 (1.2%)	4 (2.8%)
Level of D-dimer at initial visit (ng/mL)			
Median [25%, 75%]	269.00 [175.00, 575.00]	334.50 [175.75, 575.75]	267.00 [173.00, 546.00]
Missing	86	16	70
Level of D-dimer (categorical)			
Elevated	43 (30%)	24 (34%)	19 (27%)
Normal	98 (70%)	46 (66%)	52 (73%)
Missing	86	16	70

SD, standard deviation.

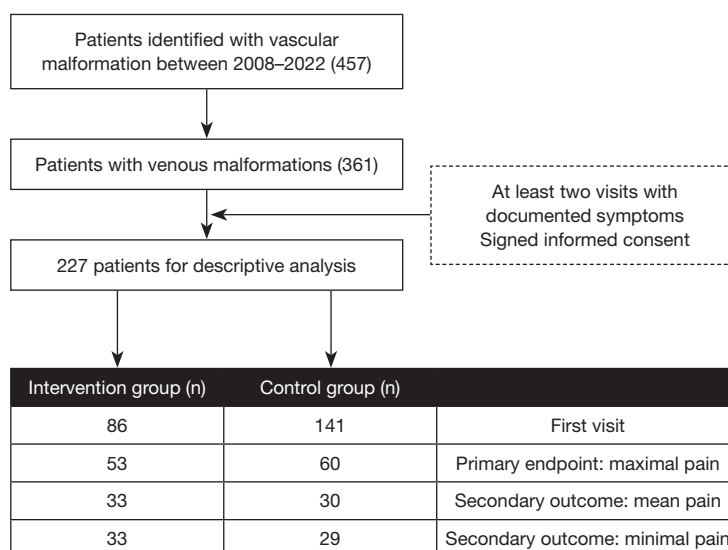


Figure 1 Flowchart of the study population.

Table 2 Estimates of a linear mixed-effect model investigating the variation in maximal pain in relation to the time since initial visit with inverse probability of treatment weighting

Variable	Estimate	95% CI	P value
Intercept (control patients at initial visit)	4.424	3.700, 5.147	<0.001
Time to FU visit	−0.0026	−0.0049, −0.0004	0.02
Alcohol emb. (vs. control)	0.6021	−0.4385, 1.643	0.25
Alcohol emb. × time to FU visit	−0.0027	−0.0061, 0.0007	0.12

P values are derived from an omnibus ANOVA with Wald's χ^2 . ANOVA, analysis of variance; CI, confidence interval; emb., embolization; FU, follow-up.

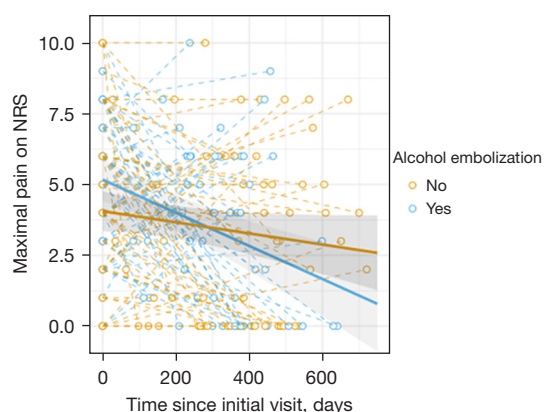


Figure 2 Scatter plot of maximal pain level at initial visit and at follow-up visits closest to 1 year (but no later than 2 years) in control patients and in patients who received alcohol embolization. NRS, Numerical Rating Scale

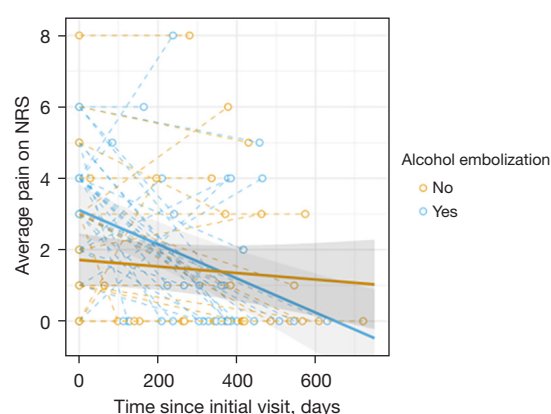


Figure 3 Scatter plot of mean pain level at initial visit and at follow-up visit closest to 1 year in control patients and in patients who received alcohol embolization. NRS, Numerical Rating Scale

with IPTW, we found that both groups decreased or remained at similar levels of mean pain. Specifically, over one year, the mean pain level decreased by approximately -0.44 points (estimate -0.0012 per day; 95% CI: -0.0029 , 0.0006 ; $P=0.18$) in the control group. Patients who received alcohol embolization experienced a more pronounced reduction in pain, reflected in an additional daily pain reduction of -0.0029 points per day (95% CI: -0.0055 , -0.0003 , $P=0.02$), corresponding to an additional 1 point

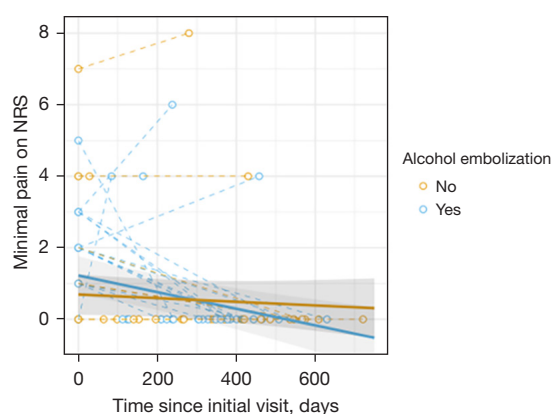


Figure 4 Scatter plot of minimal pain level at initial visit and at follow-up visit closest to 1 year in control patients and in patients who received alcohol embolization. NRS, Numerical Rating Scale.

reduction per year (Figure 3 and Table 3).

Effect of alcohol embolization on minimal pain

At baseline, minimal pain scores were 1.12 for treated patients and 0.9 for controls. Using the same approach, the reduction in minimum pain reached 0.12 points in the control group (estimate -0.0003 points per day; 95% CI: -0.0013 , 0.0008 , $P=0.58$). In the alcohol embolization group, patients experienced an additional reduction of 0.69 points (estimate -0.0019 points per day; 95% CI: -0.0035 , -0.0004 , $P=0.01$). The smaller difference compared to the mean pain score may be due to a floor effect, as minimal pain scores tended to be close to zero (Figure 4 and Table 4).

Complications

In total we observed complications in 12 of 86 (14%) treated patients included in the descriptive analysis. Most of these complications were either transient or did not require any further medical intervention ($n=7$; 8%). These included local transient swelling and pain experienced by four patients, hypoesthesia in two patients, and paresthesia in the treated area for one patient. In terms of severe complications ($n=5$; 6%), we documented a flexion deficit that required surgical adhesiolysis, asymptomatic osteonecrosis of the femur, deep venous thrombosis, skin necrosis in the treated area, and nerve paralysis leading to

Table 3 Estimates of a linear mixed-effect model investigating the variation in mean pain in relation to the time since initial visit with inverse probability of treatment weighting

Variable	Estimate	95% CI	P value
Intercept (control patients at initial visit)	1.930	1.158, 2.703	<0.001
Time to FU visit	-0.0012	-0.0029 , 0.0006	0.18
Alcohol emb. (vs. control)	0.9998	-0.0772 , 2.077	0.07
Alcohol emb. $\times$ time to FU visit	-0.0029	-0.0055 , -0.0003	0.02

P values are derived from an omnibus ANOVA with Wald's χ^2 . ANOVA, analysis of variance; CI, confidence interval; emb., embolization; FU, follow-up.

Table 4 Estimates of a linear mixed-effect model investigating the variation in minimal pain in relation to the time since initial visit with inverse probability of treatment weighting

Variable	Estimate	95% CI	P value
Intercept (control patients at initial visit)	0.7012	0.1114, 1.291	0.02
Time to FU visit	-0.0003	-0.0013 , 0.0008	0.58
Alcohol emb. (vs. control)	0.4955	-0.3166 , 1.308	0.22
Alcohol emb. $\times$ time to FU visit	-0.0019	-0.0035 , -0.0004	0.01

P values are derived from an omnibus ANOVA with Wald's χ^2 . ANOVA, analysis of variance; CI, confidence interval; emb., embolization; FU, follow-up.

chronic motor deficiency; these complications occurred each in one patient. There were no registered deaths, nor were there any cases of pulmonary embolism or pulmonary spasm following the alcohol embolization procedure. Documented complications occurred at any time between treatment and the focal follow-up visit.

Discussion

We found that alcohol embolization significantly improved mean and minimal pain levels in patients with venous malformations. However, there was no significant difference in the management of maximal pain levels between treated patients and controls. Complications occurred in 14% of treated patients, ranging from transient to persistent symptoms, but no serious outcomes such as death or pulmonary embolism were reported. In addition, we found no evidence that gender, age, or history of previous therapies affected the impact of alcohol embolization on pain management.

This study is inevitably subject to certain limitations due to its retrospective design and data collection. An important issue is to ensure comparability between the control and intervention groups. To address this, the study used IPTW and pre-specified potential confounders that have been shown to influence pain in other studies (4,5,7,9,10). Despite the use of IPTW to remove confounders and attempt to statistically address causality (22), there may be some uncontrolled factors that limit this method. At least for those that were controlled, the study groups were evenly distributed after implementation of IPTW (Table S2). Another concern is missing data. However, missing were equally distributed in both groups and unlikely to be related to the value of the outcome suggesting missing at random (MAR). For instance, secondary outcomes minimal pain and mean pain were decided to be included in the analysis in a second step, which explains why most early patients, both in the control and the intervention group, have missing values for those outcomes. Therefore, we believe that, if anything, missing values render our analysis more conservative due to loss of power, but do not bias our sample. Another challenge was the difference in follow-up time. Patients in the intervention group were evaluated more frequently—at 2 weeks, 3, 6, and 12-month intervals—compared with the primarily annual evaluations of those who did not receive therapy. To standardize our comparisons, we specifically sought data from follow-up visits that were closest to the one-year time point. In addition, our outcome measure,

while relevant, has inherent limitations due to its self-report nature and simplicity. The pain scores also did not reflect a specific time frame, but rather an aggregate reflection of the pain a patient experienced due to the malformation. Nevertheless, by categorizing pain into minimal, mean, and maximal levels, we aimed to provide a nuanced and more informative perspective on the patient's experience.

Our study suggests that alcohol embolization is only moderately effective in reducing pain compared to non-invasive treatment. This is consistent with existing literature when patient-reported outcomes are included in the evaluation (24,25). These studies highlight not only a moderate reduction in pain, but also little improvement in other symptoms and overall functionality after alcohol embolization. Nonetheless, it is crucial to acknowledge the cosmetic and aesthetic benefits associated with alcohol embolization, which are well-documented across various studies (26–31). Such benefits have been considered in evaluations presenting alcohol embolization as potentially superior to other sclerosing agents (15,16). However, the current lack of systematic evaluation of patient-oriented outcome measures for evaluation of therapy necessitates a cautious approach towards such claims of superiority. Interestingly, our study did not reveal a higher incidence of toxic effects associated with alcohol compared to other methods, with a complication rate of 14%. This is comparable to recent large-scale studies that reported an overall complication rate of 11.6%, for presumably less toxic agents than alcohol (32). Given the emergence of new treatment options and the absence of randomized comparisons, the search for the optimal sclerosing agent—especially from the perspective of patient-reported outcomes—remains an important area for further investigation.

This study provides insight into the effectiveness of non-invasive supportive care for adolescents and adults with venous malformations, highlighting the reduction in maximal experienced pain and at least stable levels of mean and minimal pain. This underscores the importance of conservative treatment approaches for effective pain management in patients with venous malformations. Despite a generally pessimistic outlook on progression and worsening of symptoms over time, with only 12% of patients remaining stable over their lifetime (10–13), our research shows a maintenance or reduction in all types of pain between 1 and 2 years after initial presentation, without invasive treatment. However, there is a greater reduction in minimal and mean pain in the intervention

group, which may be more relevant to patients' daily quality of life. This finding has implications for shared decision making with patients, suggesting a reassessment of the need for interventional treatment after 1 year of non-invasive treatment, or if the patient experiences more constant pain than intermittent exacerbations, to be more prone to suggest intervention.

Our study also highlights the need to distinguish visual from symptomatic venous-malformation progression. The study by Hassanein *et al.* (12), defines progression as both visual and symptomatic, without distinguishing between those who experienced an increase in size versus those who experienced an increase in symptoms or both. Our findings suggest that symptomatic progression may be transient and it may be beneficial to assess visual and symptomatic changes independently. In addition, the inclusion of a control, non-invasive treatment group in our study appears to be critical to a comprehensive evaluation of the effects of therapy, as it takes into account the effect of compression and anticoagulation as well as ability of patients to adapt to symptoms over time.

Using pain as the sole outcome measure presents as many advantages as challenges. The 10-point numeric pain scale is straightforward for patient reporting and for interpreting potential treatment effects, providing a practical tool for inclusion in all types of research. These scales have been validated and the minimal clinically important difference has been established, albeit for other conditions (33). However, the scale has several problems—self-report is prone to recall bias and it is not clear what time frame should be used. Given the chronic nature of the disease and fluctuating episodes of exacerbation due to factors such as local thrombosis or increased volume due to physical activity, it may be necessary to differentiate pain levels during exacerbations and stable phases, as well as pain experienced during activity or standing, and morning versus evening. Standardization of these nuances across prospective studies is crucial to enable valid comparisons at a higher level.

The introduction of the internationally recommended disease-specific surveys—Outcome measures for Vascular MALformations (OVAMA)—addresses some of these challenges. This survey covers a wide range of patient-reported outcomes, including general symptoms, appearance, treatment satisfaction, and head and neck specific issues. To capture the impact on functionality and quality of life, it is proposed to integrate Patient-Reported Outcomes Measurement Information System

(PROMIS) scales that assess overall quality of life, daily activities, mobility, ability to work or study, self-confidence, self-esteem, and emotional well-being (6,8,17). The effectiveness of such a multidimensional approach in daily practice and clinical research, as well as the determination of the minimal clinically relevant difference, remains to be evaluated. Nevertheless, the introduction of these measures has already changed our clinical practice. Future studies will report on the use of these metrics, and we advocate their consistent application in other centers. This is especially important as the range of treatments for patients with vascular malformations continues to expand, leaving the efficacy of these treatments, particularly for patient-reported outcomes, an open question.

Outlook and future studies

While pain serves as a tangible and understandable measure for both patients and caregivers, it captures only a narrow aspect of a patient's overall quality of life. This study calls for future research to validate the internationally proposed comprehensive outcome measures and emphasizes the importance of including a control group in subsequent studies (34).

Conclusions

Non-invasive treatment helps patients with venous malformations to manage pain effectively. Alcohol embolization appears to improve pain more quickly than non-invasive treatment. However, using IPTW to adjust for baseline differences, our retrospective study found no statistical advantage of alcohol embolization over standard care in reducing maximal pain levels. Yet, for secondary outcomes, alcohol embolization resulted in faster and more pronounced reductions in mean and minimal pain levels. Treatment efficacy did not appear to be influenced by gender, age, or previous treatment history.

In the context of the treatment of venous malformations, these results highlight the potential of alcohol embolization to rapidly improve pain, but emphasize the need for extensive future research into new therapies and comprehensive outcome measures.

Acknowledgments

This abstract was presented as a poster on the ISSVA World Congress 2024 in Madrid. We are grateful to all the family

members for their invaluable participation, and thank P. Stähli for expert assistance in data science and managing the data.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://cdt.amegroups.com/article/view/10.21037/cdt-24-529/rc>

Data Sharing Statement: Available at <https://cdt.amegroups.com/article/view/10.21037/cdt-24-529/dss>

Peer Review File: Available at <https://cdt.amegroups.com/article/view/10.21037/cdt-24-529/prf>

Funding: This study was supported by the Swiss National Science Foundation under the Sinergia (project No. CRSII5_193694 to I.B., J.R., A.T., and T.A.A.), and the Fonds de la Recherche Scientifique - FNRS Grants (Nos. T.0026.14 and T.0247.19 to MV, Nos. T.0146.16 and P.C013.20 to LMB).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://cdt.amegroups.com/article/view/10.21037/cdt-24-529/coif>). L.B. and M.V. are members of the Vascular Anomaly Working Group (VASCA WG) of the European Reference Network for Rare Multisystemic Vascular Diseases (VASCERN) - Project ID: 769036. J.R. is currently an employee of Novartis Pharma AG. I.B., A.T., and T.A.A. report funding from the Swiss National Science Foundation under the Sinergia (project No. CRSII5_193694). The other authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study protocol was approved by the Cantonal Ethics Committee Bern, Switzerland, Project “Bernese VAScular COngential Malformation Cohort” (Project-ID 2017-01960). All participants gave informed consent for anonymized data analysis and publication.

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Cite this article as: Tuleja A, Döring Y, Helfenstein FN, Andreotti TA, Rössler J, Boon LM, Vikkula M, Haupt F, Hamvas G, Bernhard SM, Baumgartner I. Alcohol embolization versus non-invasive treatment for pain relief in peripheral venous malformations: a comparative study. *Cardiovasc Diagn Ther* 2025;15(3):598-609. doi: 10.21037/cdt-24-529