COMPARATIVE ANALYSIS OF THE EFFECTIVENESS OF BLEOMYCIN AND ETHOXYSCLEROL IN THE TREATMENT OF VENOUS MALFORMATIONS: Experience of the A.N. Syzganov National Scientific Center of Surgery

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Abstract

Background: Venous malformations represent congenital slow-flow vascular anomalies accounting for 45–60% of all vascular malformations. They arise from developmental defects of venous channels and are frequently associated with chronic pain, swelling, cosmetic deformity, and functional limitations.

Materials and Methods: A retrospective analysis included 40 patients with venous malformations treated at the A.N. Syzganov National Scientific Center of Surgery (2019–2024). Patients underwent two ultrasound-guided sclerotherapy sessions and were assigned to bleomycin (n = 20) or ethoxysclerol (n = 20). Outcomes included lesion-volume reduction on magnite resonance / ultrasound and changes in EQ-5D-5L and EQ-VAS scores.

Results: Mean venous malformations volume reduction after two sessions was 32.2 ± 10.1% with bleomycin and 29.6 ± 12.3% with ethoxysclerol (p = 0.42). EQ-5D-5L improved by +0.20 and +0.16, respectively (p = 0.40). Although baseline EQ-VAS was higher in the ethoxysclerol group, the gain was greater with bleomycin (+13.2 vs. +7.5; p = 0.06). No severe complications were registered; mild reactions occurred in 27.5%. Predictors of ⩾50% regression were baseline lesion volume < 35 cm^3 (OR = 2.8; p = 0.02) and body mass index < 27 kg/m^2 (OR = 2.3; p = 0.04).

Conclusion: Both sclerosants are effective and safe for treating venous malformations. Bleomycin showed a trend toward greater subjective improvement and fewer additional procedures. Personalized agent selection should consider lesion volume, body mass index, and individual clinical features.

Introduction

Venous malformations (VMs) are congenital slow-flow vascular anomalies characterized by dilated venous channels with impaired drainage and low hemodynamic flow. They account for 40–60% of all vascular malformations and affect approximately 1–2 per 10,000 individuals, most frequently involving the head and neck, extremities, and trunk.[1-3] Clinically, VMs present with chronic pain, swelling, cosmetic deformity, and functional limitations, which progressively impair patients' quality of life.[4] Localized intravascular coagulopathy may complicate extensive or symptomatic lesions, increasing the risk of thrombosis and bleeding.[5]

Diagnosis is based on clinical assessment supported by Doppler ultrasound and contrast-enhanced MRI, which provide essential information on flow characteristics, lesion depth, and anatomic extent.[6] The primary goals of treatment are symptom control, reduction of lesion volume, and prevention of recurrence. Available therapeutic options include conservative management, surgical excision, laser therapy, endovascular approaches, and sclerotherapy.[7]

Sclerotherapy is currently regarded as the first-line treatment for most VMs because it enables targeted endothelial destruction with minimal damage to surrounding tissues.[8] Among modern sclerosants, ethoxysclerol (polidocanol) and bleomycin are widely used due to their established efficacy and favorable safety profiles. Ethoxysclerol acts as a non-ionic detergent producing endothelial spasm and thrombosis, whereas bleomycin induces fibrosis through cytotoxic and sclerosing mechanisms.[9]

Recent clinical studies and meta-analyses confirm the high effectiveness of both agents, although differences exist in their depth of action, tissue response, and frequency of required treatment sessions.[10-12] Bleomycin is often associated with more pronounced fibrosis and durable regression, while ethoxysclerol is considered less aggressive and cosmetically better tolerated. Severe complications are rare for both agents when administered in controlled, low-dose protocols.[13]

Despite extensive international data, evidence from Central Asia—including Kazakhstan—remains limited. Many patients in the region present with advanced, long-standing lesions, emphasizing the need to evaluate optimal treatment strategies in local clinical settings. Over the past five years, the A.N. Syzganov National Scientific Center of Surgery has accumulated substantial experience in the endovascular management of vascular malformations, including the use of bleomycin and ethoxysclerol.

Therefore, the aim of this study was to perform a comparative analysis of the clinical efficacy and safety of bleomycin and ethoxysclerol sclerotherapy in patients with venous malformations treated.

The aim of the study is compare the clinical efficacy and safety of bleomycin versus ethoxysclerol in the sclerotherapy of venous malformations.

Materials and Methods

Study Design and Setting: The study was conducted at the A.N. Syzganov National Scientific Center of Surgery (Almaty, Kazakhstan), within the Departments of X-ray Surgery, Interventional Cardiology and Arrhythmology, and Angiosurgery. A retrospective analysis of medical records and procedural logs was performed for the period 2019–2024.

General Characteristics of the Cohort: Over this five-year period, 2,078 patients with various forms of vascular malformations were treated. Among them, 1,324 (63.7%) were first-time consultations and 735 (36.3%) were repeat visits, reflecting a high recurrence rate of the disease. Women accounted for 63.4% (n = 1,315) of the cases and men for 36.6% (n = 762). Patient ages ranged from 1 to 72 years (mean age 24.3 ± 8.9 years). By regional origin, most patients were from southern and central Kazakhstan. The highest numbers were from: Almaty Region – 273 (13.1%), Almaty City – 264 (12.7%), Turkestan Region – 125 (6.0%), Kyzylorda Region – 98 (4.7%), Zhambyl Region – 84 (4.0%), Shymkent – 76 (3.6%), Karaganda Region – 59 (2.8%), Aktobe Region – 51 (2.4%), East Kazakhstan Region – 48 (2.3%), Other regions (North Kazakhstan, Kostanay, Pavlodar, Atyrau, etc.) – 1,000 patients (48.1%).

Thus, approximately 40% of the total patient flow originated from the southern region, including Almaty and Almaty Region, reflecting both the regional concentration of specialized vascular care and the transport accessibility of the Center.

Procedures and Agents. Throughout the study period, a total of 2,078 endovascular and sclerotherapeutic interventions were performed.

The most commonly used agents and techniques were: Ethoxysclerol (Polidocanol 3%) – 1,027 procedures (52.6%), Bleomycin – 150 procedures (7.7%), Ethanol 90–96% – 272 procedures (13.9%). Embolic materials (*Embo Gold, SQUID, Interlock, Azur, Onyx, Amplatzer Plug*) – 629 procedures (30.3%)

In terms of anatomical localization, the majority of angiographic procedures involved the lower extremities (31%), upper extremities (15.4%), and facial angiomata (6.7%), consistent with the general distribution of vascular malformations in clinical practice.

Study Sample for Comparative Analysis. From the total cohort, 40 patients (1.9%) with a confirmed diagnosis of venous malformation (based on clinical, Doppler ultrasound, and contrast-enhanced MRI findings) were selected for the comparative study.All patients underwent two consecutive sessions of sclerotherapy.

Patients were divided into two groups according to the agent used:Group I (n = 20): Bleomycin (1 mg/mL solution), Group II (n = 20): Ethoxysclerol (Polidocanol 3%).

The mean age of patients was 32.7 ± 9.4 years in the bleomycin group and 31.5 ± 8.7 years in the ethoxysclerol group.

Sex distribution was as follows: women — 12 (60%) and 11 (55%), men — 8 (40%) and 9 (45%) in Groups I and II, respectively.

Inclusion criteria: confirmed diagnosis of venous malformation (ISSVA classification)[12]; age ⩾18 years; absence of active inflammatory or malignant disease; completion of at least two sclerotherapy sessions;

Exclusion criteria: arteriovenous malformations; systemic coagulopathies; pregnancy or lactation; known allergy to sclerosing agents.

*Outcome Measures.*Treatment efficacy was assessed using the following parameters:change in lesion volume — percentage reduction on ultrasound and MRI 3 months after the second sclerotherapy session; quality of life (EQ-5D-5L) — evaluation across five domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression); EQ-VAS score (0–100) — patient-reported overall health status; adverse events (pain, swelling, inflammation, necrosis, allergic reactions) and subjective treatment satisfaction were also recorded.

Ethical Approval: The study was conducted in accordance with the Declaration of Helsinki (2013) and approved by the Ethics Committee of the A.N. Syzganov National Scientific Center of Surgery (Protocol №5, dated October 25, 2025).All participants provided written informed consent for inclusion and for the use of their anonymized medical data for scientific purposes.

Statistical Analysis. All data were entered into standardized case forms and analyzed using SPSS Statistics v25.0 and GraphPad Prism v10.0.Non-parametric tests were applied: the Wilcoxon signed-rank test for paired samples, the Mann–Whitney U-test for independent groups, and the x^2 test (Pearson) for categorical variables.Results are presented as mean ± standard deviation (M ± SD), and statistical significance was set at $p < 0.05$.

Results

A total of 40 patients with venous malformations (VMs) were included in the analysis, equally distributed between the bleomycin group (n = 20) and the ethoxysclerol group (n = 20). The groups were comparable in key demographic and clinical characteristics.

In the bleomycin group, women accounted for 60% (12/20) and men for 40% (8/20); in the ethoxysclerol group, 55% (11/20) were women and 45% (9/20) were men (x^2, p = 0.77).

The mean age was 32.7 ± 9.4 years in the bleomycin group and 31.5 ± 8.7 years in the ethoxysclerol group (Mann–Whitney, p = 0.68).

The mean body mass index (BMI) was 24.8 ± 3.6 kg/m² and 25.2 ± 3.9 kg/m², respectively (p = 0.62).

The proportion of overweight patients (BMI 25.0–29.9 kg/m²) was 35% vs. 40%, while obesity (BMI ⩾30 kg/m²) was observed in 10% of both groups (x^2, p = 0.94).

The *Charlson* Comorbidity Index (CCI) median was 1 [0–2] in both groups, with no intergroup difference (p = 0.74).

Patients without significant comorbidities (CCI = 0) accounted for 40% vs. 35%; those with mild comorbidity (CCI = 1–2) for 45% vs. 50%; and with CCI ⩾3 for 15% vs. 15% (x^2, p = 0.93).

Thus, the bleomycin and ethoxysclerol groups were statistically comparable in terms of sex, age, BMI, and comorbidity burden, allowing a valid comparison of efficacy and safety outcomes.

All patients had a diagnosis of venous malformation confirmed by col-

or Doppler ultrasonography and contrast-enhanced magnetic resonance imaging (MRI).

The main presenting complaints at baseline were chronic pain (85%), cosmetic deformity (70%), soft-tissue swelling or heaviness (55%), and movement limitation of the affected limb (22.5%).

The mean disease duration was 6.8 ± 3.2 years (range 2–17 years): 7.1 ± 3.0 years in the bleomycin group and 6.4 ± 3.5 years in the ethoxysclerol group (p = 0.52, not significant).

Pain intensity on the Visual Analogue Scale (VAS) averaged 6.2 ± 1.1, with no significant difference between groups (p = 0.67).

Regarding anatomical localization, the most frequent sites were the lower limbs (40%), face and neck (25%), upper limbs (17.5%), trunk and back (10%), and intraoral or facial soft tissues (7.5%; tongue, lip, cheek).

Multiple or bilateral lesions were present in 12.5% of patients. Most VMs were classified as slow-flow types according to the ISSVA classification.

The mean baseline lesion volume (by MRI) was 32.6 ± 11.8 cm^3 in the bleomycin group and 30.9 ± 10.7 cm^3 in the ethoxysclerol group (p = 0.63).

Volumes ranged from 8 cm^3 to 68 cm^3. Soft-tissue or subcutaneous localization occurred in 85% of cases, while muscular involvement was observed in 15%.

Intravascular thrombosis was noted in 15% of patients, predominantly with extensive lower-limb lesions.

Doppler ultrasonography demonstrated a slow-flow phlebolithic pattern in 82.5% of patients and moderate venous outflow with collateral dilation in 17.5%.

The mean flow velocity was 6.8 ± 1.4 cm/s, and the mean diameter of draining veins was 0.42 ± 0.11 cm; no hemodynamically significant arteriovenous shunts were detected.

Among comorbid conditions, chronic venous insufficiency was present in 20% of patients, arterial hypertension in 12.5%, obesity in 10%, and type 2 diabetes mellitus in 7.5%.

The median *Charlson* Comorbidity Index remained 1 [0–2], indicating a low systemic risk profile across both cohorts.

No statistically significant differences were found between the groups by sex (60% vs. 55%, p = 0.77), age (32.7 ± 9.4 vs. 31.5 ± 8.7 years, p = 0.68), BMI (24.8 ± 3.6 vs. 25.2 ± 3.9 kg/m^2, p = 0.62), or CCI (p = 0.74).

Accordingly, both groups were statistically well-matched in baseline demographic and clinical parameters, ensuring the validity of the subsequent comparative assessment of the efficacy and safety of bleomycin versus ethoxysclerol.

Table 1.
Baseline demographic and clinical characteristics of patients (n = 40)

Parameter	Bleomycin Group (n = 20)	Ethoxysclerol Group (n = 20)	p-value
Femalesex, n (%)	12 (60%)	11 (55%)	0.77
Mean age, years (M ± SD)	32.7 ± 9.4	31.5 ± 8.7	0.68
BMI, kg/m^2 (M ± SD)	24.8 ± 3.6	25.2 ± 3.9	0.62
Overweight, n (%)	7 (35%)	8 (40%)	0.94
Obesity (BMI ⩾30), n (%)	2 (10%)	2 (10%)	0.94
CharlsonIndex, median [IQR]	1 [0–2]	1 [0–2]	0.74
Duration of disease, years (M ± SD)	7.1 ± 3.0	6.4 ± 3.5	0.52
Painintensity (VAS, 0–10)	6.2 ± 1.1	6.3 ± 1.0	0.67
Note. Data are presented as mean ± standard deviation (M ± SD), median [interquartile range (IQR)], or number (percentage). P-values were calculated using the Mann–Whitney U test for continuous variables and the x^2 (Pearson) test for categorical variables.BMI – body mass index; VAS – visual analogue scale; CCI – Charlson Comorbidity Index.			

After two sessions of sclerotherapy, all patients demonstrated positive dynamics on clinical examination, ultrasound, and contrast-enhanced MRI.

The mean reduction in venous malformation (VM) volume after the first session was 24.6 ± 9.3% in the bleomycin group and 21.8 ± 10.1% in the ethoxysclerol group (p = 0.41).

Following the second session, regression increased to 32.2 ± 10.1% and 29.6 ± 12.3%, respectively (p = 0.42), indicating no statistically significant difference in overall efficacy between the two agents.

A marked regression (≥ 50%) was achieved in 25% of bleomycin-treated and 20% of ethoxysclerol-treated patients.

Dynamic MRI follow-up revealed that bleomycin therapy more often produced uniform tissue consolidation and decreased contrast enhancement, whereas ethoxysclerol cases more frequently exhibited residual vascular patterns and heterogeneous sclerosis—suggesting a more prolonged sclerosing action of bleomycin.

Self-reported outcomes on the EQ-5D-5L scale demonstrated significant improvement across all domains: pain scores decreased from 2.8 ± 0.6 to 1.7 ± 0.4 (p < 0.001); mobility and self-care improved by 25–30%; anxiety/depression scores by 18–22%.

The overall EQ-5D-5L index increased from 0.65 ± 0.12 to 0.85 ± 0.09 in the bleomycin group and from 0.67 ± 0.11 to 0.83 ± 0.10 in the ethoxysclerol group (p = 0.48).

On the EQ-VAS (0–100) scale, baseline scores were 70.2 ± 6.2 for bleomycin and 76.0 ± 10.5 for ethoxysclerol (p = 0.03), reflecting a slightly higher initial self-perceived health status in the latter group. Post-treatment, EQ-VAS scores rose to 83.4 ± 9.5 and 83.5 ± 4.8, respectively (p = 0.97).

The mean gain was +13.2 points in the bleomycin group versus +7.5 points in the ethoxysclerol group, showing a trend toward greater subjective improvement with bleomycin (p = 0.06). Overall clinical efficacy—defined as ≥ 25% lesion regression combined with an EQ-5D-5L gain ≥ 0.15—was achieved in 90% of bleomycin and 85% of ethoxysclerol patients (p = 0.67).

Complete or near-complete regression (< 10% residual volume) was observed in 15% and 10%, respectively.

An analysis by lesion location showed that bleomycin produced the most pronounced effects in lower-limb lesions (35.4 ± 9.2%) and facial regions (31.6 ± 8.7%), whereas ethoxysclerol was more effective for small superficial lesions of the neck and trunk (up to 33.2 ± 10.4%).

In extensive, multilayer lesions (> 40 cm^3), both agents were less effective; however, bleomycin required significantly fewer additional sessions (2.1 ± 0.6 vs 2.7 ± 0.8; p = 0.04).

In summary, both bleomycin and ethoxysclerol provided comparable objective efficacy, substantial quality-of-life improvement, and a favorable safety profile.

Bleomycin demonstrated a trend toward greater subjective benefit (Δ EQ-VAS = +13.2 vs +7.5) and a significantly lower need for repeated procedures, suggesting a more sustained sclerosing effect (Table 2).

Table 2.
Comparative efficacy of bleomycin and ethoxysclerol sclerotherapy in venous malformations (n = 40)

Parameter	Bleomycin (n = 20)	Ethoxysclerol (n = 20)	p-value	Interpretation
VM volume reduction after 1st session, %	24.6 ± 9.3	21.8 ± 10.1	0.41	No difference
VM volume reduction after 2nd session, %	32.2 ± 10.1	29.6 ± 12.3	0.42	No difference
Patients with ≥ 50% regression, n (%)	5 (25%)	4 (20%)	0.71	No difference
EQ-5D-5L before treatment	0.65 ± 0.12	0.67 ± 0.11	0.55	No difference

EQ-5D-5L after treatment	0.85 ± 0.09	0.83 ± 0.10	0.48	No difference
Δ EQ-5D-5L (change)	+0.20	+0.16	0.40	No difference
EQ-VAS before (0–100)	70.2 ± 6.2	76.0 ± 10.5	0.03*	Higher baseline in ethoxysclerol group
EQ-VAS after (0–100)	83.4 ± 9.5	83.5 ± 4.8	0.97	No difference
Δ EQ-VAS (change)	+13.2	+7.5	0.06	Trend in favor of bleomycin
Complete regression (< 10%), n (%)	3 (15%)	2 (10%)	0.64	No difference
Mean number of sessions	2.1 ± 0.6	2.7 ± 0.8	0.04*	Fewer with bleomycin

Note. Data are presented as mean ± standard deviation (M ± SD) or number (percentage). P-values were calculated using the Mann–Whitney U test for continuous variables and the x^2 (Pearson) test for categorical variables. VM – venous malformation; EQ-VAS – EuroQol Visual Analogue Scale; EQ-5D-5L – EuroQol 5-Domain 5-Level Index.

All sclerotherapy procedures were performed under ultrasound guidance, following standard safety precautions, including slow agent administration and subsequent elastic compression. Overall, both treatment methods demonstrated good tolerability. No procedure-related systemic or life-threatening complications were recorded.

The overall complication rate was 27.5% (11 out of 40 patients). Complications occurred in 5 patients (25%) in the bleomycin group and 6 patients (30%) in the ethoxysclerol group (p = 0.73).

Most events were mild to moderate local reactions and did not require hospitalization.

The most common adverse effects were pain or burning at the injection site in 8 patients (20%), localized edema and erythema in 7 (17.5%), superficial phlebitis in 3 (7.5%), post-procedural skin hyperpigmentation in 4 (10%), and transient hyperthermia in 2 (5%).

In the bleomycin group, local inflammatory reactions occurred less frequently (15% vs. 25%, p = 0.42), whereas moderate injection-site pain was observed slightly more often (20% vs. 15%, p = 0.68).

In the ethoxysclerol group, superficial phlebitis (10% vs. 5%, p = 0.56) and hyperpigmentation (15% vs. 5%, p = 0.31) were somewhat more common.

No severe adverse events—such as tissue necrosis, allergic reactions, deep vein thrombosis, embolic phenomena, or systemic toxicity—were observed in either group.

Importantly, no signs of bleomycin-induced pulmonary fibrosis or systemic toxicity were detected, as confirmed by clinical examination and follow-up chest radiography.

The mean duration of local reactions was 2.6 ± 1.1 days and required no additional medical treatment.

Patient-rated tolerability scores (0 = no discomfort, 10 = maximum discomfort) averaged 2.8 ± 1.3 in the bleomycin group and 3.1 ± 1.5 in the ethoxysclerol group (p = 0.59), indicating good subjective tolerance of both procedures.

In summary, sclerotherapy using bleomycin or ethoxysclerol for venous malformations demonstrated a high safety profile and satisfactory tolerability, with no severe or systemic complications reported.

The frequency of mild local reactions did not exceed 30% and was statistically comparable between groups, confirming the acceptable safety margin of both agents when administered under controlled endovascular conditions (Table 3).

Table 3.
Complications after sclerotherapy (n = 40)

Type of complication	Ethoxysclerol (n = 20)	Bleomycin (n = 20)	OR	95%CI	p-value
Any complication	6(30%)	5(25%)	1.28	[0.3;5.2]	0.73
Painorburning	3(15%)	4(20%)	0.71	[0.1:3.6]	0.68
Edema / erythema	4(20%)	3(15%)	1.40	[0.3:7.3]	0.68
Superficial Phlebitis	2(10%)	1(5%)	2.10*	[0.2:25.3]	0.56
Hyperpigmentation	3(15%)	1(5%)	3.35*	[0.3:35.4]	0.31
Transient Hyperthermia	1(5%)	1(5%)	1.0	-	1.00
Severe Complications	0	0	-	-	–
Mean tolerability score (0–10)	3.1 ± 1.5	2.8 ± 1.3	-	[0.6:1.2]	0.50
Note. Data are presented as mean ± standard deviation (M ± SD) or percentage of patients.p-values were calculated using the x^2 (Pearson) test for categorical variables and the Mann–Whitney U test for continuous variables.No severe systemic reactions or hospitalizations occurred in either group.					

The percentage reduction in venous malformation (VM) volume after the second treatment stage (ΔV) demonstrated significant negative correlations with baseline lesion volume (r = –0.41, p = 0.01), disease duration (r = –0.35, p = 0.03), and body mass index (BMI; r = –0.32, p = 0.04).

The association with the Charlson Comorbidity Index (CCI) was weaker and statistically nonsignificant (r = –0.25, p = 0.11), while age showed only a borderline trend (r = –0.28, p = 0.08).

Improvement in subjective health correlated strongly with lesion regression: ΔEQ-VAS vs. ΔV (r = 0.62, p < 0.001) and moderately with the EQ-5D-5L index (r = 0.46, p = 0.004).

In the multivariate logistic regression model (endpoint: ≥50% regression after the second stage), significant predictors were: Baseline lesion volume < 35 cm^3 (OR = 2.8; 95% CI: 1.2–6.7; p = 0.02) and BMI < 27 kg/m^2 (OR = 2.3; 95% CI: 1.0–5.4; p = 0.04).

Low comorbidity (CCI ⩽ 1) showed a borderline association (OR = 1.9; p = 0.09).The type of sclerosing agent (bleomycin vs. ethoxysclerol) was not an independent predictor of ≥50% regression (OR = 1.3; p = 0.42).

The model demonstrated good discrimination (AUC ROC = 0.74) and acceptable calibration (Hosmer–Lemeshow test: p = 0.48). Factors associated with the need for a third treatment session included baseline lesion volume > 40 cm^3 (OR = 3.1; p = 0.03) and multifocal disease (OR = 2.7; p = 0.04).Facial or cervical localization showed no significant effect (OR = 1.5; p = 0.28).

Predictors of adverse events included obesity (BMI ⩾ 30 kg/m^2) (OR = 2.4; p = 0.05; borderline significance) and facial/neck localization (OR = 1.9; p = 0.09), whereas the type of agent had no significant impact (bleomycin vs. ethoxysclerol: OR = 1.2; p = 0.66).The interaction term "agent × lesion volume" was nonsignificant (p = 0.61).

The correlation and prognostic analyses indicate that the efficacy of sclerotherapy for venous malformations primarily depends on baseline anatomical and metabolic patient characteristics rather than the choice of agent.Patients with smaller lesions (<35 cm^3) and normal body weight (BMI < 27 kg/m^2) exhibited greater lesion regression and better improvement in quality of life.

In contrast, long disease duration (>10 years) and multifocal involvement reduced the likelihood of significant regression and increased the need for additional treatment sessions.

A direct relationship was observed between the degree of lesion regression and improvement in quality-of-life indices (EQ-VAS and EQ-5D-5L): the greater the reduction in lesion volume, the higher the subjective health assessment (r = 0.62; p < 0.001).

Although the type of agent was not an independent prognostic factor, bleomycin showed a trend toward greater improvement in EQ-VAS scores and a lower number of additional procedures. Thus, the most favorable response was seen in younger and middle-aged patients, those with limited lesion size, and with low comorbidity.

Overall, the effectiveness of sclerotherapy is determined more by individual anatomical and metabolic features of the malformation and the patient than by the choice of sclerosant (tables 4, 5).

Table 4. Correlation factors associated with sclerotherapy efficacy in venous malformations (n = 40)

Variable	Correlation coefficient (r)	p-value	Interpretation
Baselinelesionvolume	–0.41	0.01	Larger volume associated with lower efficacy
Diseaseduration	–0.35	0.03	Longerdurationreduceseffectiveness
Bodymassindex (BMI)	–0.32	0.04	Higher BMI associated with poorer response
CharlsonComorbidityIndex (CCI)	–0.25	0.11	Weak, nonsignificantrelationship
Age	–0.28	0.08	Trend, notsignificant
ΔEQ-VAS vs. ΔV	0.62	<0.001	Greater regression → better subjective health
ΔEQ-5D-5L vs. ΔV	0.46	0.004	Moderatepositivecorrelation

Note. Pearson's correlation coefficient; p — statistical significance level. Positive r values indicate direct correlation, negative values indicate inverse correlation.Bold values denote statistically significant correlations (p < 0.05).

Table 5. Multivariate predictors of sclerotherapy efficacy and complications

Factor	OR (95% CI)	p-value	Interpretation
Baseline volume< 35 cm^3	2.8* (1.2–6.7)	0.02	Independent predictor of ⩾50% regression
BMI < 27 kg/m^2	2.3 (1.0–5.4)	0.04	Independent predictor of treatment success
CCI ⩽ 1	1.9 (0.9–3.8)	0.09	Borderline, not significant
Agent (bleomycinvs. ethoxysclerol)	1.3 (0.6–2.7)	0.42	No effect on out come
Baselinevolume> 40 cm^3	3.1 (1.1–8.5)	0.03	Increases risk of third session
Multifocal disease	2.7 (1.0–7.0)	0.04	Increases risk of third session
Obesity (BMI ⩾ 30 kg/m^2)	2.4 (1.0–5.8)	0.05	Borderline risk factor for complications
Facial / necklocalization	1.9 (0.9–4.1)	0.09	Trend toward higher risk
Model quality: AUC ROC	0.74	—	Satisfactory predictive accuracy
Hosmer–Lemes how test	p = 0.48	—	Good model calibration

Note. OR — odds ratio; CI — confidence interval; p — statistical significance.AUC ROC — area under the receiver operating characteristic curve, indicating model discrimination (0.7–0.8 = acceptable accuracy). Hosmer–Lemeshow test (p > 0.05) confirms adequate model calibration.

Discussion

In this retrospective comparative analysis, we evaluated the clinical efficacy and safety of bleomycin and ethoxysclerol for the treatment of venous malformations (VMs). The study demon-

strated that both agents provided comparable objective outcomes, with mean lesion regression of 32.2% for bleomycin and 29.6% for ethoxysclerol, consistent with previously published international data.[14-17]

Our findings align with global epidemiological trends showing a predominance of females and typical involvement of limbs, head, and neck regions.[1-4] Similar regression levels have been reported in large-scale studies and meta-analyses. *Sun J, et al.* reported a 90–94% overall improvement following bleomycin sclerotherapy, with a serious complication rate below 1.5%. [15] Ethoxysclerol demonstrated 85–90% efficacy in the retrospective analysis by *Cay F, et al.* [16] and comparable results in further reviews.[17]

Comparative studies from Asia (*He B. et al.; Mukul S.K. et al; Lai J,et al.*) show no significant difference in objective efficacy between these agents, although bleomycin tends to produce a stronger fibrotic response and may require fewer treatment sessions.[14,17,18] Our data mirror these trends: patients treated with bleomycin required fewer sessions (mean 2.1 vs. 2.7; p = 0.04) and demonstrated a greater improvement in EQ-VAS scores.

The biological behavior of VMs is driven by somatic mutations in the *TEK/TIE2* and *PIK3CA* genes, which activate the PI3K/AKT/mTOR signaling pathway and lead to endothelial hyperplasia and aberrant vascular development.[9,10] These alterations explain the tendency toward chronic progression and incomplete response to therapy. Hormonal changes and trauma can further promote lesion enlargement.[12]

In this context, our observed predictors of treatment success—baseline volume < 35 cm^3 and BMI < 27 kg/m^2—agree with mechanistic insights into endothelial proliferation and venous stasis. *He B. et al.* demonstrated similar predictors in a 2024 meta-analysis,[17] while *Wu Z. et al.* identified lesion size and multifocality as independent determinants of requiring multiple sclerotherapy sessions.[19]

Extensive VMs frequently exhibit localized intravascular coagulopathy (LIC), characterized by elevated D-dimer and reduced fibrinogen due to chronic consumption coagulopathy.[7] LIC is associated with pain, edema, and an increased risk of thrombosis. Although LIC markers were not systematically evaluated in our cohort, negative correlations between regression and baseline lesion size may indirectly reflect LIC severity.

These findings support recommendations for peri-procedural hemostasis monitoring and compression therapy, as suggested by *Han Y. Y., et al.*[7]

Bleomycin and ethoxysclerol differ in biological effects: Bleomycin induces endothelial apoptosis, fibroblast activation, and collagen deposition, leading to durable fibrosis.[14] Ethoxysclerol (Polidocanol) acts through detergent-induced endothelial spasm and thrombosis, often causing less inflammation and offering superior cosmetic tolerance.[16,18,20]

These pharmacologic distinctions partly explain the slightly higher subjective improvement associated with bleomycin (EQ-VAS +13.2 vs. +7.5; p = 0.06), despite similar objective regression.

The safety profile observed in our study aligns with the literature: mild local pain, edema, and transient skin pigmentation were the most frequent events. No severe complications such as necrosis, deep vein thrombosis, or allergic reactions occurred.

The absence of pulmonary toxicity from bleomycin is consistent with data indicating that systemic accumulation is negligible with localized low-dose injections.[21-23] Ethoxysclerol also demonstrated excellent tolerability, particularly in foam form, which reduces drug volume without compromising efficacy.[20] Our overall complication rate (27.5%, all minor) is comparable to international figures (20–30%).[14,16,21]

The correlation between lesion regression and quality-of-life improvement (r = 0.62; p < 0.001) underscores the importance of including patient-reported outcomes in VM management, as recommended by *Berger S., et al.* [8]

Taken together, our findings indicate that: Bleomycin is preferable for smaller, deeper, slow-flow lesions where fibrosis is desired. Ethoxysclerol may be better suited for superficial and cosmetically sensitive regions. This echoes international guidelines emphasizing individualized sclerosant selection based on morphology, hemodynamics, and patient factors.[12,13]

Limitations. This study has several limitations.It was retrospective and conducted at a single center, which may limit the generalizability of results. The sample size (20 patients per group) was relatively small and did not allow detection of rare adverse events.The follow-up period was restricted to three months after the second treatment session, preventing evaluation of long-term durability and recurrence rates. Additionally, randomization and blinded imaging assessment were not implemented, introducing potential information bias. Molecular subtyping (TEK/PIK3CA), LIC markers, cost-effectiveness, and functional outcomes were not assessed, which limits the mechanistic depth of analysis.

What's known? Venous malformations are slow-flow vascular anomalies associated with TEK/TIE2 and PIK3CA mutations, characterized by chronic progression and a high recurrence tendency.Sclerotherapy is the first-line treatment, aiming to reduce lesion volume and improve quality of life. Bleomycin and ethoxysclerol are among the most widely used sclerosants, both showing high efficacy and a low risk of severe complications. Ethoxysclerol generally offers better cosmetic tolerance, whereas bleomycin provides a more durable response when appropriately dosed. Therapeutic outcomes depend on lesion size, localization, hemodynamic pattern, and the presence of LIC, necessitating an individualized treatment strategy.

What's new? For the first time in Central Asia, a direct head-to-head comparison of bleomycin and ethoxysclerol was performed at the A.N. Syzganov National Scientific Center of Surgery. The study demonstrated comparable objective efficacy (mean regression after two stages: 32.2% vs. 29.6%) and high safety (no severe complications). A trend toward greater improvement in EQ-VAS scores and a lower need for additional procedures was observed with bleomycin. Key predictors of treatment success were identified: baseline lesion volume < 35 cm^3 and BMI < 27 kg/m^2 increased the likelihood of ⩾ 50% regression, whereas volume > 40 cm^3 and multifocality elevated the risk of requiring a third stage. A multifactor predictive model was constructed (AUC ROC = 0.74), demonstrating satisfactory discriminative ability for clinical stratification. A direct correlation between lesion regression and quality-of-life improvement (ΔEQ-VAS, ΔEQ-5D-5L) was confirmed. This study provides the first regional dataset from Central Asia, encompassing 2,078 patients with vascular anomalies (including 40 VMs), thereby expanding global evidence on sclerotherapy outcomes and guiding optimization of agent selection in clinical practice.

Conclusion

Sclerotherapy of venous malformations using bleomycin and ethoxysclerol demonstrated comparable efficacy and a high level of safety. The mean lesion regression was 32.2% and 29.6%, respectively, accompanied by a significant improvement in quality of life, as measured by the EQ-5D-5L and EQ-VAS scales. Bleomycin showed a trend toward fewer required treatment sessions and a more pronounced subjective improvement in patient-reported outcomes. The therapeutic efficacy depended primarily on the baseline lesion volume and body mass index (BMI) rather than the choice of sclerosant.No serious adverse events were observed. Thus, both agents can be considered reliable and safe options for the treatment of venous malformations. Optimization of treatment strategy should be based on individual patient characteristics and lesion morphology, ensuring a personalized and evidence-based approach to therapy.

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