Effectiveness and Safety of Bleomycin Sclerotherapy in Pediatric Low-Flow Vascular Malformations: A Retrospective Cross-Sectional Study

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Abstract

Background:

Low-flow vascular malformations (LFVMs) are congenital vascular anomalies commonly managed using sclerotherapy. Among available sclerosant agents, bleomycin has demonstrated favorable therapeutic efficacy and safety profiles in pediatric vascular malformations, although treatment responses remain variable across different lesion types and morphologies.

Methods:

This retrospective cross-sectional study evaluated pediatric patients with LFVMs who underwent bleomycin sclerotherapy at Dharmais Cancer Hospital between January 2019 and May 2025. Demographic characteristics, lesion profiles, treatment sessions, cumulative bleomycin doses, therapeutic outcomes, and treatment-related adverse events were analyzed. Therapeutic responses were categorized into Grade 0-3 outcomes.

Result:

A total of 41 pediatric patients with LFVMs were included in the study. Patients aged 0-5 years represented the largest age group (51.2%), while the head and neck region was the most common lesion location (41.4%). Venolymphatic malformations (51.2%) and microcystic lesions (65.8%) were the predominant lesion subtypes. Grade 2 clinical response was the most frequently observed therapeutic outcome (58.5%), whereas Grade 3 response was identified in 17.1% of patients. The mean number of treatment sessions was 5.80 +/- 2.42. Treatment-related adverse events were minimal, with pain and edema observed in one patient each (2.4%), and no cases of pulmonary injury or major systemic complications identified. No significant association was found between treatment sessions or cumulative bleomycin dose and therapeutic outcomes ($p>0.05$).

Conclusions:

Bleomycin sclerotherapy demonstrated favorable effectiveness and safety profiles in pediatric patients with LFVMs. Therapeutic outcomes appeared to be influenced more strongly by lesion characteristics than by treatment intensity or cumulative bleomycin dose.

Introduction

Low-flow vascular malformations (LFVMs) are congenital vascular anomalies that include venous malformations, lymphatic malformations, and combined lymphatico-venous lesions.

According to the classification proposed by the International Society for the Study of Vascular Anomalies, these lesions are categorized as slow-flow vascular malformations and are associated with abnormalities in vascular development during embryogenesis. Lymphatic malformations are among the most common vascular anomalies in the pediatric population, with an estimated incidence ranging from 1 in 200 to 1 in 4,000 live births.[17,22]

Clinical manifestations of LFVMs vary according to lesion subtype, anatomical location, and lesion extent. Lesions involving the head and neck region may cause airway obstruction, dysphagia, recurrent infection, hemorrhage, and cosmetic deformity, resulting in substantial morbidity among pediatric patients.[12,16] Management strategies include surgical excision, sclerotherapy, systemic therapy, and combined interventions. Among these modalities, sclerotherapy has become one of the preferred treatment approaches because of its minimally invasive nature and favorable clinical outcomes, particularly in macrocystic lesions.[17]

Bleomycin is one of the most widely used sclerosant agents for LFVMs. Previous studies demonstrated favorable therapeutic responses and acceptable safety profiles following intralesional bleomycin administration in pediatric vascular malformations.[4,17,18] However, treatment responses remain variable, and the number of procedures required differs among patients. Therefore, this study aimed to evaluate the effectiveness and safety of bleomycin sclerotherapy in pediatric patients with low-flow vascular malformations and to assess the association between therapeutic factors and treatment outcomes.

Material And Methods

Study design and population

This retrospective cross-sectional study was conducted at Dharmais Cancer Hospital. Medical records of pediatric patients diagnosed with low-flow vascular malformations who underwent bleomycin sclerotherapy between January 2019 and May 2025 were reviewed. The study aimed to evaluate the effectiveness and safety profile of bleomycin-based sclerotherapy and to assess the association between cumulative bleomycin dose, number of sclerotherapy sessions, and therapeutic outcomes. Ethical approval for the study was obtained from the institutional ethics committee prior to data collection.

Patients were included if they fulfilled the following criteria: diagnosis of slow-flow vascular malformations based on ultrasonography or magnetic resonance imaging findings; age ≤ 18 years at the time of the first bleomycin sclerotherapy session; underwent bleomycin sclerotherapy as part of treatment; and availability of complete medical records containing lesion characteristics, treatment details, and therapeutic outcomes. Patients were excluded if they had high-flow vascular malformations, including arteriovenous malformations or arteriovenous fistulas, age >18 years, absence of bleomycin sclerotherapy during the treatment period, or incomplete medical records required for analysis. Participants with insufficient or contradictory data were also excluded from the study.

Data collection and outcome assessment

Data collection was performed retrospectively through review of electronic medical records using a standardized data extraction form. Demographic variables included age and sex. Lesion characteristics included anatomical location, lesion depth, lesion subtype, and cystic morphology based on clinical and radiological evaluation.

Therapeutic variables included the total number of sclerotherapy sessions and cumulative bleomycin dose administered throughout the treatment period. Therapeutic outcomes were evaluated based on documented clinical and radiological follow-up findings and classified into Grade 0, Grade 1, Grade 2, and Grade 3 responses. Treatment-related

adverse events, including pain, edema, erythema, hyperpigmentation, fever, and pulmonary injury, were also recorded from post-procedural monitoring documentation.

Statistical analysis

Descriptive analyses were performed to evaluate demographic characteristics, lesion characteristics, therapeutic outcomes, and treatment-related adverse events among pediatric patients with low-flow vascular malformations who underwent bleomycin sclerotherapy. Numerical variables were presented as mean +/- standard deviation, whereas categorical variables were expressed as frequencies and percentages. Comparative analyses were conducted to assess differences in the number of sclerotherapy sessions and cumulative bleomycin dose according to therapeutic outcome categories. Statistical significance was defined as a p-value <0.05.

Result

Patient characteristics

A total of 63 patients with vascular malformations were initially identified during the study period. Among them, 19 patients with high-flow vascular malformations and one patient aged above 18 years were excluded. The remaining 41 patients with slow-flow vascular malformations fulfilled the inclusion criteria and were included in the final analysis.

Among the 41 included patients, radiological evaluation was available in 22 patients, clinical evaluation in 16 patients, while three patients could not be evaluated. Demographic characteristics, lesion characteristics, treatment outcomes, safety profiles, and the association between treatment cycles and therapeutic outcomes were analyzed.

Table 1. Demographic and clinical characteristics of patients with slow-flow vascular malformations (n = 41)

Variables	Category	n (%)
Age distribution	0-5 years	21 (51.2)
	6-10 years	10 (24.4)
	11-15 years	5 (12.2)
	16-18 years	5 (12.2)
Gender	Male	24 (58.5)
	Female	17 (41.5)
Anatomical location	Head and neck	17 (41.4)
	Extremities	15 (36.5)
	Trunk	3 (7.3)
	Genital region	2 (4.8)
	Multisite (>=2 regions)	4 (9.7)
Lesion depth	Deep	16 (39.0)
	Superficial	25 (61.0)
Lesion subtype	Lymphatic malformation	14 (34.1)
	Venolymphatic malformation	21 (51.2)
	Venous malformation	6 (14.6)
Cystic morphology	Macrocystic	7 (17.1)
	Microcystic	27 (65.8)
	Mixed	7 (17.1)

Variables	Category	n (%)
Clinical outcome	Grade 0	6 (14.6)
	Grade 1	1 (2.4)
	Grade 2	24 (58.5)
	Grade 3	7 (17.1)
	Non-evaluable	3 (7.3)

The age distribution showed that patients aged 0-5 years represented the largest group (51.2%), followed by patients aged 6-10 years (24.4%). Patients aged 11-15 years and 16-18 years each accounted for 12.2% of cases. Male patients were more frequently affected than female patients (58.5% vs. 41.5%). The anatomical distribution of lesions demonstrated that the head and neck region was the most common site (41.4%), followed by the extremities (36.5%). Trunk involvement was observed in 7.3% of patients, genital involvement in 4.8%, and multisite involvement (>=2 anatomical regions) in 9.7%.

Regarding lesion depth, superficial lesions were more common than deep lesions (61.0% vs. 39.0%). Venolymphatic malformations represented the most common lesion subtype (51.2%), followed by lymphatic malformations (34.1%) and venous malformations (14.6%). According to cystic morphology, microcystic lesions predominated (65.8%), whereas macrocystic and mixed lesions each accounted for 17.1%. Clinical outcome assessment demonstrated that Grade 2 response was the most frequently observed outcome (58.5%), followed by Grade 3 response (17.1%) and Grade 0 response (14.6%). Grade 1 response was identified in one patient (2.4%), while three patients (7.3%) could not be evaluated.

Treatment characteristics

The mean number of treatment sessions among the 41 patients was 5.80 +/- 2.42 sessions. Six treatment sessions represented the most frequently administered number of procedures (24.3%), followed by five sessions (22.0%) and two sessions (12.2%). Only one patient underwent a single treatment session.

Table 2. Treatment characteristics with slow-flow vascular malformations (n = 41)

Variables	Category	n (%)
Number of treatment sessions	1 session	1 (2.4)
	2 sessions	5 (12.2)
	3 sessions	0 (0)
	4 sessions	3 (7.3)
	5 sessions	9 (22.0)
	6 sessions	10 (24.3)
	7 sessions	4 (9.7)
	8 sessions	3 (7.3)
	9 sessions	3 (7.3)
	10 sessions	2 (4.8)
	11 sessions	0 (0)
	12 sessions	1 (2.4)
Mean number of sessions	Mean +/- SD	5.80 +/- 2.42

Treatment-related adverse events

Most patients did not experience treatment-related adverse events. Pain and edema were observed in one patient each (2.4%). No cases of erythema, hyperpigmentation, fever, or pulmonary injury were identified during the study period.

Table 3. Treatment-related adverse events (n = 41)

Variables	Present n (%)	Absent n (%)
Pain	1 (2.4)	40 (97.6)
Edema	1 (2.4)	40 (97.6)
Erythema	0 (0)	41 (100)
Hyperpigmentation	0 (0)	41 (100)
Fever	0 (0)	41 (100)
Pulmonary injury	0 (0)	41 (100)

Association between treatment characteristics and therapeutic outcomes

A total of 38 patients were included in the analysis evaluating the association between treatment characteristics and therapeutic outcomes.

Table 4. Comparison of treatment characteristics according to therapeutic outcomes (n = 38)

Variables	Grade 0-1	Grade 2	Grade 3	p-value
Treatment sessions, mean +/- SD	6.86 +/- 3.20	6.04 +/- 4.76	5.71 +/- 3.20	0.532
Bleomycin dose, mean +/- SD	172.43 +/- 248.44	124.21 +/- 369.54	109.29 +/- 248.44	0.724

The mean number of treatment sessions was 6.86 +/- 3.20 in patients with Grade 0-1 outcomes, 6.04 +/- 4.76 in patients with Grade 2 outcomes, and 5.71 +/- 3.20 in patients with Grade 3 outcomes. No statistically significant difference was observed among outcome groups (p=0.532). Similarly, the mean cumulative bleomycin dose did not significantly differ across outcome groups. Mean bleomycin doses were 172.43 +/- 248.44, 124.21 +/- 369.54, and 109.29 +/- 248.44 in Grade 0-1, Grade 2, and Grade 3 outcomes, respectively (p=0.724). No statistically significant association was identified between the number of treatment sessions or cumulative bleomycin dose and therapeutic outcomes (p>0.05).

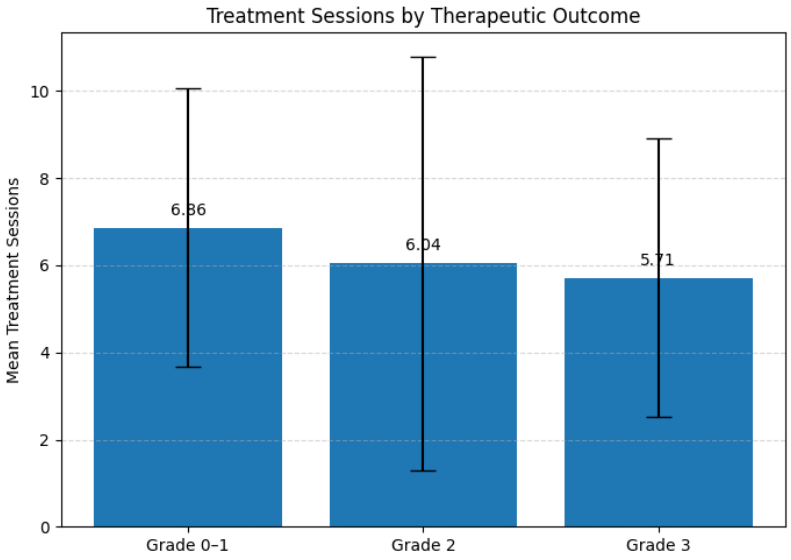

Figure 1. Treatment sessions by Therapeutic Outcome

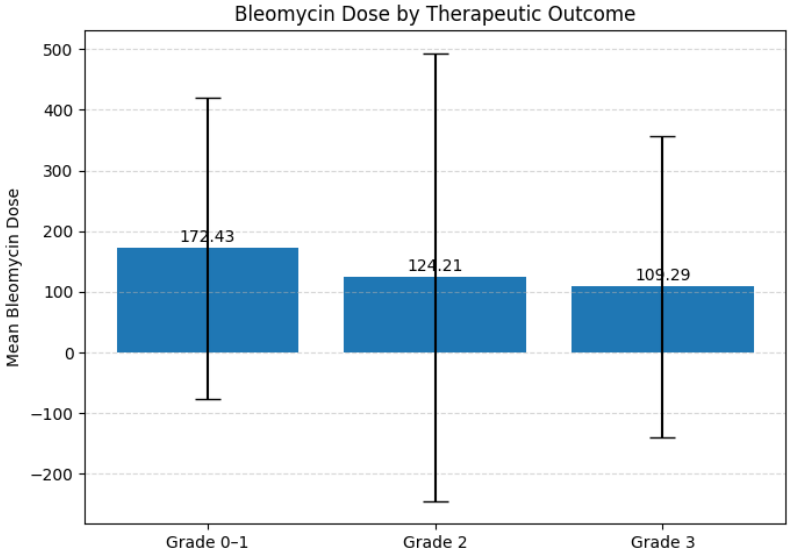

Figure 2. Bleomycin Dose by Therapeutic Outcome

Discussion

The present study shows pediatric patients with low-flow vascular malformations undergoing bleomycin sclerotherapy were predominantly within the 0-5-year age group. This finding is consistent with previous reports describing that vascular malformations are commonly identified during early childhood, particularly after lesions become clinically apparent or produce functional symptoms.[16] Lesions were predominantly located in the head and neck region, which is in agreement with previous studies reporting this anatomical region as the most frequent site of involvement in pediatric vascular malformations.[12,18] Venolymphatic malformations and microcystic lesions represented the predominant lesion characteristics in the present cohort. Similar lesion distributions have been described in previous studies, particularly in lesions with infiltrative morphology and complex anatomical extension.[17,22]

Most patients in the study achieved Grade 2 clinical responses, whereas complete responses were identified in a smaller proportion of patients. The mean number of treatment sessions was approximately five to six procedures, indicating that repeated sclerotherapy sessions were commonly required to achieve satisfactory lesion control. Previous studies similarly demonstrated that staged or repeated interventions are frequently necessary in the management of low-flow vascular malformations because complete lesion regression may not occur after a limited number of procedures.[5,18] The heterogeneous therapeutic responses observed in vascular malformations have been associated with lesion morphology, cystic architecture, and the intralesional distribution of sclerosant agents.[17,22]

The safety profile observed in the present study was favorable, with only minor local adverse events identified, including pain and edema. No cases of pulmonary injury or major systemic complications were observed throughout the treatment period. Similar findings were reported by Finitsis et al. and Schmidt et al., who described low incidences of major complications following intralesional bleomycin administration.[4,18] These findings support the relatively safe profile of bleomycin-based sclerotherapy in pediatric low-flow vascular malformations, particularly when administered using controlled cumulative doses.

Compared with other sclerosant agents, bleomycin demonstrated a comparatively favorable safety profile. Doxycycline has similarly been associated predominantly with local inflammatory reactions, including pain, edema, and swelling, with relatively low rates of systemic complications.[6,13,19] OK-432 also demonstrated acceptable safety profiles, mainly consisting of transient inflammatory reactions without major tissue injury.[17,20] In contrast, ethanol has been associated with substantially higher complication rates, including tissue necrosis, nerve injury, pulmonary thrombosis, and cardiovascular complications related to systemic absorption.[8,14] Previous studies also reported temporary nerve palsy and severe postprocedural swelling following ethanol sclerotherapy.[10,21] Systemic therapies such as sirolimus demonstrated different adverse-event profiles, including mucositis, hyperlipidemia, and bone marrow suppression requiring long-term monitoring.[9,11]

No statistically significant association was identified between the number of sclerotherapy sessions and therapeutic outcomes in the present study. Similar observations were reported by Horbach et al., who stated that repeated interventions are frequently required during the course of vascular malformation treatment; however, increasing numbers of procedures do not necessarily correlate linearly with clinical improvement.[7] Ahmad further suggested that lesion-related factors, including lesion subtype, anatomical location, and morphological complexity, may have greater influence on therapeutic response than procedural frequency alone.[1] The variability in therapeutic response observed in the present study may therefore reflect differences in lesion structure and intralesional sclerosant distribution rather than treatment intensity itself.[17,22]

Similarly, cumulative bleomycin dose was not significantly associated with therapeutic outcomes. This finding suggests that higher cumulative doses do not necessarily produce superior clinical responses. Wang et al. reported that the effectiveness of bleomycin therapy is influenced not only by cumulative dose but also by lesion morphology, cystic architecture, and the ability of the sclerosant agent to adequately penetrate the target lesion.[22] Dave et al. also noted that dose escalation does not consistently improve therapeutic efficacy and should be balanced against potential systemic toxicity.[3] Previous reports demonstrated substantial variability in therapeutic responses among pediatric patients with low-flow vascular malformations, indicating that lesion characteristics may play a greater role than cumulative dose alone in determining treatment outcomes.[17]

Consideration of cumulative dose nevertheless remains important because excessive systemic exposure may increase the risk of pulmonary toxicity and other systemic adverse events.[2]

Conclusion

Bleomycin sclerotherapy demonstrated favorable effectiveness and safety profiles in pediatric patients with low-flow vascular malformations. Most patients achieved moderate clinical improvement following repeated treatment sessions, whereas complete responses were observed in a smaller proportion of cases. Treatment-related adverse events were limited predominantly to minor local reactions, without major systemic complications or pulmonary injury. Neither cumulative bleomycin dose nor the number of sclerotherapy sessions demonstrated significant associations with therapeutic outcomes, suggesting that lesion characteristics may play a greater role in determining treatment response. Further prospective studies with larger sample sizes and standardized radiological follow-up are necessary to better define prognostic factors and optimize treatment protocols in pediatric low-flow vascular malformations.

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