Cryoablation Of Congenital Venous Malformations: A Systematic Review

Alexander Moushey

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Cryoablation of Congenital Venous Malformations: A Systematic Review

A Thesis Submitted to the Yale University School of Medicine
in Partial Fulfillment of the Requirements for the Degree of Doctor of Medicine

by

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Yale School of Medicine Class of 2022
ABSTRACT

Objective
To systematically review the potential efficacy, safety and technical aspects of cryoablation in the treatment of venous malformations, and provide the groundwork for future prospective studies.

Materials and Methods
Venous malformations (VMs) are a common slow-flow type congenital vascular malformation made up of a “mass-like” network of dysplastic venous structures. A systematic review was performed following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A search in PubMed and Google Scholar for clinical studies utilizing percutaneous cryoablation of VMs was performed and all relevant articles were then manually reviewed. Prospective, retrospective and case studies related to primary or secondary treatment of venous malformations with percutaneous cryoablation were included for review. These selected studies were then evaluated for: patient characteristics, cryoablation technique, technical success rate (as defined by the ice ball covering the entire lesion), pre and post lesion size, pre and post pain scores (scored 1-10 with 10 being the worst pain), and adverse outcomes. The methodologic quality of these studies were analyzed utilizing the Newcastle-Ottawa Quality Assessment Scale (NOS). Random effects model was utilized to compute the standardized mean differences in the pre- and post-procedural volume and pain score.
changes. A funnel plot was performed to assess standardized mean differences between the studies.

Results

There were 54 patients with 55 cases of cryoablation for VMs identified. Of these cases, 27 cases recorded change of lesion volume, and 31 recorded changes in pain scores. The weighted mean post-procedure decrease in lesion size was 92.0% (raw average of 71.7%). The weighted mean reduction in pain score was 77% (raw average of 78.2%), with 20 of 31 cases (64.5%) reporting complete resolution of pain and complete or partial improvement in 94.5% of patients. Common post-procedural symptoms included pain, bruising, swelling and numbness, lasting under two weeks. There were two major adverse events (3.7%), with both cases due to persistent dysesthesia. Patients with history of prior sclerotherapy demonstrated lower pre- and post-procedural pain scores (4.7 and 1.3), compared with patients without prior treatments (5.8 and 2.8).

Conclusions

Cryoablation of venous malformations appears to be potentially safe and effective on limited short-interval follow-up. Larger prospective studies with longer follow-up periods are needed.
Key Points

- Cryoablation of venous malformations appears to be effective in reducing pain and lesion size, with 63.6% of patients reporting complete resolution in pain and 94.5% with overall improvement.
- Initial and post-procedural pain scores were lower in patients with prior sclerotherapy. However, a significant difference in the reduction of pain and lesion size between the two groups was not observed.
- Major adverse events occurred in 3.7% of the treated population, with all cases due to persistent dysesthesia at final follow-up.
ACKNOWLEDGEMENTS

First and foremost, I would like to thank my thesis mentor, Todd Schlachter, MD, Assistant Professor of Radiology and Biomedical Imaging at Yale School of Medicine, for his invaluable advice and continuous support during the process of writing this thesis. Additionally, I would like to express my deepest appreciation to Adam Fish, MD, resident physician in the Yale Diagnostic Radiology Residency program, who led the charge in creating the original systematic review manuscript from which this thesis was derived. My gratitude extends to many other mentors throughout medical school, most notably to my clinical skills instructor, Joseph DeMayo, MD, my videography and educational research mentors, Long Tu, MD and Sarah Maurrasse, MD, and my first medical school research mentor, Steven Tommasini, PhD. Lastly, I’d like to thank my family and friends, because without them, medical school would be far less fun.
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INTRODUCTION

Background

Venous malformation (VM) is the most common type of congenital vascular anomaly and may cause significant morbidity and pain. While surgery has historically been useful in the management of VMs, percutaneous sclerotherapy has become standard treatment for VMs, requiring less operative time and associated with less blood loss per lesion volume compared to surgery. Percutaneous sclerotherapy has a technical success rate ranging between 71 and 100% depending on lesion location, volume, and operator experience, with complete relief of symptoms in 27-68% of patients and overall response of 67-100%. For patients experiencing persistent symptoms after sclerotherapy, and for select patients for which a multidisciplinary committee has deemed alternative primary treatments appropriate, percutaneous cryoablation has shown to serve as a potential treatment option. However, there are limited prospective studies evaluating the safety and efficacy of cryoablation in venous malformations.

Statement of Purpose

In this study, we perform a systematic review of percutaneous cryoablation for VMs in regards to safety, technical success, clinical response, and adverse events.
**Epidemiology**

Venous malformations are vascular anomalies comprised of ectatic venous channels found most commonly in the limbs, trunk, head, and neck. Venous malformations are present at birth and typically grow without spontaneous regression, however they are often not clinically evident until later in life when the patient stops growing. The incidence of venous malformations is between 1/5000 and 1/10000 births and is the most common vascular anomaly seen in referral centers.

**Genetics**

While venous malformations are most commonly sporadic, patients with suspected familial inheritance have been studied for genetic patterns. A gene on the short arm of chromosome 9 was the first locus found to be linked to the venous malformation phenotype. Subsequent studies of different families with inherited venous malformations demonstrated genetic linkage to the same region on chromosome 9. The first study utilizing positional cloning and candidate gene analyses for venous malformations demonstrated that two families with inherited venous malformations had a mutation in the gene encoding the angiopoietin receptor, endothelial specific receptor tyrosine kinase TIE2, specifically discovering a single amino acid substitution at R849W, affecting the intracellular kinase domain. This finding was supported by subsequent studies that identified additional loss-of-function mutations in the angiopoietin receptor gene TIE2/TEK.
In later studies, patients with venous malformations have been discovered to have upregulation of tissue growth factor beta (TGF-beta) and basic fibroblast growth factor (beta-FGF).\textsuperscript{14} Additionally, progesterone receptors have been identified in venous malformations, which helps explain the clinical observation that venous malformations tend to grow more rapidly during hormonal changes, such as puberty, pregnancy, and use of oral contraceptive pills.\textsuperscript{15}

As genetic studies continued to be performed, venous malformations were found to be associated with other genetic loci and therefore multiple genetic syndromes. The International Society of the Study of Vascular Anomalies (ISSVA) has compiled lists of these associated syndromes and their causal genes. Awareness of these associated syndromes can help physicians identify need for further workup in patients presenting with venous malformations.

Notable syndromes linked to the TIE2/TEK gene include Blue Rubber Bleb Nevus Syndrome (BRBNS, or Bean’s syndrome) and Multiple Cutaneous and Mucosal Venous Malformations syndrome (VMCM).\textsuperscript{16} BRBNS presents with multifocal venous malformations of the skin and gastrointestinal tract. Skin lesions are typically the first manifestations identified clinically, and appear as rubbery, dark-blue venous nodules or as skin-colored compressible protuberances.\textsuperscript{17} These patients are prone to developing anemia due to chronic GI bleeding, and therefore require lifelong iron and blood
transfusions. In rare cases, central nervous system manifestations are seen late in disease progression, where compression from venous malformations in the brain can lead to seizures and focal neurological deficits. VMCM is an autosomal dominant syndrome that presents with small, multifocal bluish cutaneous and mucosal venous malformations. While new lesions appear over time, lesions are typically present at birth. These venous malformations are usually small and asymptomatic, although larger lesions can invade subcutaneous muscle and cause pain.

PIK3CA-related overgrowth spectrum (PROS) includes a variety of heterogenous overgrowth phenotypes due to somatic PIK3CA activating mutations. Two notable PROS syndromes that include vascular malformations are CLOVES syndrome (Congenital Lipomatous Overgrowth, Vascular Malformations, Epidermal Nevi, Scoliosis/Skeletal and Spinal) and Klippel-Trenaunay syndrome (KTS). KTS presents with capillary malformations, venous malformations, limb overgrowth, and may or may not include lymphatic malformations. Clinically, KTS presents with a triad of extremity varicosities, cutaneous vascular malformations (often a port-wine stain), and hypertrophy of soft tissues and long bones, which may cause pain, edema, ulcerations, and pruritis.

Other genetic syndromes associated with venous malformations include Servelle-Mortorell syndrome, which presents with limb venous malformations and bone undergrowth, Maffucci syndrome, which is associated with the IDH1/IDH2 gene and may present with spindle-cell hemangiomas and enchondromas, Proteus syndrome,
which is associated with the AKT1 gene and presents capillary malformations and asymmetrical somatic growth, and Bannayan-Riley-Ruvalcaba syndrome, which is associated with the PTEN gene and presents with AVMs, macrocephaly, and lipomatous overgrowth.\textsuperscript{16}

**Clinical Presentation**

The classic presentation of venous malformations includes chronic extremity pain and swelling that is worsened in the dependent position and early mornings (secondary to blood-pooling). Episodes of acute pain are common, secondary to micro-thrombosis, and may improve with non-steroidal anti-inflammatory medications (NSAIDs). For the purposes of documenting treatment response, most institutions assess an overall pre- and post- treatment pain score. Out of 54 patients reviewed, all but one patient presented with pain.

The average patient age was 35.5 years old and 71.0\% of patients were female. Lesion location was reported in 51 out of 55 cases, with the most common lesion location being in the lower extremities (36 cases, 70.6\%), followed by the upper extremities (7 cases, 13.7\%), thoracic wall (4 cases, 7.8\%) and abdominal wall (4 cases, 7.8\%).

Intramuscular versus extra muscular location was reported in 37 cases, with 34 cases being intramuscular 91.9\%. Prior sclerotherapy treatment was noted in 31 of 54 patients (57.4\%), including six patients with multiple treatments (11.1\%). Prior surgeries were
noted in seven patients (13.0%). Table 2 summarized prior treatments. The initial pain scores in patients with previous sclerotherapy treatments was 4.7, compared to 5.0 in patients with prior surgery, and 5.8 in patients without prior sclerotherapy or surgery.

Classification of Vascular Anomalies

The International Society for the Study of Vascular Anomalies (ISSVA) has established a classification system which utilizes pathologic and hemodynamic features of vascular anomalies to categorize them.\textsuperscript{16, 22} When using the ISSVA system, congenital vascular anomalies are first determined to be either vascular tumors or vascular malformations. This distinction is critical as many vascular malformations are misdiagnosed as hemangiomas, the most common vascular tumor.\textsuperscript{23} One study reports that up to 71.3% of hemangioma cases are misclassified, leading to suboptimal medical management in up to 20.6% of those diagnosed with a hemangioma.\textsuperscript{24} Vascular tumors, such as hemangiomas, will demonstrate evidence of mitosis in endothelial cells on histopathology, confirming increased endothelial cell turnover. Vascular malformations, on the other hand, will demonstrate structural abnormalities of the vasculature or lymphatic system on histopathology, without evidence for increased endothelial cell turnover.\textsuperscript{25}

Once the lesion has been determined to be a vascular malformation as opposed to a vascular tumor, imaging may be used to help further differentiate types of vascular
malformations. Ultrasound is used to determine if the lesion is a low-flow vascular malformation, which suggests capillary, venous, or lymphatic components, versus high-flow vascular malformation, which suggests arterial components.\textsuperscript{25}

Ultrasound can further differentiate the type of low-flow vascular malformation by considering if the lesion appears cystic, indicating a mostly lymphatic lesion, versus if the lesion appears solid, indicating a mostly venous lesion. MRI is primarily used for evaluation of lesion extent and to help the medical team create a treatment plan.\textsuperscript{25}

Additional details regarding the diagnosis of venous malformations can be found in the \textit{Diagnosis of Venous Malformations} section below.

\textbf{Diagnosis of Venous Malformations}

The diagnosis of a venous malformation was made with imaging, with all studies utilizing ultrasound and MRI, and biopsy in three of the eight studies (17 of 55 cases, 30.9\%).\textsuperscript{26-28} The exact imaging criteria utilized in these studies was somewhat heterogenous and not clearly defined in all papers. This is further discussed in the limitations section. However, in general on sonography venous malformations appear as tubular, compressible, structures with internal flow. Spectral doppler is used to confirm venous flow and exclude the presence of arterial wave forms which may suggest an arteriovenous component. On MRI, VM typically appear as homogenous tubular or cystic T2 bright structures which may be focal or diffusely infiltrative. Examples of venous
malformations obtained from the authors’ institution is included in Figures 2 and 3. On occasion, imaging presentation may be atypical and features can overlap with Fibro-Adipose Vascular Anomalies (FAVA). In these circumstances biopsy is helpful to confirm the diagnosis.

Morphologically, venous malformations may appear focal and “mass-like”. However, on T1 they will appear more spongy or cavernous, as opposed to vascular tumors which will appear as well circumscribed solid masses. Alternatively, venous malformations may be diffuse at times with impressive invasion of the various tissue planes. This may on occasion mimic the infiltrative nature of an arteriovenous malformation (AVM), which can be differentiated with ultrasound. Lastly, T2 signal voids in venous malformations are often seen due to the presence of phleboliths. This can be differentiated from the flow-voids seen in AVMs and hemangiomas on susceptibility weighting imaging (SWI) or Gradient Echo Imaging (GRE). If available, radiographs can also confirm the presence of phleboliths. Of course, the lack of phleboliths does not exclude the presence of a venous malformation.

When performed with contrast, venous malformations tend to fill heterogeneously due to the variations in flow. Special note should be made of large draining veins, as this helps plan sclerotherapy technique. On occasion, computed tomography (CT) can be helpful to evaluate the adjacent bony structures, as venous malformations can lead to
bony remodeling and tissue hypertrophy (though less significantly than AVMs) (Figure 3).

**Standard of Care and Alternative Therapies**

Patients with symptomatic venous malformations are frequently referred for treatment by interventional radiologists, however, a multidisciplinary approach is necessary to determine if treatment is likely to be successful. Consultation with dermatologists, surgeons, and other specialists can help design a complete treatment regimen specific to patient concerns.¹ Venous malformations of the limbs usually present with worse symptoms and higher recurrence than truncular venous malformations, and therefore are more likely to require treatment.²⁹ Indications for treatment of venous malformations includes disabling pain, functional impairment, bleeding (including subdermal, intramuscular, or retroperitoneal hematomas, hematuria, rectal bleeding, hematemesis, hemoptyisis, and intracerebral or intraspinal bleeding), lesions that are in close anatomical proximity to important structures or vessels, lesions in areas with high probabilities of complications, lesions with ultrasound evidence revealing excessively adverse hemodynamic effects, excessive cosmetic implications, and recurrent thrombosis.¹

Larger venous malformations are associated with consumptive coagulopathies such as localized intravascular coagulation (LIC), which is characterized by elevated D-dimer and
decreased fibrinogen levels. LIC causes localized pain and thrombosis within a lesion, and can lead to further hemorrhagic or thrombotic complications, such as severe bleeding during surgery or in the event of trauma. LIC is primarily managed with low-molecular-weight-heparin (LMWH) and other anticoagulation in order to prevent decompensation to disseminated intravascular coagulopathy (DIC).

When immediate treatment of a venous malformation is not required, it is important to manage complications such as pain or anemia caused by bleeding. Compression stockings can be used in patients with venous malformations in the extremities to force venous blood out of stagnant venous malformations, thereby reducing swelling and risk for thrombophlebitis. Pain may also be managed with daily aspirin-81, although there are limited studies evaluating the efficacy of this management strategy.

When definitive treatment of a venous malformation is indicated, treatment strategies may include surgery, sclerotherapy, ablative techniques, or a combination of the aforementioned therapies. Surgical intervention is considered when the lesion is anticipated to be able to be completely resected with minimal anatomic or functional complications. Truncular venous malformations are most amenable to surgery as they are typically large and localized. Additionally, they have minimal chance of recurrence post-resection due to their embryonic nature. Surgery for truncular venous malformations may or may not include adjunct sclerotherapy or N-butyl cyanoacrylate (nBCA) injections 24-48 hours prior to excision. Venous malformations of the
Extremities are less amenable to surgery as they are often more complex and diffusely infiltrative lesions, often involving multiple layers of fascia and muscle. This lesion complexity increases risk for secondary intraoperative bleeding and increases chance of recurrence. Instead, venous malformations of the extremities are often treated with sclerotherapy, a more cost-effective alternative that greatly decreases risk of bleeding due to the use of minimally invasive techniques.

Ethanol sclerotherapy is the most common sclerosant used to treat venous malformations. Ethanol denudes endothelial cells from the venous walls and cause fractures at the level of the internal elastic lamina. Treated tissue undergoes necrosis and apoptosis, leading to platelet aggregation, intravascular thrombosis, and a painful inflammatory response that requires general anesthesia. In a systematic review of sclerosing agents for vascular malformations of the head and neck, ethanol complications are observed in up to 18% of cases and may include collateral tissue or skin necrosis, nerve damage, paresthesias, vascular spasms, ischemia, acidosis, hypoglycemia, and secondary intravascular hemolysis. Other sclerosants such as pinyangmycin, OK-432, ethanolamine oleate, bleomycin, polidocanol, doxycycline, and sodium tetradecyl sulfate (STS) have complication rates between 0-6%, but are more expensive and have not yet been proven to be superior to ethanol in terms of treatment success. All of these sclerosants, including ethanol, have response rates between 71-100%, although the authors of the systematic review cite high rates of bias in their source data.
Endovenous laser and radiofrequency ablation therapies have been used in cases where surgery or sclerosants have shown limited success. These therapies have been used primarily in patients with truncular venous malformations experiencing symptomatic venous insufficiency of the lower extremities. These techniques relieve symptoms by ablating incompetent venous reflux channels. One study utilizing ultrasound-guided endovenous diode laser therapy for venous malformations found a 100% success rate for treatment symptoms of pain and activity limitation, but a final clinical success rate of 63% when including residual swelling and cosmetic complaints.

This systematic review focuses on the use of cryoablation for venous malformations, evaluating treatment efficacy in terms of reduction of pain and lesion size, as well as the risk for complications. Treatment plans vary widely between institutions, operator experience, and patient needs. Due to considerations of cost to the patient, complications, and potential need for additional treatment, we emphasize the importance of creating a treatment plan as a part of a multidisciplinary team.

**Representative Case Report**

This systematic review contains data from one case report, which details the clinical presentation, treatment, and outcome for a patient who undergoes cryoablation for a venous malformation. We will review the details from this case report to demonstrate a
patient experience from the diagnosis of their venous malformation through definitive treatment with cryoablation.

Case Report: Amin et al. (2018)

In this case, a 35-year-old woman presented with pain in the right leg. Ultrasound and MRI suggested a 1.5 cm venous malformation in the right vastus lateralis muscle may the causal lesion, and biopsy of the lesion confirmed the diagnosis of venous malformation.\(^{38}\) As discussed in the Classification of Vascular Anomalies section above, the use of ultrasound and MRI is ideal for the diagnosis of venous malformations, however, the use of biopsy to confirm the lesion identity on histopathology can be important if there is concern that the lesion may be confused with a vascular tumor, such as a hemangioma.\(^{25}\)

As a first-line attempt to manage the patient’s leg pain, nonsteroidal anti-inflammatory drugs (NSAIDs) were given. When conservative pain management provided minimal relief, the patient was offered sclerotherapy treatment.\(^{38}\) Despite the use of NSAIDs as the standard of care for a patient who is newly diagnosed with a painful venous malformation, Nguyen et al. discusses the limited data supporting the efficacy of this conservative management strategy.\(^{33}\) The patient underwent multiple attempts at sclerotherapy but the lesion persisted on imaging and the patient continued to report pain scores as high as 9 out of 10. It was then decided by the care providing team to attempt cryoablation of the lesion.\(^{38}\)
Utilizing computed tomography and ultrasound for needle guidance, a cryoprobe was inserted percutaneously over the lateral distal thigh, overlying the venous malformation. The procedure was performed with local anesthesia only. Hydro dissection of tissue was performed before cryoablation of the venous malformation began. To hydro dissect, normal saline was injected into the subcutaneous tissue superficial to the venous malformation.

The use of hydro dissection in this case was cited for protection of the surrounding skin and fascial layers from damage during freezing cycles which are intended to target the intramuscular lesion only.\(^\text{38}\) Hydro dissection is only used in 4 of the 52 cases in this systematic review, when operators determined that structures within 5 mm of the target lesion, such as surrounding nerves, muscle, fascia, or skin may be damaged by the ice ball.\(^\text{7, 27, 28}\)\(^\text{39}\) There were not enough cases with detailed outcome data in this series to determine with statistical significance if hydro dissection provides a better safety profile in terms of reduced complications.

Once the tip of the cryoprobe was placed within the lesion on imaging, cryoablation was performed. This case used two freezing cycles, one 7 minutes and one 9 minutes, with 12 minutes of passive thawing in-between. The cryoprobe was removed after a final round of passive thawing.\(^\text{38}\) The total freeze time in this case was 16 minutes, which is
lower than the mean total freeze time of 20.9 minutes amongst the 28 cases in this systematic review that detailed freeze times.\textsuperscript{7, 26, 40, 27}

Computer tomography and ultrasound were used to confirm that the ice ball encapsulated the lesion, and a final ultrasound demonstrated no evidence of hematoma formation during the procedure.\textsuperscript{38} Evaluating for hematomas is important in all interventional radiology procedures, as a large hematoma is at risk for infection or pocket dehiscence.\textsuperscript{41} In rare cases, very large hematomas have been shown to lead to hypovolemic shock in the patient.\textsuperscript{42} In the event of that a hematoma is identified and raises concern for these dangerous sequelae, it is recommended to immediately evacuate the hematoma.\textsuperscript{41} While hematomas are an important complication to be aware of, interventional radiology procedures are far less likely to cause bleeding when compared to surgery for the treatment of venous malformations.\textsuperscript{1} One article from this systematic review reports a case where a minor hematoma was identified post-procedure. This hematoma resolved without further complications.\textsuperscript{28}

8 months after the patient underwent cryotherapy for their venous malformation, the patient was evaluated in a follow-up visit. The patient reported no residual pain or recurrence of symptoms.\textsuperscript{38} This complete resolution of patient symptoms is especially impressive as the patient had undergone multiple sessions of sclerotherapy and had continued to report pain scores as high as 9 out of 10. As is later detailed in the \textit{Results} section of this systematic review, our analysis demonstrates that 20 of the 31
cryoablation patients (64.5%) which report pre- and post- procedure pain data reported no residual pain at final follow-up.
MATERIALS AND METHODS

Student Contributions

Literature search, study selection, data extraction, and organization of data were performed by Alexander Moushey. The *Diagnosis of Venous Malformations* section was written by Adam Fish, MD. *Discussion* and *Limitations* sections were originally written by Adam Fish, MD and expanded upon by Alexander Moushey. Statistical analysis was performed by Lawrence Staib, PhD, Professor of Radiology and Biomedical Imaging at Yale School of Medicine. Mentorship and thesis review was provided by Todd Schlachter, MD, Assistant Professor of Radiology and Biomedical Imaging at Yale School of Medicine.

Search Strategy

An electronic-based literature search for clinical studies utilizing percutaneous cryoablation of VMs was performed in PubMed and Google Scholar using the following terms or combinations of terms: “cryoablation”, “percutaneous cryoablation”, “venous malformation”, and “low flow vascular malformation”. The search was limited to human trials up to July 2021. Titles and abstracts were screened to identify relevant articles, and references within relevant articles were manually reviewed. An IRB was not required for systematic literature review.
Study Selection Criteria

All retrospective reviews, prospective non-randomized studies, and case reports related to primary or secondary treatment of venous malformations with percutaneous cryoablation were included for review. Articles were excluded if they did not describe the technical approach or specific outcomes listed below. VM cases within these selected studies were then evaluated by: (1) patient characteristics (age, sex, method of diagnosis); (2) indication for cryoablation (symptoms, prior treatments); (3) cryoablation technique (number and timing of freezing cycles); (4) technical success rate; (5) follow-up (clinical success rate, morbidity, and change in lesion size on post-procedure imaging); and (6) requirement for additional procedures or medical management. Amongst selected articles, patients were excluded if their treated lesions were diagnosed as FAVA or hemangioendothelioma, or if the VM was treated with interventions other than cryoablation. The studies were selected and evaluated by two authors (A.M. and A.F.). Patient selection flow-chart is diagramed in Figure 1.

Data Extraction

The review was performed following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Study characteristics are demonstrated in Table 1. In order to study the safety of the cryoablation procedure, all studies identified were included in the safety analysis. Adverse events were graded according to the Society of Interventional Radiology (SIR) classification system.
Aggregates of treatment techniques were recorded, including number and timing of freeze cycles. Note was made of whether or not patients had previously received sclerotherapy or whether cryoablation was used as a first-line treatment option. **Table 2** demonstrates a summary of the associated clinical history. In order to reduce heterogeneity in assessing treatment outcomes, only cases with pre and post procedural pain scores (scored 1-10) and volume measurements were included for variable analysis. Pain scales included the visual analog scale (VAS) and numerical pain rating scale (NPRS).  

**Study Risk Bias**

Analysis of the methodologic quality of the studies included in this systematic review was performed utilizing a modified version of the Newcastle-Ottawa Quality Assessment Scale (NOS). This tool is designed for use in Case Control studies, so modification was necessary to assess risk of bias in selected studies that do not include a control group. We focused on the following questions from the NOS tool: 1) Is the case definition adequate, with clearly defined inclusion and exclusion criteria for patient selection? 2) Were procedures clearly detailed? 3) Was clinical follow-up satisfactory? and 4) Were outcomes clearly reported? **Table 3** summarizes the heterogeneity of the selected papers and **Table 4** demonstrates the NOS scores.
Data Analysis

A quantitative meta-analysis was performed for pre- and post-procedural change of volume and change of pain. Heterogeneity, measured by Higgins $I^2$. Due to the relatively small sample sizes, stratified variable analysis such as history of sclerotherapy, freezing times, and initial lesion volume were unable to be performed. Averages for pre- and post- pain scores for the sclerotherapy group were calculated.
RESULTS

Literature Search

The initial literature search yielded 73 articles. We excluded 59 articles upon review of the abstracts and titles. 14 articles were selected for full-text screening, of which 8 met inclusion criteria. The remaining 6 articles were excluded for reasons including 1) non-cryoablation interventions performed (4 articles) and 2) use of unclear terminology making it difficult to determine if the treated lesions were VMs, hemangiomas, or lymphatic malformations and limited outcomes reporting (2 articles). Between the 8 studies included, a total of 67 patients were available for data analysis. A total 54 of the patients, with 55 VMs, met inclusion criteria as their lesion was a VM and was treated by cryoablation. The remaining 13 patients were excluded for reasons including 1) the treated lesion was identified as FAVA (6 patients), 2) the treated lesion was identified as hemangioendothelioma (2 patients), and 3) alternative therapies were used and thus cryoablation was not attempted to treat the VM (5 patients).

Characteristics of Included Studies

A summary of the study characteristics used in this systematic review is included in Table 1. After critical evaluation of clinical studies detailing treatment of venous malformations with cryoablation, eight articles fit inclusion criteria listed above and are included in cumulative data analysis. Six articles are retrospective reviews\textsuperscript{6, 7, 26, 40, 39, 27,}
one article is a case report\textsuperscript{38}, and one article is a prospective non-randomized trial.\textsuperscript{28} The cumulative data comprised of 54 patients (55 total cases) with a mean age of 35.2 years (range of 10-71). Of the 55 venous malformation cases, 21 cases (38.2\%) had no prior treatment and 31 cases (56.2\%) had prior sclerotherapy which did not completely resolve patient symptoms. Treatment history for venous malformations is summarized in Table 2.

Treatment Technique

Cryoablation technique varied between the articles reviewed, in part due to the variability in size and location and in part due to the lack of unified treatment regimen. The most common treatment regimen employed was with general anesthesia, CT guidance, and two ten-minute freeze cycles per cryoprobe. CT guidance was employed in 36 cases (65.5\%), US guidance in 14 cases (25.5\%) and MRI in 5 cases (9.0\%). Of the 52 cases which reported the number of freeze cycles utilized, 51 cases required two freeze cycles and only one case required four freeze cycles. Freeze times were reported in 28 cases with a mean total freeze time of 20.9 minutes.\textsuperscript{7, 26, 40, 27} The median number of cryoprobes used per case were 2 (range 1-10). Additional methods employed included hydro dissection (used in 4 cases) for peripheral lesions with less than <1cm of overlying subcutaneous tissue.\textsuperscript{7, 27, 28, 39} Technical success, as defined by the ice ball covering the entire lesion, was achieved in 54 of 55 cases.
Procedural Outcomes

Volume change:

Random effects analysis performed included three studies (27 cases) which provided quantitative results allowing for pooled analysis.\textsuperscript{26-28} Amongst the 27 cases, pre-procedure lesion volume averaged 24.6 mL (median of 6.1 mL, range of 0.62 to 155.6). An overall volume decrease of 21.96 cc (95% CI 3.08 – 40.90) which corresponds with a weighted mean decrease of 92% (raw mean of 71.7%, median of 83.5%, range -17.6% to 100%). Heterogeneity, measured by Higgins $I^2$, was not found to be significant ($I^2 = 44\%$, $p = 0.17$). Mean follow-up time was 27 months (median of 6 months, range of 6 to 78 months). A random effects model (Figure 4a) and funnel plot (Figure 4b) demonstrate the effect size for each study included in the weighted mean.

Pain score change:

Five of the eight studies, 31 of 55 cases, reported pain associated with the lesion pre-procedure and post-procedure. To quantify pain, three articles used VAS\textsuperscript{26-28}, one article used NPRS\textsuperscript{7}, and one case report used self-reported numerical score\textsuperscript{38}, all of which rank pain between 0 and 10 with a score of 0 indicating no pain and a score of 10 being the most severe.
The initial pain scores in patients with previous sclerotherapy treatments was 4.7, compared to 5.0 in patients with prior surgery, and 5.8 in patients without prior sclerotherapy or surgery.

Random effects analysis included two studies (23 cases) which provided quantitative results allowing for pooled analysis. An overall decrease in pain of 3.84 (95% CI 1.71 – 5.98) was found which corresponded with a weighted mean decrease of 77%. Heterogeneity, was not found to be significant ($I^2 = 58\%, p = 0.12$). A random effects model (Figure 5a) and funnel plot (Figure 5b) demonstrate the effect size for each study included in the pain score weighted mean. When including all studies that provided pre- and post-procedural pain scores, including Cornelis 2013\textsuperscript{45} which provided mean pain scores (without individual results), and Autrusseau 2020\textsuperscript{46}, which used NPRS pain scores, a non-weighted mean reduction in pain score was 78.2% +/- 42.8% across the 31 cases. 20 of 31 cases (64.5%) reported complete resolution of symptoms with no residual pain.

Three articles that did not quantify pre- vs post-procedural change chose to report pain outcomes in different ways. Thompson et al report complete resolution of pain in two out of three venous malformation cases (66.7%), with the remaining case recording a residual moderate pain at 3-month follow-up, later requiring laser therapy treatment which resulted in complete resolution of symptoms.\textsuperscript{6} Ramaswamy et al report complete resolution of pain in seven of nine cases (77.8%) with the remaining two patients reporting residual pain at final follow-up.\textsuperscript{39} Carabin et al report complete relief of
symptoms in 6 of 11 patients (54.5%) who completed follow-up. 4 of 11 (36.3%) reported partial relief, and 1 of 11 (9.1%) reported no improvement.\textsuperscript{40}

When including all cases that had pain evaluated at final follow-up, complete resolution of pain was seen in 35 of 55 cases (63.6%) and overall (complete or partial) improvement of pain was seen in 52 of 55 cases (94.5%).

**Adverse Events**

Hospital stays ranged from 0 to 3 days across all studies, with 17 of the 55 procedures being performed outpatient (30.1%). Rationale for hospital stay was provided in a few studies, citing desire to monitor for neurovascular injury. Immediately post-procedure, pain was reported in 18 cases (33.3%), swelling in 10 cases (18.5%), and numbness or dysesthesia in seven cases (13.0%). These symptoms were transient for most patients, lasting under two weeks. There were two major adverse events (3.7%), with both cases due to continued numbness or dysesthesia at their final follow-up, one experiencing sciatic paralysis.

Cornelis et al. notes that the patient with sciatic paralysis was included in their study inappropriately, as the sciatic nerve was less than 5 mm away from the treated lesion, at the limit of their eligibility criteria.\textsuperscript{28} This patient had partial recovery at 6 months.\textsuperscript{28} In order to avoid nerve complications, Cornelis et al. proposes extensive protective
dissection with saline or CO₂ if critical structures are closer than 5 mm to the targeted lesion. They also propose performing cryoablation under local anesthesia or conscious sedation to allow for direct patient feedback in the event that nerve damage is perceived.²⁸

There were four cases of minor adverse events not related to pain (7.4%), include two cases reporting skin blisters that resolved within two weeks³⁹, one minor hematoma, and one small myositis treated medically without complication.²⁸ There were zero cases (0.0%) resulting in death, life-threatening complications, or escalation in care.
DISCUSSION

Cryoablation for venous malformations is a novel and potentially promising treatment option. However, prospective studies evaluating the efficacy and safety are limited. To address this issue, we performed a systematic review of eight studies, consisting of 54 patients, in which venous malformations were treated with cryoablation.

Cryoablation was shown to be effective in reducing volume size and pain. There were three studies which included pre- and post-procedural volumes, including 27 cases, which allowed for pooled analysis. These three studies demonstrated insignificant heterogeneity as measured by Higgins $I^2$. A total of five studies, including 31 patients, provided pre- and post-procedural pain scores, allowing for unweighted averaging of pain score changes. Of these studies, only two studies, including 23 cases, met criteria allowing for pooled analysis. Pooled analysis of these two studies demonstrated insignificant heterogeneity as measured by Higgins $I^2$. It is worth noting that the difference between the weighted and non-weighted mean decrease in pain-scores was very small (77% and 78.2% respectively; difference of 1.2%).

The issue of pre-procedural sclerotherapy is undoubtably an important one. However, due to the small populations, pooled variable analysis was not able to be performed. Therefore, non-weighted averages were calculated. The initial and post-treatment pain scores for the sclerotherapy group were smaller (4.7 and 1.3, compared with 5.0 and 3.3
with prior surgery and 5.8 and 2.8 with no prior treatment). This may suggest a benefit of sclerotherapy prior to cryoablation. Additionally, the benefit of sclerotherapy is likely underestimated by the selection bias of choosing lesions that did not demonstrate complete resolution to sclerotherapy.

Adverse events were documented and analyzed for all 54 patients. Cryoablation of venous malformations were found to be generally safe, though additional studies are needed. Known complications of cryoablation generally include hemorrhage, abscess and non-target tissue damage.\textsuperscript{47} There were four cases of minor adverse events (9.3%), including temporary blistering, self-resolving hematoma and myositis treated pharmacologically. There were two major adverse events (3.7%) due to persistent dysesthesia at the time of final follow-up. These events may be avoidable by limiting ice-ball margins to greater than 5mm or by employing the use of neuromonitoring. There were no cases resulting in death, life-threatening morbidity, or escalation in care.

Limitations

There are significant limitations in this study due to the small patient population and heterogeneity of the included studies, which are primarily retrospective. There were no set standards for diagnosing a venous malformation. In three of the eight studies (17 of 55 patients, 30.9%) biopsies were utilized to confirm the diagnosis, with five studies relying on imaging a lone. Though, biopsy is not typically necessary to confirm the
diagnosis\textsuperscript{48}, in some instances biopsy or venography is necessary to differentiate between diffusely infiltrative VMs and FAVAs\textsuperscript{49}. Of note, 29 of the 38 patients (76.3\%) that were not biopsied, had sclerotherapy and could presumably be diagnosed by venography, however this was not specifically discussed in the papers. While six patients were identified as having FAVAs and therefore excluded from the study, it is possible that some of the larger VMs that were not biopsied may have been diagnosed. This may pose as a confounding factor as a growing body of literature has demonstrated the efficacy of cryoablation in FAVAs\textsuperscript{49, 50}.

Another important potential confounding factor was the lesion size. The median lesion size of 6.1 mL compared to the average of 24.6 mL is considerably smaller, which suggests significant selection bias that may overestimate the efficacy of cryoablation compared to other standards of treatment. However, this may also suggest that smaller, more focal lesions are better candidates for cryoablation. Considering the reduced post-treatment scores of the sclerotherapy group, it may be that a combined regimen of sclerotherapy and cryoablation for smaller, more focal lesions is optimal. Future randomized trials should be performed comparing sclerotherapy and cryoablation, including treatment groups with sclerotherapy and cryoablation, sclerotherapy alone and cryoablation alone.

An additional challenge of the study is in uniformly evaluating pain. In order to mitigate this issue, only studies using a 1-10 pain scale before and after the procedure were
included in assessing changes in pain. Furthermore, changes in pain were compared alongside changes in volume, which were found to be similar.

The different pain scales used include the visual analog scale (VAS), the numerical pain rating scale (NPRS), and a self-reported numerical score from 1-10. The VAS is a scale consisting of a 10 cm long horizontal line with end points of “no pain” and “worst possible pain”. The patient marks a point on the scale to communicate their pain level. The NPRS is a verbal scale where the patient is asked to rate their pain from 0 (“no pain”) to 10 (“worst possible pain”). Many studies evaluating the differences in data collected between VAS and NPRS systems found their respective scores to be strongly correlated with one another.\textsuperscript{51,52} In a study evaluating patients with chronic low back pain, severe disability can be predicted with a score of 6 in VAS or NPRS, while moderate disability can be predicted with a VAS score of 4 or an NPRS score of 3.\textsuperscript{52} While these slight differences in pain scales may affect documentation of the true qualitative pain or disability experienced by a patient, this systematic review evaluates pre- vs post-procedure change in pain, as opposed to a post-procedure pain score alone.

An additional obstacle in the evaluation of change in pain or change in lesion volume is due to the large variability in follow-up times between studies. Fujiwara et al. collected pain data at three time points: before cryoablation, 12 months after the procedure, and a final follow-up 4-7 years after the procedure.\textsuperscript{27} To contrast, Cornelis et al. collected
pain data at three different time points: before cryoablation, 7 days after the procedure, and a final follow-up 6 months after the procedure.\textsuperscript{28}

Cryotherapy technique varied widely (or was sparsely reported) from study to study and likely played a role in treatment outcomes. While most studies utilized two freeze cycles, freezing time per cycle ranged from 6.3 to 40 minutes.\textsuperscript{40, 27} Thawing times between freeze cycles were not reported in every study. Additionally, some studies utilized hydro dissection to separate nearby tissues from target freezing areas, with the goal of reducing the rate of complications.

Lastly, this study found a significantly increased improvement in pain reduction in females when compared to males. While this may be valid, this conclusion is limited due to the small population of males and subjectivity in pain scores. Larger studies are needed to confirm this finding.
CONCLUSION

Cryoablation of venous malformations is potentially safe and effective for select patients. Additional prospective studies with clear diagnostic criteria including possible biopsies to exclude FAVAs and longer follow-up time periods are needed to further investigate this treatment option.
FIGURES

Figure 1: Study Selection

Figure 1 – A flow chart demonstrates the study selection process.
Figures 2 and 3 – Images from author’s institution demonstrating example lesions (not included in the study).

Figure 2 - A sagittal STIR (left) demonstrates a T2 intense cavernous/spongy lesion within the posterior thoracic muscles. Sagittal CT of the same patient demonstrates small phleboliths (arrows).
Figure 3- Grayscale and color ultrasound (top images) demonstrating infiltrative cavernous hypoechoic lesion made up of dysplastic vessels. STIR axial (bottom left) and coronal (bottom right) from the same patient demonstrates T2 hyperintense infiltrative lesion within the anterior, lateral and posterior compartments of the thigh.

Figures 4a and 4b: Volume change random effects model and Funnel plot

Figure (4a) - Random effects model calculating the standardized mean difference. This corresponded with a weighted mean decrease of 29.66cc or 92%. Figure (4b) - A funnel plot demonstrates the effects estimates from each study.
Figures 5a and 5b: Pain score random effects model and Funnel plot

**Figure 5a** - Random effects model calculating the standardized mean difference of pre- and post-procedural pain score changes. This corresponded with a weighted mean decrease of 3.84 (CI 1.71 – 5.98) or 77%. **Figure 5b** - A funnel plot demonstrates the effects estimates from both studies.
**Table 1: Study Characteristics**

| Author          | Year | State | Design                          | Patients (n) | Average age (years) | Sex (male %) | Prior sclerotherapy (%) | Initial lesion volume median (mL) | Volume decrease at final follow-up (%) | Initial pain score median (1-10) | Pain score decrease at final follow-up (%) | Average follow-up time period (mo) |
|-----------------|------|-------|---------------------------------|--------------|--------------------|--------------|-------------------------|----------------------------------|-----------------------------------|-------------------------------------|--------------------------------------|
| Fujiwara et al. | 2021 | Japan | Retrospective review            | 9            | 36.6               | 22.20%       | 66.67%                 | 2.49                             | 83.40%                           | 7                                  | 80.74%                              | 69.1                                 |
| Autrusseau et al.| 2020 | France | Retrospective review            | 3            | 40                 | 33.30%       | 0%                     | 35                               | Not included                      | Not included                       | Not included                        | 23.2                                 |
| Thompson et al. | 2015 | USA   | Retrospective review            | 3            | 27.3               | 66.70%       | 100%                   | Not Included                     | Not included                      | Not included                        | N/A                                 | 5.3                                  |
| Cornelis et al. | 2013 | France | Retrospective review            | 4            | 41.8               | 0%           | 50%                    | 49                               | 95.00%                           | 5                                  | 100.0%                              | 6.5                                  |
| Ramaswamy et al.| 2019 | USA   | Retrospective review            | 8            | 30.3               | 54.5%*       | 75%                    | 10.96                            | Not included                      | Not included                       | Not included                        | 6.0                                  |
| Carabin et al.  | 2020 | France | Retrospective review            | 12           | 42                 | 58.30%       | 0%                     | 32.5                             | 90.77%                           | 7                                  | 86%                                 | 14.8                                 |
| Amin et al.     | 2018 | USA   | Case Report                     | 1            | 35                 | 0%           | 100%                   | Not Included                     | Not included                      | Not included                        | 9                                  | 100%                                | 8.0                                  |
| Cornelis et al. | 2017 | France | Prospective non-randomized trial| 14           | 30.3               | 35.70%       | 92.86%                 | 5.55                             | 57.55%                           | 4                                  | 64.05                               | 6.0                                  |

Table 1 – Summary of study characteristics.

* 54.5% of the 11 patients in the study are male, however 3 of the patients had FAVA and were excluded from the study. Sex distribution of the remaining 8 patients is unknown.

**Table 2: Associated clinical history**

<table>
<thead>
<tr>
<th>Associated clinical history for VMs</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior sclerotherapy</td>
<td>31 (57.4)</td>
</tr>
<tr>
<td>Prior sclerotherapy (x2 or more)</td>
<td>6 (11.1)</td>
</tr>
<tr>
<td>Prior surgery</td>
<td>7 (13.0)</td>
</tr>
<tr>
<td>Prior surgery and sclerotherapy</td>
<td>4 (7.4)</td>
</tr>
<tr>
<td>Any previous treatment (sclerotherapy or surgery)</td>
<td>34 (63.0)</td>
</tr>
<tr>
<td>No previous treatment (sclerotherapy or surgery)</td>
<td>21 (38.9)</td>
</tr>
</tbody>
</table>

Table 2 – Summary of associated clinical features.
Table 3: Study Heterogeneity

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients (n)</th>
<th>Average age (years)</th>
<th>Sex (male %)</th>
<th>Study included how lesion was diagnosed</th>
<th>Study included total freezing time used</th>
<th>Study included at least one follow-up (5 months or longer)</th>
<th>Study included change in lesion volume</th>
<th>Study included change in pain score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fujiwara et al.</td>
<td>2021</td>
<td>9</td>
<td>36.6</td>
<td>22.2%</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Autrusseau et al.</td>
<td>2020</td>
<td>3</td>
<td>40</td>
<td>33.3%</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Thompson et al.</td>
<td>2015</td>
<td>3</td>
<td>27.3</td>
<td>66.7%</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cornelis et al.</td>
<td>2013</td>
<td>4</td>
<td>41.8</td>
<td>0%</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ramaswamy et al.</td>
<td>2019</td>
<td>8</td>
<td>30.3</td>
<td>54.5%*</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Carabin et al.</td>
<td>2020</td>
<td>12</td>
<td>42</td>
<td>58.3%</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Amin et al.</td>
<td>2018</td>
<td>1</td>
<td>35</td>
<td>0%</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Cornelis et al.</td>
<td>2017</td>
<td>14</td>
<td>30.3</td>
<td>35.7%</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Table 3 – List of studies and summary of variables assessed.

* 54.5% of the 11 patients in the study are male, however 3 of the patients had FAVA and were excluded from the study. Sex distribution of the remaining 8 patients is unknown.
### Table 4: Risk of Bias – Newcastle-Ottawa Quality Assessment Score

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Design</th>
<th>Patients (n)</th>
<th>NOS for pain score</th>
<th>NOS for lesion size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fujiwara et al.</td>
<td>2021</td>
<td>Retrospective review</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Autrusseau et al.</td>
<td>2020</td>
<td>Retrospective review</td>
<td>3</td>
<td>9</td>
<td>8&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Thompson et al.</td>
<td>2015</td>
<td>Retrospective review</td>
<td>3</td>
<td>7&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>7&lt;sup&gt;b,d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cornelis et al.</td>
<td>2013</td>
<td>Retrospective review</td>
<td>4</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Ramaswamy et al.</td>
<td>2019</td>
<td>Retrospective review</td>
<td>8</td>
<td>7&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>7&lt;sup&gt;a,d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Carabin et al.</td>
<td>2020</td>
<td>Retrospective review</td>
<td>12</td>
<td>8&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Amin et al.</td>
<td>2018</td>
<td>Case Report</td>
<td>1</td>
<td>9</td>
<td>8&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cornelis et al.</td>
<td>2017</td>
<td>Prospective trial</td>
<td>14</td>
<td>8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Table 4 - The Newcastle-Ottawa Quality Assessment Scale (NOS) (out of 9 stars); utilized to assess the risk of bias.**

- a = Lost 1 star due to lack of satisfactory clinical follow-up
- b = Lost 1 star due to lack of clearly reported procedural details
- c = Lost 1 star due to lack of clearly reported change in pain scores
- d = Lost 1 star due to lack of clearly reported change in lesion volume
REFERENCES


44. Lazaridou A, Elbaridi N, Edwards RR, Berde CB.