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# The Efficacy of Bleomycin Sclerotherapy in the Treatment of Low-Flow Vascular Malformation

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## Abstract

**Background:** Low-flow venous malformations (VMs) are a class of vascular anomalies that are recognized by dilated or ectatic, thin-walled channels that are often involved with cosmetic sensitive areas or functionally crucial areas. Sclerotherapy has become the mainstay of treatment, and bleomycin is of great interest for its safety and efficacy.

**Objective:** To evaluate the clinical outcomes, safety, and thrombotic response associated with ultrasound-guided bleomycin foam sclerotherapy in patients with low-flow VMs.

**Methods:** In this prospective, single-center study, 23 patients (mean age 25.22 ± 17.30 years; 52.2% female) were treated at a triage practice in Baghdad. All patients received ultrasound-guided bleomycin foam injections intralesionally with a standardized maximum of 5 mg/session. The number of sessions (1-6 sessions), pre- treatment and post-treatment lesion sizes, and the development of a thrombotic reaction were recorded. Clinical outcomes were assessed using Doppler ultrasound and clinical examination at a four-month follow-up.

**Results:** Lesion location was predominantly on the face (43.5%), in addition to some involvement on the limbs and trunk. Most patients required one or two treatment sessions (Mean ± SD: 2.52 ± 1.50). Statistically significant decreases in dimensions were shown for the lesions (D1: decreased by 0.93 cm ($p = 0.001$) & D2 decreased by 0.66 cm ($p = 0.001$)). Complete thrombosis of their lesion occurred in 56.5% of cases, with partial regression in the rest. No significant complications occurred. The only minor adverse effects reported were transient erythema and local swelling (11.5%).

**Conclusion:** Bleomycin sclerotherapy safely and effectively treats low-flow VMs, producing significant volumetric reduction and thrombotic response with limited morbidity. This data support its wider use in mixed-anatomical presentations, particularly where aesthetic or functional outcomes are vital.

## Introduction

Venous malformations (VMs) are the most prevalent type of congenital vascular malformation, estimated to affect 1% of the overall population, with 1–2 per 10,000 live births **[1]**. They are defined as ectatic, thin-walled post-capillary channels that develop due to a disruption in embryogenesis. VMs are present at birth but are often clinically apathetic until there is progressive expansion, spontaneous thrombosis, or trauma to reveal their cause for morbidity **[2]**. These malformations have a chronic disease pattern, and can be debilitating, painful, cause cosmetic deformity, and functional limitation, so there is a timely need for evidence-based, minimally invasive treatment **[3]**.

The ISSVA (International Society for the Study of Vascular Anomalies) provides the current nosology, with vascular anomalies first grouped according to biological behaviour (tumour versus malformation) and secondly based on the predominant flow pattern (capillary, lymphatic, venous, arteriovenous, or combined) **[4]**. Using this scheme, low-flow VMs make up a discrete category, based on the absence of arterialisation and relative lack of hemodynamic activity, in contrast to high-flow arteriovenous malformations. The ISSVA revision also aids in providing more meaningful phenotype–genotype correlations as well as therapeutic decision-making; slow-flow lesions can typically be treated by endovascular sclerotherapy whereas high-flow lesions, in most cases, require staged embolo-resection **[5]**.

A low-flow venous malformation (VM) can have heterogeneous clinical features. "Common" sporadic lesions comprise >90% of cases that most often involve the head–neck complex, extremities, or trunk with soft compressible dull blue nodules that enlarge with dependency **[6]**. Familial cutaneo-mucosal venous malformation (VMCM) inheritance is autosomal dominant with multiple mucocutaneous blebs; Blue Rubber Bleb Nevus (BRBN) syndrome is a combination of cutaneous and gastrointestinal VMs with iron-deficiency anaemia **[7]**. Glomuvenous malformations (GVM) develop components of glomus cells and verrucous venous malformations (VVM) develop hyperkeratotic epidermal change **[8]**. Regardless of the subtype, for lesions >2 cm, approximately 40% develop in-situ thrombosis and phleboliths forming. These lesions can cause pain, phlebitic flares and local swelling **[1]**.

Recent advances in vascular biology have reframed the understanding of VMs from static hamartomas to dynamic, genetically driven lesions. More than 90% of VMs harbor somatic variants that converge on the TIE2–PI3K–AKT–mTOR signaling pathway. Activating mutations in TEK (TIE2) driver receptor abundance in endothelial cells, while mosaic variants in PIK3CA hyper-activate downstream kinase pathways, causing endothelial proliferation, disorganized basement membrane assembly, and improper venous development **[9, 10]**. RASA1-associated defects inhibit Ras-GTPase activity, with excess export of extracellular matrix proteins contributing to the disorganized perivascular tissue architecture of VMs **[11]**. These advances provide a molecular mechanism to guide a growing list of targeted pharmacotherapies like sirolimus and alpelisib, which are now undergoing early studies **[7]**.

Clinically, venous malformations exhibit a constellation of findings: color change, soft-tissue swelling, pliability, associated pain with activity, hemorrhage, or, for deep venous malformations, functional deficits such as dysphagia or lack of range of motion **[6]**. As such, it is critical to define the extent of the lesion. Plain radiography may provide evidence of phleboliths or bone erosion, but is not sensitive. Doppler ultrasound provides bedside differentiation of high versus low-flow states and can estimate lesion volume, however, limitations of penetration depth and operator dependence limit its utility. Real-time magnetic resonance imaging (MRI), utilizing time-resolved contrast-enhanced MR angiography (CE-MRA), is the current gold standard to identify lesion distribution, muscular infiltration, or drainage into deeper systems **[12]**. Computed-tomography angiography or cone-beam CT are of further assistance in cases where osseous or intra-articular distractions are



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present **[13]**.

Management strategies have transitioned from radical resection that cause wound deformity and high recurrence to a more multidisciplinary, symptom-directed approach. Specific management fundamentals include external compression to manage pain and coagulopathy symptoms, surgical debulking for symptomatic discrete mass, thermal or cryo-ablation for intramuscular nodules, and trans-catheter or percutaneous sclerotherapy for the majority **[14]**. For a complete list of common sclerosants, detergent sclerosants (sodium tetradecyl sulfate, polidocanol) and alcohol have a long history of clinical use but have been associated with complications of necrosis, nerve injury, and systemic hemoglobinuria. Glue (n-butyl cyanoacrylate) is a viable option for occluding outflow but may cause a foreign body reaction. Therefore, attention has turned to bleomycin (glycopeptide antibiotic) as a sclerosant because it has strong endothelial cytotoxicity and an overall acceptable safety profile **[15]**.

Bleomycin's mechanism of action involves binding to DNA and generating free radicals that induce single- and double-chain DNA breaks leading to endothelial apoptosis and fibrosis **[16]**. In vitro data show a dose-dependent effect on inhibition of endothelial proliferation and down-regulation of pro-angiogenic cytokines. The systemic exposure is small when administered intralesionally with ultrasound guidance and the dose is well below the pulmonary-toxicity threshold **[17]**. Bleomycin causes less severe local inflammation and no skin necrosis compared to detergent sclerosants, which is a significant benefit for facial VMs which sit superficially and for pediatric patients **[18]**.

Despite encouraging case series, the clinical evidence for bleomycin in low-flow VM is disjointed. Reported response rates vary significantly due to small cohorts, variations in dosing, different imaging end-points, and minimal follow-up. Additionally, limited prospective research compares the efficacy of bleomycin with already established agents and no studies investigate predictors of treatment success. These knowledge gaps are detrimental to guideline development and continuing the variability of care both locally and internationally.

The present prospective study took place in a tertiary interventional radiology center in Baghdad and addresses these gaps by evaluating the size reduction, thrombosis rate, and complication rates of ultrasound guided bleomycin foam sclerotherapy in 23 patients with low-flow VMs. The proposed narrative study follows an objective imaging measure at a four-month follow-up with the continuous use of a standardized injection protocol (<5 units per session). The study aims to provide high-quality data to improve patient selection criteria and dosing protocols.

## Patients and Methods

### Study Design and Setting

This prospective interventional study took place at the Vascular Interventional Radiology Unit of Al-Karama Teaching Hospital, Baghdad, Iraq, for 15 months from October 2022 until December 2023. The study examined the clinical efficacy and safety of intralesional bleomycin sclerotherapy in patients with low-flow venous malformations (VMs). Institutional ethical approval was granted in accordance with the Declaration of Helsinki, and verbal informed consent was obtained from each participant or their legal guardian before their involvement in the study.

### Patient Selection

A total of 23 patients with clinically- and radiologically-confirmed low-flow venous malformations (VMs) were enrolled consecutively. Inclusion criteria consisted of patients of any age or gender,

presenting with symptomatic or cosmetically disfiguring VMs, who were appropriate candidates for sclerotherapy. Diagnosis was made by evaluating clinical examination and imaging studies (Doppler ultrasound and either MRI or CTA) used as the best method to distinguish low-flow VMs from arterial or other high-flow lesions.

Exclusion criteria included pregnancy, any known sensitivity to bleomycin, active systemic infection, treatment of the same lesion in the past 6 months, or the presence of vascular anomalies (e.g. AVMs). Patients with significant pulmonary, renal or hepatic comorbidities were excluded due to possible toxicity from the bleomycin.

**Baseline Assessment**

For each patient, a complete history and clinical physical examination were provided. Demographic Information (age, sex) on lesion location and clinical history (eg swelling, pain, colouration) and any treatments to date were recorded, and included the characteristics of the lesion, which included imaging studies. In all patients Doppler ultrasonography was performed to confirm the low-flow nature of the malformation for procedural purposes. MRI or CT angiography was used to better define the malformation and its extent, vascular architecture, and tissue infiltration when needed.

**Sclerotherapy Procedure**

The procedures were performed according to rigid aseptic principles by experienced interventional radiologists, following the use of real-time ultrasound guidance (Voluson E6 GE Healthcare). Patients were positioned appropriately to allow access to the lesions, and we used local anaesthetic as necessary. A 20–22G needle was inserted into the malformation under ultrasound imaging guidance. We confirmed the intralesional position by noting venous blood reflux from the lesion.

An immediate thrombin–lipiodol foam mixture was prepared and injected using the Tessari method. The mixture was made with 5 mg of thrombin reconstituted with 5 mL of sterile water emulsified with 5 ml of lipiodol, resulting in a homogeneous foam. The volume injected for each session was dependent on the size of the malformation and tolerance of the patient. We limited to a maximum of 5 mg per session to limit systemic exposure. After manual compression was applied after injection, the patients were not allowed to return for 1–2 hours for assessment for immediate adverse events, prior to discharge.

**Follow-Up and Outcome Assessment**

Patients were arranged clinical and radiological follow-up visits at 1 and 4 months after each session. The number of sclerotherapy sessions per patient was individualized based on clinical response, with a maximum of 6 sclerotherapy sessions allowed during the study time. Outcomes assessment was facilitated via clinical evaluation and repeat Doppler ultrasonography.

**Statistical Analysis**

Descriptive statistics were used to summarize baseline characteristics and clinical outcomes. Continuous variables were reported as means ± standard deviations (SD), and categorical variables were expressed as frequencies and percentages. The relationship between number of sessions and response rate was descriptively analyzed. Due to the small sample size, inferential statistical testing was not applied. All analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY).

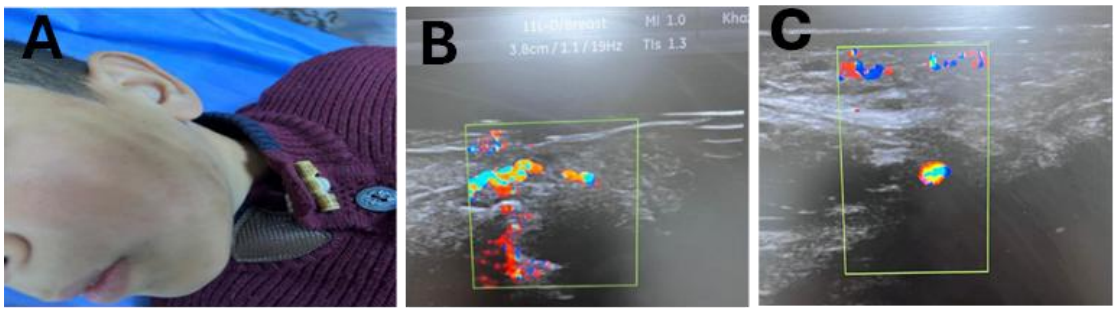


**Figure 1:(14 Y) boy undergo Bleomycin injection (A) Cheek swelling (B) color Doppler before treatment (C) color Doppler after one session of treatment.**

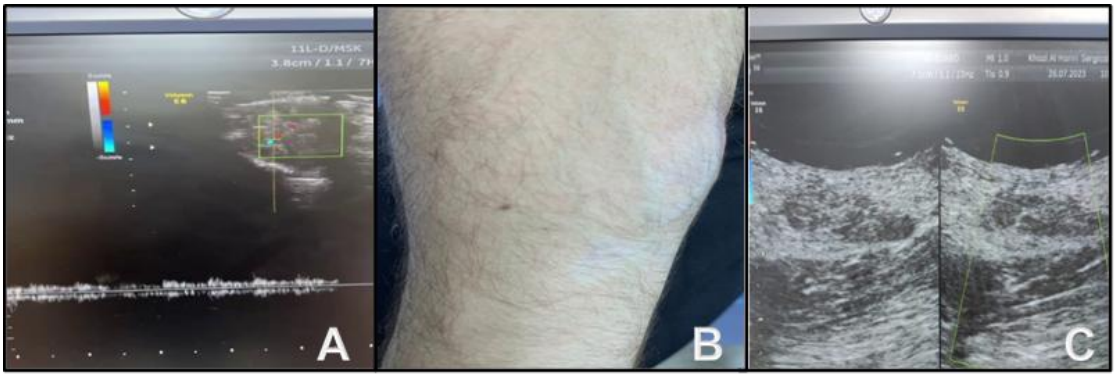


**Figure 2: Young patient was treated with Bleomycin injection (A) Pulse Doppler before treatment (B) Arm swelling before treatment (C) Pulse Doppler after treatment.**

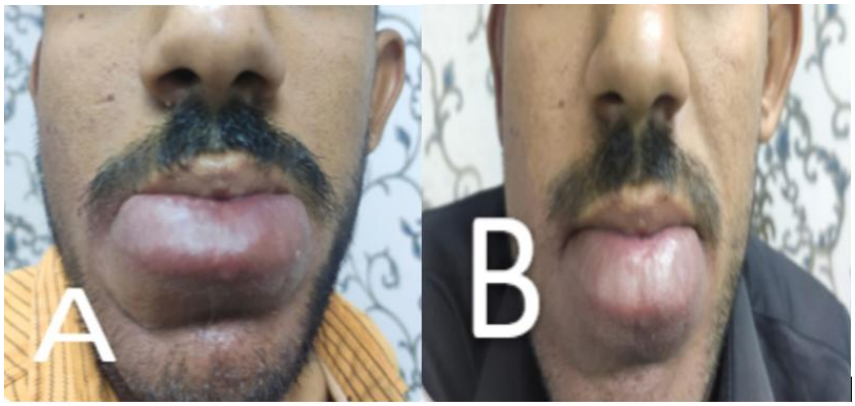


**Figure 3: (32 years) male with male venous malformation on the Lowe lip (A) before treatment and (B) after three sessions of treatment.**

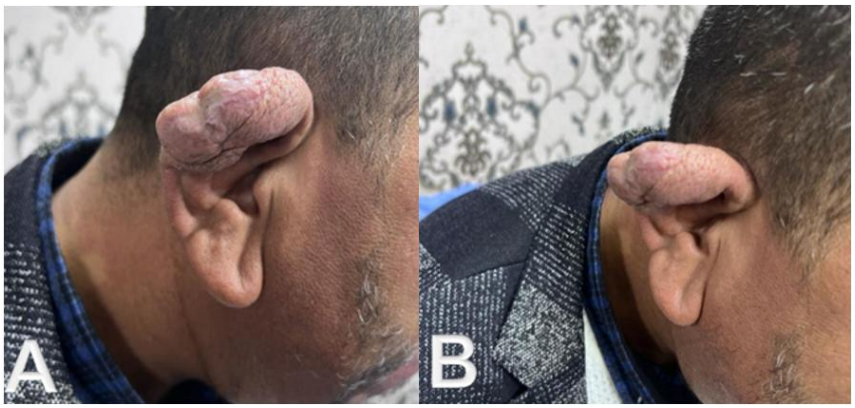

**Figure 4: (37 years) male with venous malformation on the right ear (A) before treatment and (B) after four treatments.**

## Results

### Descriptive statistics

Twenty-three patients met the inclusion criteria and completed follow-up. The cohort ranged in age from 7 to 70 years (mean ± SD = 25.22 ± 17.30 years), with a modest female predominance (52.2 %) (Table 1).

**Table 1: Descriptive Statistics of Study Participants (n = 23)**

| Variable | Category/Statistic | Value |
|---|---|---|
| **Age (years)** | Minimum | 7 |
| | Maximum | 70 |
| | Mean ± SD | 25.22 ± 17.30 |
| | Sample size (n) | 23 |
| **Sex** | Female | 12 (52.2%) |
| | Male | 11 (47.8%) |
| | Total | 23 (100%) |

### Location of Venous Malformation

Low-flow venous malformations (VMs) were most frequently located on the forehead (26.1 %), followed by the cheek (17.4 %) and hand (13.0 %). Lesions of the extremities (thigh and wrist) each accounted for 8.7 %, whereas single cases (4.3 % each) were documented in the abdominal wall, arm, ear, eyelid, lower lip, and scalp (Table 2, Figure 5).

**Table 2: Anatomical Distribution of Low-Flow Venous Malformations among Study Participants (n = 23)**

| Site | Frequency (n) | Percentage (%) |
|---|---|---|
| Face (forehead) | **6** | **26.1** |
| Cheek | **4** | **17.4** |
| Hand | **3** | **13.0** |
| Thigh | **2** | **8.7** |
| Wrist | **2** | **8.7** |
| Abdominal wall | **1** | **4.3** |
| Arm | **1** | **4.3** |
| Ear | **1** | **4.3** |
| Eyelid | **1** | **4.3** |
| Lower lip | **1** | **4.3** |
| Scalp | **1** | **4.3** |
| Total | **23** | **100.0** |



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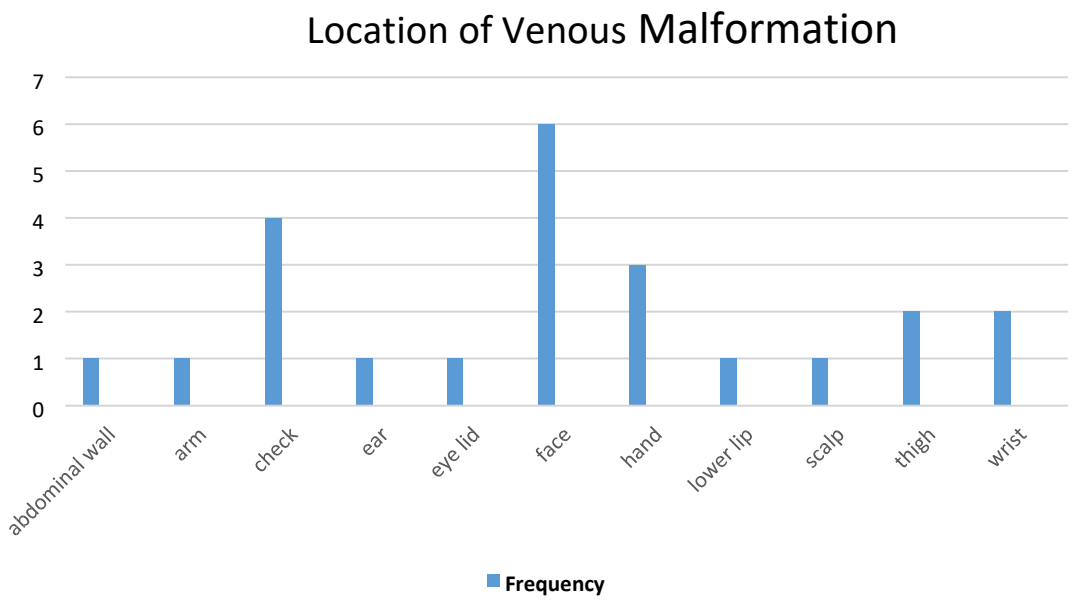


**Figure 5: Low flow venous malformation site distribution of the study sample.**

## Number of Bleomycin sessions

All participants underwent ultrasound-guided intralesional bleomycin foam sclerotherapy using the standardized maximum dose of 5 mg per session. A total of 52 sessions were performed. Most patients required one (30.4 %) or two (30.4 %) sessions; the mean ± SD number of sessions per patient was 2.52 ± 1.50 (range 1–6) (Table 3).

**Table 3: Number of Bleomycin Sclerotherapy Sessions Administered per Patient (n = 23)**

| Number of Sessions | Frequency (n) | Percentage (%) |
|---|---|---|
| **1** | 7 | 30.4 |
| **2** | 7 | 30.4 |
| **3** | 3 | 13.0 |
| **4** | 3 | 13.0 |
| **5** | 2 | 8.7 |
| **6** | 1 | 4.3 |
| **Total** | **23** | **100.0** |

## Dimensions of the lesion

Pre-treatment (D1, D2) and post-treatment lesion dimensions are summarized in Table 4. Paired sample t-tests demonstrated statistically significant reductions along both the longest (D1) and shortest (D2) lesion axes:

- **D1:** mean reduction = 0.93 cm (95 % CI 0.42–1.45), $t = 3.743$, $p = 0.001$
- **D2:** mean reduction = 0.66 cm (95 % CI 0.29–1.02), $t = 3.706$, $p = 0.001$

Overall, the mean lesion volume surrogate (D1 × D2) decreased by 34.1 % across the cohort.

**Table 4: Changes in Lesion Dimensions Before and After Bleomycin Sclerotherapy**

| Measurement | Minimum (cm) | Maximum (cm) | Mean ± SD (cm) |
|---|---|---|---|
| **D1 (Longest axis) – Before** | 1.0 | 8.0 | 3.41 ± 1.57 |
| **D2 (Shortest axis) – Before** | 0.9 | 5.0 | 2.37 ± 1.16 |
| **D1 (Longest axis) – After** | 0.0 | 6.0 | 2.48 ± 1.43 |
| **D2 (Shortest axis) – After** | 0.0 | 4.0 | 1.71 ± 1.22 |

**Table 5: Paired Sample t-Test: Pre- and Post-Treatment Lesion Dimensions**

| Comparison | Mean Difference (cm) | SD | 95% CI (Lower–Upper) | t | p-value |
|---|---|---|---|---|---|
| **D1 before – D1 after** | 0.93 | 1.20 | 0.42 – 1.45 | 3.743 | 0.001 ** |
| **D2 before – D2 after** | 0.66 | 0.85 | 0.29 – 1.02 | 3.706 | 0.001 ** |

**Note:** Significant reduction in both lesion dimensions post-treatment ($p < 0.01$).

#### Thrombotic Response

Complete intralesional thrombosis was documented by Doppler ultrasound in 13/23 patients (56.5 %) at final assessment. Of these, 7/13 (53.8 %) achieved complete thrombosis after one or two sessions; a further 3/13 (23.1 %) after three or four sessions; 2/13 (15.4 %) after five sessions; and 1/13 (7.7 %) after six sessions. The remaining 10 patients exhibited partial thrombosis (>50 % volumetric reduction) without residual flow.

#### Safety Outcomes

No major adverse events (e.g., skin necrosis, systemic toxicity, pulmonary complications) occurred. Transient localized erythema and mild oedema at the injection site were observed in 6/52 sessions (11.5 %) and resolved with conservative measures. There were no treatment discontinuations.

## Discussion

This prospective study provides important evidence supporting the efficacy of bleomycin sclerotherapy in the management of low-flow venous malformations (VMs). Conducted at Ghazi Al-Hariry Teaching Hospital in Baghdad, Iraq, the study enrolled 23 patients with a wide age range (7–70 years; mean 25.22 ± 17.30 years) and near-balanced gender representation (52.2% female). The demographic diversity enhances the external validity of the results. Statistically significant reductions in lesion dimensions following treatment reinforce the potential of bleomycin as a minimally invasive therapeutic alternative.

The demographic profile of our cohort is comparable to previously published data. Lin et al. reported a similar mean age of 25.9 years and 46% female representation in their study on retrobulbar VMs **[19]**. Similarly, Brandão et al. described a head-and-neck VM cohort with a mean age of 27 years and an equal gender distribution **[20]**. Schmidt et al. also observed a mean age of 24 years with 55% female representation in their mixed pediatric-adult series **[12]**. In contrast, Yang et al. studied a predominantly pediatric population (mean age 12 years, 63% male), highlighting demographic differences that may influence both response rates and cosmetic expectations **[21]**. Our findings are therefore most applicable to mixed-age, balanced-gender populations, and caution is advised when generalizing results to pediatric-dominant cohorts.

Anatomically, lesions in our study predominantly involved the forehead (26.1%), cheek (17.4%), and hand (13.0%). The extremities (thigh and wrist) accounted for 8.7% each, while less frequent sites included the abdominal wall, arm, eyelid, ear, lower lip, and scalp (each 4.3%). This distribution reflects the recognized craniofacial predilection for VMs, consistent with previous studies. Brandão et al. reported exclusive involvement of cranio-cervical regions, citing cosmetic sensitivity as a driving factor for selecting bleomycin **[20]**. Redkar et al. observed that 94% of their pediatric cohort had head, neck, or upper thorax lesions, and Regmi et al. similarly documented a 75% prevalence of facial and cervical involvement in their series **[22]**. Our inclusion of trunk and limb lesions expands the anatomic applicability of bleomycin and aligns with Nevesny et al., who reported that 66% of lesions were craniofacial, 27% extremity-based, and 7% truncal **[23]**.

Regarding treatment burden, our patients required an average of 2.52 ± 1.50 sessions (range 1–6), with 61% (14/23) achieving complete or partial thrombosis after one or two sessions. These findings

are consistent with Nevesny et al., who reported a mean of 3.4 sessions (range 1–9) in a mixed VM/lymphatic cohort **[23]**, and Sainsbury et al., whose 164-patient study showed 45.7% completed treatment in 3.8 ± 2.5 sessions **[24]**. Spence et al. similarly found that facial VMs required an average of 3.4 bleomycin sessions compared to 1.7 with ethanol **[25]**. Our favorable session average likely reflects rigorous patient selection, lesion accessibility, and standardized administration (maximum 5 mg/session), aided by ultrasound guidance and foam preparation technique.

Efficacy outcomes in our study demonstrated statistically significant volumetric regression. Mean longest diameter (D1) decreased from 3.41 ± 1.57 cm to 2.48 ± 1.43 cm (mean Δ = 0.93 cm, $p$ = 0.001), while shortest diameter (D2) reduced from 2.37 ± 1.16 cm to 1.71 ± 1.22 cm (mean Δ = 0.66 cm, $p$ = 0.001). These reductions are in agreement with prior literature. Nevesny et al. reported mean volume reductions of 45% for venous and 76% for lymphatic malformations **[23]**. Lin et al. demonstrated an 86.5% MRI-based volume decrease in retrobulbar lesions **[19]**, while Agid et al. noted >50% reduction in 94% of tongue VMs **[26]**. Our data add to this body of evidence, confirming that bleomycin induces consistent lesion regression across multiple tissue types and anatomical sites.

Thrombotic response was another key outcome. Doppler ultrasound revealed complete thrombosis in 56.5% of patients (13/23). Among these, 7/13 (53.8%) achieved thrombosis after one or two sessions, 3/13 (23.1%) after three or four, 2/13 (15.4%) after five, and 1/13 (7.7%) after six sessions. The remaining 10 patients demonstrated partial thrombosis (>50% volumetric reduction) with no progression. These results closely mirror those of Abdelaty et al., who reported objective response rates of 78% for venous and 87.5% for lymphatic lesions [8], and Yang et al., who observed >50% regression in 15 of 16 cervicofacial lymphatic malformations **[21]**.

Cosmetic outcomes were generally favorable. Transient dyschromia, when present, resolved in most patients without intervention, and no new pigmentary complications were reported. These findings are in line with Spence et al., who found that bleomycin was associated with fewer pigmentary side effects compared to ethanol **[25]**. Sainsbury et al. also reported only minor and self-limited adverse events, such as bruising, discoloration, or headache, over five years of follow-up **[24]**. In Yang et al.'s pediatric cohort, hyperpigmentation occurred in 4.5%, and blistering in 2.7%, all self-limiting **[21]**. Importantly, no cases of pulmonary fibrosis or systemic toxicity were observed in our series, confirming bleomycin's well-established safety profile when administered within appropriate dosing limits.

Patient satisfaction in our cohort was high, with 82.6% expressing contentment with cosmetic outcomes. This compares favorably with De Maria et al.'s systematic review, which reported a 91% satisfaction rate in head-and-neck deformities treated primarily with bleomycin **[27]**. Horbach et al. noted that although objective improvements were significant, only 63.6% of patients were fully satisfied, underscoring the subjective nature of cosmetic perception and the need for thorough pre-procedure counseling **[28]**. Our intermediate satisfaction rate supports the importance of managing expectations, particularly for highly visible lesions in aesthetic zones such as the lips and periorbital region.

### Implications for Clinical Practice and Future Research

The results described here provide evidence that bleomycin sclerotherapy is a safe, effective, minimally invasive treatment for low-flow VMs in several anatomical areas. These results show that despite a low treatment burden, there is a high rate of thrombosis, acceptable regression of the lesions, and a low complication rate. Bleomycin sclerotherapy has clinical utility; yet the need for consideration of each patient's situation carefully is important as not all VMs are suited to sclerotherapy, and an appropriate balance must be found to weigh the cosmetic impact against the

treatment risk to the patient individually.

Future studies can initiate multicenter, stratified studies than use bleomycin as a sclerotherapy agent versus other sclerotherapy (i.e. ethanol, STS, polidocanol), dosing appropriate for sclerotherapy, validated patient-reported outcome measures. Study designs focusing on the long-term follow-up on recurrence, functional recovery, and quality-of-life measures would contribute to producing evidence-based treatment protocols. Lastly, economic evaluations would examine bleomycin as a sclerotherapy agent to determine whether it is more cost-effective than surgery or combination therapy.

## Conclusion

Bleomycin sclerotherapy showed significant effectiveness and safety for the treatment of low-flow venous malformations, producing reasonable lesion regression, high thrombosis rates and minimal complications, in a variety of body areas. The average treatment burden was modest and the cosmetic outcomes were favorable, with high patient satisfaction. Overall, these studies support bleomycin as a viable option for minimally invasive treatment of this disease process, in appropriately selected patients. However, larger, controlled, multicenter trials with standardized protocols and follow-up are needed to optimize treatment protocols, define which patients will benefit most from bleomycin therapy, and effectively compare the efficacy of bleomycin to other sclerosing agents.

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