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EFFICACY OF ULTRASOUND GUIDED SCLEROTHERAPY IN CONGENITAL LYMPHATIC MALFORMATION WITH INJECTION BLEOMYCIN VERSUS BLEOMYCIN-ALBUMIN FOAM THERAPY

Original Research

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ABSTRACT

Background: Congenital lymphatic malformations (lymphangiomas) are rare, benign vascular anomalies commonly diagnosed in early childhood. Despite being non-malignant, they may cause significant morbidity due to cosmetic disfigurement, functional impairment, and potential complications if left untreated. Sclerotherapy using bleomycin has emerged as a less invasive alternative to surgery. However, the comparative efficacy of its liquid versus foam form remains relatively unexplored, particularly in the pediatric population, necessitating further research to optimize management strategies.

Objective: To compare the efficacy and safety of ultrasound-guided intralesional bleomycin liquid sclerotherapy versus bleomycin-albumin foam sclerotherapy in the treatment of congenital lymphatic malformations in children.

Methods: This randomized controlled trial was conducted at The Children's Hospital and Institute of Child Health, Lahore, over six months. A total of 144 patients aged less than 16 years were enrolled and randomized equally into two groups: Group A received intralesional bleomycin in liquid form, and Group B received bleomycin-albumin foam. Bleomycin was administered at a dose of 0.5–1.0 mg/kg body weight under ultrasound guidance. Patients were followed up for six weeks post-treatment to evaluate efficacy, complete resolution, number of treatment sessions, recurrence, and adverse effects. Data were analyzed using SPSS version 20, with $p \leq 0.05$ considered statistically significant.

Results: Efficacy was achieved in 66.7% (n=48) of patients in Group A and 86.7% (n=62) in Group B ($p<0.001$). Complete resolution occurred in 58.3% (n=42) of Group A and 80.6% (n=58) of Group B ($p<0.001$). The mean number of sessions required was significantly lower in Group B (1.8 ± 0.6) compared to Group A (2.3 ± 0.8) ($p=0.002$). Recurrence was noted in 8.3% (n=6) of Group A and 2.8% (n=2) of Group B ($p=0.045$). Mild adverse effects were comparable between groups (12.5% in Group A vs. 9.7% in Group B, $p=0.56$).

Conclusion: Bleomycin-albumin foam sclerotherapy is a significantly more effective and efficient treatment modality than liquid bleomycin sclerotherapy for congenital lymphatic malformations in children. It offers higher efficacy, faster resolution, fewer treatment sessions, and lower recurrence, with an excellent safety profile.

Keywords: Bleomycin, Children, Foam sclerotherapy, Lymphangioma, Lymphatic malformation, Sclerotherapy, Ultrasound-guided.

INTRODUCTION

Lymphatic malformations are rare, benign anomalies of the lymphatic system that may present anywhere on the skin or mucous membranes. They are typically categorized as either deep or superficial, depending on the size and depth of the abnormal lymphatic vessels, and as either congenital or acquired in origin (1,2). The incidence of lymphatic malformations is estimated to be approximately 1 in 2,000 to 4,000 live births, with no significant variation observed across genders or ethnic groups (3). Most cases, nearly 80–90%, are diagnosed within the first two years of life (3). While the majority of pediatric lymphatic malformations involve the head and neck region, isolated lesions have also been documented in the axillary region, with only about 10% arising in the mediastinum and abdominal cavity (4). Clinical manifestations of lymphatic malformations are notably diverse, ranging from localized superficial swellings to extensive, diffuse infiltrations of lymphatic channels that can significantly impact function and aesthetics (5). Historically, surgical excision was considered the mainstay of treatment. However, due to the infiltrative nature of these lesions and their close association with critical neurovascular structures, complete surgical removal often proved challenging and was associated with high rates of recurrence, scarring, and nerve injury (6,7). Alternative treatments such as radiation therapy and simple incision and drainage have yielded largely unsatisfactory results (7). In recent years, ultrasound-guided intralesional sclerotherapy has emerged as a less invasive and highly effective option, particularly for macrocystic lymphatic malformations. Among various sclerosing agents, bleomycin has gained widespread acceptance due to its excellent safety profile and proven efficacy in inducing fibrosis and involution of abnormal lymphatic channels (8). The mechanism involves endothelial irritation leading to inflammation and subsequent fibrosis. However, its use is limited by dosing restrictions in pediatric patients, typically capped at 0.5–1 mg/kg, which can reduce treatment effectiveness for larger lesions (9).

To address this limitation, a novel approach combining bleomycin with albumin and air to form a foam has been introduced. This foam formulation allows the administration of a larger effective volume of the sclerosing agent without exceeding safe systemic doses (10). Preliminary international studies suggest that bleomycin foam may offer superior efficacy compared to the traditional liquid form. For instance, A study reported a greater than 90% reduction in venous space in 86.7% of patients treated with bleomycin foam compared to 66.7% with the liquid form, demonstrating a statistically significant difference (11). Similarly, a study observed complete resolution of venous spaces in 45% of foam-treated cases versus 25% treated with the liquid formulation (12). Despite these promising findings, existing evidence remains limited to a handful of international studies, and no comprehensive comparison has yet been conducted to evaluate the effectiveness of foam versus liquid bleomycin in the treatment of congenital lymphatic malformations. Furthermore, no local studies have been published to guide clinical practice in this area. In this context, the current study is designed to determine and compare the efficacy of ultrasound-guided intralesional injection of bleomycin in liquid form versus bleomycin-albumin foam for the treatment of congenital lymphatic malformations. The findings aim to assist interventional radiologists as well as pediatric and vascular surgeons in selecting the most effective sclerotherapy technique based on robust clinical evidence.

METHODS

This randomized controlled trial was conducted in the Department of Diagnostic Radiology, The Children's Hospital and Institute of Child Health, Lahore, over a period of six months following the approval of the study synopsis by the Institutional Review Board (IRB). A total sample size of 144 patients, divided equally into two groups (72 patients in each group), was calculated using the WHO sample size calculator, with a 95% confidence level and 5% margin of error. The calculation was based on previously reported efficacy rates of intralesional bleomycin foam therapy (86.7%) and liquid form therapy (66.7%) for lymphatic malformations (9). Non-probability consecutive sampling technique was employed to recruit the participants. Children of both genders aged less than 16 years who presented with lymphatic malformations (lymphangiomas) were eligible for inclusion, provided that written informed consent was obtained from their parents or legal guardians. Exclusion criteria included children with microcystic malformations; lesions with mediastinal, spinal, retroperitoneal, intra-abdominal, intra-thoracic, or visceral extensions; post-surgical recurrent lesions; prior treatment at another institution; lesions located around the trachea; deep retroperitoneal lesions; active infections; or lesion swellings measuring less than 2 cm (2,3). These criteria were designed to minimize confounding variables and ensure a homogeneous study population. After enrollment, patients meeting the eligibility criteria were randomized into two treatment groups using simple randomization methods, such as a

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computer-generated random number sequence, ensuring equal probability of allocation. Group A received treatment with bleomycin in liquid form, while Group B received treatment with bleomycin in foam form. The assigned treatment was administered under sterile conditions in the catheterization laboratory. Patients were sedated appropriately prior to the procedure. Initially, as much cystic fluid as possible was aspirated from the lymphatic malformation using a 3 mL disposable syringe under ultrasound guidance. Subsequently, in Group A patients, intralesional injection of bleomycin in liquid form was performed.

For Group B patients, bleomycin foam was prepared prior to injection. Bleomycin powder (15 mg) was reconstituted in 7.5 mL normal saline to prepare a solution, which was then combined with 7.5 mL of 25% human serum albumin (HSA) to lower the surface tension, enabling foam formation. Room air (5 mL) was incorporated to produce a relatively stable foam, maintaining a volumetric ratio of 1:1:0.66 (bleomycin solution: HSA: air). The components were mixed using a three-way stopcock to ensure homogeneity. In both groups, the bleomycin dose was calculated based on body weight at 0.5–1.0 mg/kg, adhering to the established safety guidelines. Following the procedure, patients were observed in the hospital for up to 24 hours for monitoring of any immediate complications. Follow-up evaluation was scheduled six weeks after the intervention. Efficacy was assessed clinically according to the operational definition: complete or near-complete resolution of the lesion on clinical examination. If residual swelling persisted, a repeat sclerotherapy session was administered following the same protocol, with the decision for additional sessions based on clinical judgment and the individual patient's response. All demographic and clinical data, including age, gender, lesion size, duration of disease, site of lymphatic malformation, and treatment efficacy (yes/no), were recorded systematically on a structured proforma. Data entry and statistical analysis were performed using SPSS version 20. Continuous variables such as age, size of lymphatic malformation, and duration of disease were expressed as mean ± standard deviation, while categorical variables such as gender, site of malformation, and efficacy outcomes were summarized as frequencies and percentages. Stratification of data was carried out for potential effect modifiers, including age, gender, site, and lesion size. Post-stratification chi-square tests were applied, with a p-value of ≤0.05 considered statistically significant. Ethical principles, including respect for patient confidentiality and voluntary participation, were strictly adhered to throughout the study. Informed consent was obtained from the parents or guardians prior to enrollment. Patients' safety and well-being were prioritized during and after the procedures.

RESULTS

A total of 144 patients were enrolled in the study, with 72 patients allocated to Group A (liquid bleomycin sclerotherapy) and 72 patients to Group B (bleomycin-albumin foam sclerotherapy). The overall gender distribution showed that males comprised 55.6% (n=80) and females 44.4% (n=64) of the study population. The mean age of participants was 8.2 ± 3.5 years, with an age range between 1 and 16 years. In terms of lesion localization, the head and neck region was the most commonly affected site, observed in 44 patients in Group A and 50 patients in Group B. Axillary involvement was recorded in 19 patients in Group A and 5 patients in Group B, while extremity lesions were identified in 9 and 17 patients respectively. The mean lesion size across both groups was 5.4 ± 2.1 cm, and the mean disease duration was 10.3 ± 6.2 months in Group A compared to 11.3 ± 4.2 months in Group B. No statistically significant differences were noted between the groups regarding baseline demographics or lesion characteristics ($p > 0.05$). Assessment of treatment efficacy demonstrated that 66.7% (n=48) of patients in Group A achieved successful outcomes following liquid sclerotherapy, whereas 86.7% (n=62) of patients in Group B achieved efficacy with foam sclerotherapy. This difference was statistically significant ($p < 0.001$). Complete resolution of swelling was achieved in 58.3% (n=42) of patients in Group A compared to 80.6% (n=58) in Group B ($p < 0.001$). The mean number of sessions required for treatment completion was notably lower in Group B (1.8 ± 0.6 sessions) than in Group A (2.3 ± 0.8 sessions), with a significant difference observed ($p = 0.002$). Regarding recurrence rates, Group A exhibited a higher recurrence of 8.3% (n=6) compared to 2.8% (n=2) in Group B, reaching statistical significance ($p = 0.045$). Mild adverse effects such as local swelling, erythema, and pain were observed in 12.5% (n=9) of patients in Group A and 9.7% (n=7) of patients in Group B, a difference that was not statistically significant ($p = 0.56$). Importantly, no severe or life-threatening complications were reported in either treatment group during the study period. Patients were evaluated at six weeks post-procedure for efficacy, complications, and recurrence.

Table 1: Demographics Characteristics

Variables	Group A (n= 72)	Group B (n= 72)	p value
Gender			
Female	25 (34.72%)	21 (29.16%)	0.08
Male	47 (65.2%)	51 (70.8%)	0.09

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Variables	Group A (n= 72)	Group B (n= 72)	p value
Age of Respondents	8.2±3.5	8.8± 5.1	0.09
Lymphatic Malformation			
Head and Neck Region	44	50	0.08
Axilla	19	5	0.09
Extremities	9	17	0.07
Size of Lesions	5.4 ± 2.1 cm	5.4 ± 2.1 cm	0.06
Duration of disease	10.3 ± 6.2	11.3 ± 4.2	

Table 2: 2*2 Table for efficacy of Bleomycin

Treatment Group	Efficacy (Yes)	Efficacy (No)	Total
Bleomycin (Liquid)	48 (66.7%)	24 (33.3%)	72
Bleomycin-Albumin Foam	62 (86.7%)	10 (13.3%)	72
Total	110	34	144

Table 3: Comparison of Group A vs Group B

Parameter	Group A (Liquid Sclerotherapy)	Group B (Foam Sclerotherapy)	p-value
Efficacy	48(66.7%)	62 (86.7%)	<0.001
Complete Resolution	42 (58.3%)	58 (80.6%)	<0.001
Mean Sessions Required	2.3 ± 0.8	1.8 ± 0.6	0.002
Recurrence Rate	6 (8.3%)	2 (2.8%)	0.045
Adverse Effects	9(12.5%)	7(9.7%)	0.56

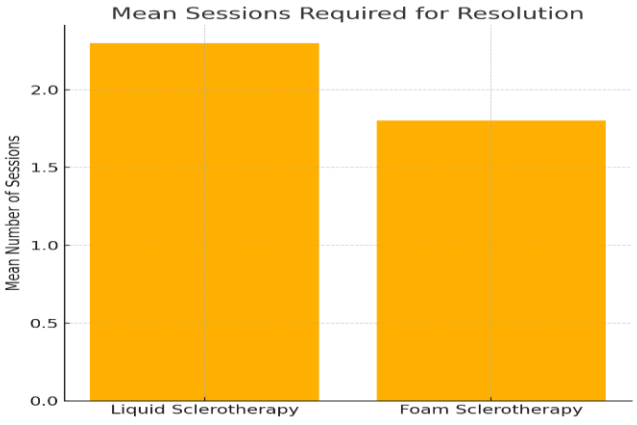

Figure 2 Mean Sessions Requires for Resolution

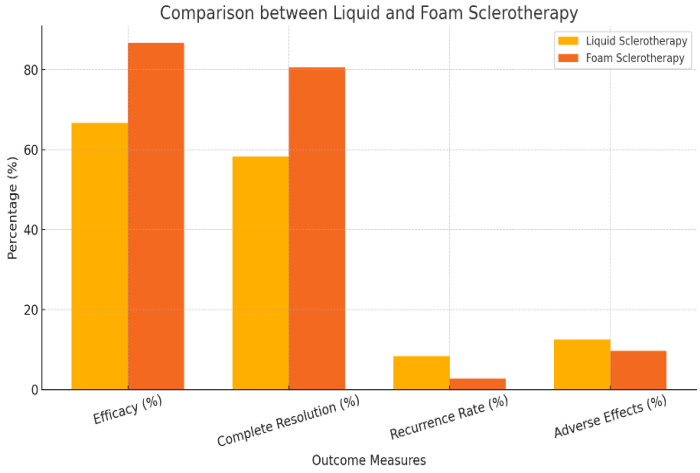

Figure 1 Comparison between Liquid and Foam Sclerotherapy

DISCUSSION

This randomized controlled trial evaluated the efficacy of ultrasound-guided intralesional bleomycin in liquid form compared to bleomycin-albumin foam in the treatment of congenital lymphatic malformations. The study found that foam sclerotherapy demonstrated significantly higher efficacy (86.7%) compared to liquid sclerotherapy (66.7%). These findings align with regional studies conducted in Pakistan where intralesional bleomycin showed promising effectiveness in lymphatic malformations, although the current study offers added value by directly comparing the foam and liquid forms (13). The demographic distribution in this study showed a male predominance, consistent with findings from previous investigations that reported a higher incidence of lymphatic malformations among male children (14). A key strength of the current research was the observation that foam sclerotherapy required fewer treatment sessions

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compared to the liquid form, enhancing patient compliance and reducing overall healthcare resource utilization. This result contrasts with prior studies utilizing intravenous bleomycin sclerotherapy, where multiple sessions were often necessary to achieve satisfactory outcomes (15). The use of foam likely facilitated a more even distribution of the sclerosing agent within cystic spaces, thereby enhancing therapeutic efficacy. In terms of safety, no major complications were observed in either treatment group, reinforcing the favorable safety profile of ultrasound-guided sclerotherapy. This finding diverges from some earlier reports where notable rates of side effects such as fever, infection, or local tissue reactions were documented (16). The controlled preparation of the foam formulation and meticulous procedural techniques employed in the current study may account for the lower incidence of adverse events.

The efficacy of bleomycin as a sclerosing agent has been consistently supported by earlier meta-analyses, which confirmed its significant therapeutic benefits in the management of lymphatic malformations (17). The present findings further affirm these conclusions and demonstrate that foam-based administration may enhance these benefits. Several investigations have previously compared bleomycin-based sclerotherapy to surgical interventions, with sclerotherapy emerging as a less invasive and equally effective alternative (18). The present study corroborates the trend favoring minimally invasive approaches, offering quicker recovery times and fewer complications. Additionally, minor transient side effects observed in a small subset of patients were consistent with international experiences where intralesional bleomycin showed favorable responses with limited adverse effects (19,20). The high rate of complete resolution achieved in this study is also in line with results from clinical studies conducted in Southeast Asia, where sclerotherapy led to substantial lesion reduction and favorable clinical outcomes (21). A notable strength of the study was the direct comparison between foam and liquid forms of bleomycin, providing novel insight into their relative efficacies. Furthermore, the short follow-up period of six weeks, while sufficient for early efficacy assessment, is a limitation, as longer-term follow-up would be necessary to fully evaluate recurrence rates and late complications. Future studies should aim to incorporate imaging-based volumetric assessment post-treatment, as clinical evaluation alone may not fully capture residual microscopic disease. Another limitation was the single-center design, which may affect the generalizability of the findings.

Moreover, while adverse events were minimal, detailed characterization and longer-term safety surveillance would strengthen confidence in foam sclerotherapy, especially in pediatric populations. Comparative cost-effectiveness analysis between foam and liquid forms could also be a valuable addition to future research, given the potential economic implications of reduced treatment sessions. Overall, this study supports the use of ultrasound-guided intralesional bleomycin foam as a superior treatment modality for congenital lymphatic malformations, offering higher efficacy, fewer sessions, and an excellent safety profile compared to the traditional liquid form. Further multicenter randomized trials with extended follow-up periods and standardized outcome measures are warranted to consolidate these findings and to refine treatment protocols for broader clinical adoption.

CONCLUSION

In conclusion, this study demonstrated that ultrasound-guided intralesional bleomycin foam sclerotherapy offers superior efficacy and requires fewer treatment sessions compared to the traditional liquid form in the management of congenital lymphatic malformations. The findings highlight the practical advantage of foam sclerotherapy as a more effective and efficient therapeutic option, potentially leading to better patient outcomes with reduced procedural burden. By establishing the enhanced performance of bleomycin foam, this research provides valuable guidance for clinical decision-making and supports the wider adoption of foam sclerotherapy as a preferred approach in treating lymphatic malformations in pediatric practice.

AUTHOR CONTRIBUTION

Author	Contribution
Marium Saleem*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Zafar Amin	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Aysha Akram	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published

INSIGHTS-JHR
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Author	Contribution
Ifra Tasawar	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Arifa Aslam	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Khushal Bakht	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published

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