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Assessment of Combined Surgical Excision with Local Bleomycin Injection in the Management of Congenital Vascular Lesions

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Abstract

Background: Vascular malformations may cause significant deformity and dysfunction and are difficult to control because of their tendency to expand. The aim of this research was to evaluate the effectiveness of intralesional injection of bleomycin as a sclerosing agent in conjunction with surgical excision of vascular lesions for the therapy of vascular lesions. **Methods:** This study was an interventional one arm trial conducted on 18 patients with vascular malformation. The lesion was grossly removed surgically, without sacrificing any important structure, bleomycin was used to be injected intralesional with injection in parts adherent to vital structure. Dilution of bleomycin and amount are tailored to each patient according to size of the lesion and total body weight. **Results:** the median age of the studied patients was 3.5 years. Nine cases (50%) were females, and nine cases (50%) were males. 14 cases had vascular anomalies in the head and neck (77.8%) while 2 cases had vascular anomalies in the back (11.1%), one

case (5.6%) had vascular anomaly in the chest wall and one case was occupying abdomen and lumbar region and extending to the groin (5.6%). most of the cases were cystic hygroma 14 cases (77.8%), two cases were venous malformation (11.1%) and two cases were hemangiomas (11.1%). No cases acquired nerve injury, visceral injury, vascular injury, solid organ injury or mortality as intraoperative complications. intraoperative bleeding in (one case) and respiratory affection in (one case). Postoperatively, the most prevalent complication was edema (nine cases), partial recurrence (six cases), unsightly scar (three cases) and transient nerve affection (two cases). 11 cases (61.1%) had good response at 1st attack, while six cases (33.3%) had satisfactory response and one case (5.6%) had poor response. 15 cases (83.3%) needed single injection with excision of the lesion intraoperative, two cases (11.1%) needed 2 injections. One intraoperative and the second time percutaneously under sedation. One case (5.6%) had venous malformation and needed 7 injections of bleomycin, one injection intraoperative and six injections thereafter. 14 parents (77.8%) were completely satisfied, 3 parents (16.7%) were moderately satisfied, and one parent was unsatisfied (5.6%). **Conclusion:** Surgical excision combined with intralesional injection of Bleomycin as a sclerosing agent is effective as a primary strategy in management of vascular malformation with better aesthetic outcomes as demonstrated by parents' and surgeons' satisfaction associated with low recurrence rates and manageable complications.

1. Introduction:

Up to 10% of neonates are affected with vascular abnormalities, which are soft tissue lesions caused by congenitally abnormal blood vessel growth **[1].** Vascular abnormalities, formerly known as vascular birthmarks or angiomas, are now classified into two primary groups: vascular malformations and vascular malignancies. The bulk of vascular abnormalities in infants are hemangiomas, which are thought to be the most common kind of vascular tumor made up of endothelial cells that proliferate quickly **[2].**

The epidemiology of congenital vascular abnormalities has not received much attention (CVM). In research including 3,573 3-year-old children, we discovered 43 instances of CVM or symptoms associated with it, representing a 1.2% incidence. There were 16 cases (37 percent) with infiltrating or localized venous and/or arteriovenous (AV) defects, 15 cases (35 percent) with port wine stain, 5 cases (12 percent) with lymphedema and lymphatic defects, 5 cases (12 percent) with phlebectasia with nevus and limb length discrepancy, and 2 cases with phlebectasia (4 percent) **[3].** Other uncommon vascular tumors include tufted angiomas, pyogenic granulomas, congenital hemangiomas, and other hemangioendotheliomas; the afflicted cell type may vary in these cases. Hemangiomas and other vascular tumors have inadequate blood vessel construction and hyperplastic cells around them. Vascular malformations, on the other hand, are not characterized by hyperplastic cells; rather, they are made up of increasingly larger aberrant and ectatic vessels that have a specific vascular architecture, such as arteries, capillaries, lymphatic vessels, veins, or mixed vessel types **[4].**

According to the primary vessel type, vascular malformations are suitably called (e.g., venous malformations, arteriovenous malformations (AVMs)). More significantly, the unique flow properties of vascular abnormalities also inform the diagnostic and therapy approaches. Because of this, vascular malformations may be further classified as slow-flow or fast-flow lesions according to the speed at which fluid moves through them. AVMs have fast-flowing properties, while capillary, venous, and lymphatic abnormalities are classified as slow-flow malformations. Vascular malformations, in contrast to hemangiomas, are uncommon, seldom retreat, continue to grow, and have high rates of recurrence after treatment **[5].**

Vascular abnormalities may be treated in a variety of ways, as described in the literature.

These include surgical excision, laser therapy, sclerotherapy, embolization, electrochemical therapy, and copper needle treatment. The kind, location, and size of the lesions, the patient's condition, and the available procedures all have a role in the therapy modalities that are chosen. The preferred course of therapy for vascular abnormalities in the head and neck region has been surgical excision. A less intrusive kind of treatment, however, may be able to save these important tissues from harm as some lesions may be difficult to remove when they penetrate and encircle key systems like the facial nerve **[6].** Surgical or interventional methods, such as bleomycin injection into the lesion, lesion excision, or embolization in the presence of a single feeding vessel, may be employed alone or in conjunction with medicinal therapy for the treatment of vascular abnormalities **[7].**

Large sections of deformity are debulked surgically. Sclerotherapy or pre-, intra-, or post-operative embolization are often used to accomplish this. Excision of a vascular abnormality is often dangerous and complicated **[8].**

Umezawa made the discovery of the cytotoxic anti-tumor antibiotic bleomycin in 1966 [9]. In human tissue, bleomycin has two different effects. Firstly, it may cause DNA breakdown in areas of the strand that are undercoiled. Furthermore, bleomycin has a particular sclerosing impact on the endothelium of blood vessels **[10].** Intralesional bleomycin injection has been shown to be an effective therapy for hemangiomas and vascular malformation lesions throughout a wide variety of appearances. There was no indication of pulmonary toxicity, and the side effects of the IBI therapy were minor and confined. The outcomes showed a high success rate, guaranteeing satisfaction for the doctor treating these difficult lesions as well as the individuals they treated **[7].**

From the importance of the utilization of bleomycin in management of vascular malformations in combination with surgical excision, we conducted this study to assess efficacy of surgical excision of vascular lesions combined with intralesional injection of bleomycin as a sclerosing agent in the management of vascular lesions with assessment of decrease in size or total eradication and complications as disfigurement, obstruction of vital structure, functional derangement, bleeding, or recurrence.

2. Patients and Methods:

We conducted this interventional one arm study on 18 patients in Beni-Suef University

hospital at the Faculty of medicine at General surgery department for18 months (start in February 2022 and end in June 2023)

Inclusion Criteria: we included patients who have congenital vascular anomalies (hemangioma or vascular malformations) aged from 7 days to 18 years old (neonate to childhood) of both genders who gave informed consent from parent(s) or guardian(s).

Exclusion Criteria: we excluded patients who are not fit for surgery, such as those with CVS problems, respiratory problems .. etc, patients with infected lesions until infection subsides, patients with skin ulceration, patients who have sensitivity to bleomycin, patients/ or guardians' refusal to participate and patients with high flow malformations.

Methods

All patients underwent full history taking, general examination, and local examination of congenital vascular lesions regarding the site, extension, depth and relation to vital structures.

Pre-operatively, patients admitted one day before the operation, fasting for about 6 hours before the operation, all patients assessed for vital signs of the patients, and proper hydration: intravenous fluids and antibiotic. Laboratory assessment was done in the form of complete blood picture and cross matching, serum creatinine, serum urea, coagulation profile and liver function tests.

Operative Technique:

Patients were prepared under sterile conditions while under general anesthesia with endotracheal intubation. A transverse skin incisions was made in most cases. After the lesion was removed, 20 mL of bleomycin aqueous solution (15 units/20 mL) was administered intralesional without compromising any structural integrity. Bleomycin dilution and dosage were customized for each patient based on lesion size and body weight. The lesion's size was used to estimate the volume, and the bleomycin dosage was determined to be 0.5 mg/kg. We first attempted to remove the cyst without making any punctures. If the lesion was closely connected to important structures, evacuation takes place. When bleomycin was injected intralesional, the lesions were aspirated after maintaining the aspiration needle's tip within the cyst lumen, we injected 15 units/20 mL of bleomycin aqueous solution into the cyst. The computed dosage is divided by the number of cysts aspirated when more than one is aspirated, and the split dose is then injected into each cyst based on its size. Closure in layers without the use of a drain or suction to prevent bleomycin

injection leakage. Following surgery, a compression dressing was applied.

Bleomycin should be stored and preserved between 2°C and 8°C (36°F and 46°F). The Food and Drug Administration (FDA) authorized bleomycin on June 3, 1996, stating that it is a safe and effective medication **[11].**

Follow up

Patients were admitted to the general surgery department's inpatient unit for a single day before being released with prescriptions for antibiotics, analgesics, and corticosteroids. In the first month, we scheduled weekly visits, then every two weeks in the second, and finally, monthly visits for the patients. Follow-up of potential consequences from upper or lower respiratory tract infections resulting from bleomycin injection-induced interstitial lung disease for about one month after surgery for each patient. To assess the degree of response, pictures are taken immediately after the procedure and one month later. MRI or U/S if the lesion becomes bigger.

The parameters considered to assess parents' satisfaction included the following

A questionnaire was taken after one month and 6 months of the initial operation (excision with bleomycin injection) with the following items discussed with the parents. the tool included the total resolve of the lesion with no recurrence or residual, shape of the wound after operation and cosmetic aspects as scar, hypertrophy and keloid formation, apparent disability or disfigurement, period of postoperative hospital stay.

Data analysis and statistics

The collected data were coded then entered and analyzed using the SPSS version 25 (Statistical package for social science). Descriptive statistics were done for categorical variables by frequency and percentage, and for numerical variables in the form of median and interquartile range.

Ethical considerations:

The study approved by the local ethical committee on research involving human subjects of Beni-Suef faculty of medicine no., FMBSUREC/01022022/ Abdelazeem.

Case presentation

Case (1):

Male patient, 2 months old, complained of swelling in the right side of the neck as well as a swelling in right axilla shortly after birth. The U/S revealed large, non-vascular septate cystic lesion is seen in the right side of fetal neck, not communicating with intrathoracic structures was likely to be cystic hygroma. The patient had right supraclavicular lesion as well as right axillary lesion communicating to each other and showed cross fluctuation between the two lesions .the patient had a single supraclavicular incision and the lesion was evacuated through the upper part of the lesion .then bleomycin was injected through the supraclavicular incision and in the axilla , the lesion was aspirated and we kept the aspiration needle within the lesion and bleomycin was injected intralesional through the needle .so the patient had only one incision for the two lesions. Patient had respiratory affection (respiratory distress) intraoperative and had decrease in Oxygen saturation due to pneumothorax. after insertion of thoracostomy tube improved dramatically and chest tube was inserted intraoperative for about 3 days then removed after chest x ray that had proved no residual pneumothorax. The patient was followed up for 18 months postoperative and showed good response with complete regression of the lesion

Case (1) Preoperatively

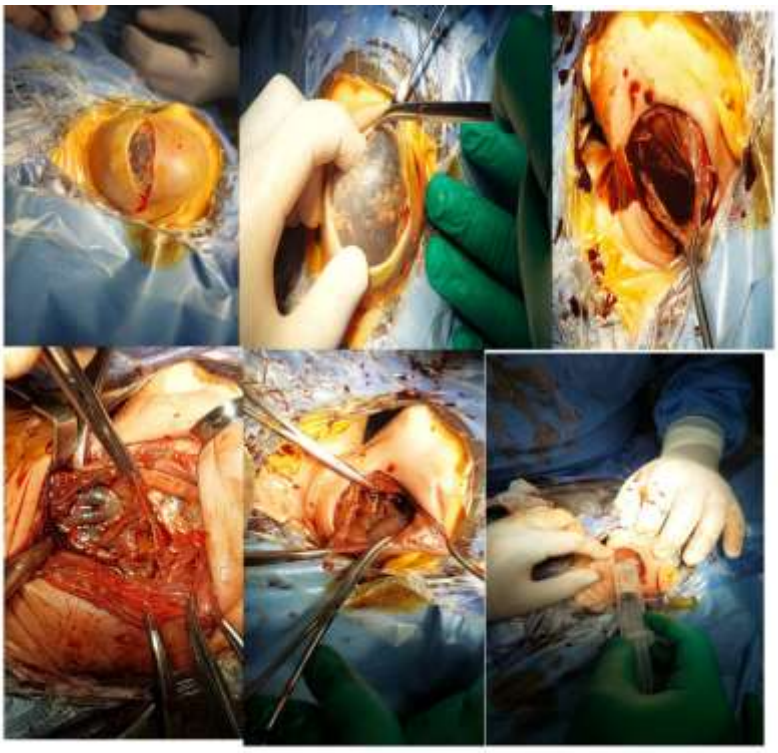
Case (1) Intraoperatively

Case (1) 6 months postoperatively

Case (2)

Female patient aged 20 days old, patient had large swelling on of left side of the neck of gradual onset sand progressive course. The swelling affected suckling of the baby (difficult and poor suckling of the baby) and started to affect the airway. The MRI revealed left side of the neck swelling, cervical cystic hygroma. Patient underwent surgical excision of the lesion with local bleomycin injection intralesional. postoperatively the patient had neurapraxia of the marginal mandibular nerve postoperative presented by deviation in the angle of the mouth to the other side and appeared during crying. Patient was followed up with anti-inflammatory and anti-edematous medications for about one month with full recovery. Patient was followed for about 1 year and showed good response with complete regression of the lesion.

Case (2) Preoperative



Case (2) Intraopertaively

Case (2) 2 weeks postoperative : showing neurapraxia of the marginal mandibular nerve and deviation in the angle of the mouth and appeared during crying postoperative

Case (2) 5 months postoperative:

3. Results:

This table shows that the median age of the studied patients was 3.5 years ranged from 7 days to 18 years. Nine cases (50%) were females, and nine cases (50%) were males. Six cases (33.3%) were neonates, five cases (27.8%) their age ranged between 1 – 5 years, four cases (22.2%) their age ranged between 6 – 10 years and three cases (16.7%) their age was more than 10 years.

Our results showed that 14 cases had vascular anomalies in the head and neck (77.8%) while 2 cases had vascular anomalies in the back (11.1%), one case (5.6%) had vascular anomaly in the chest wall and one case was occupying **abdomen** and lumbar region and extending to the groin (5.6%) **(Table 1).**

Table (1) site of the vascular anomalies in the studied cases

Items	**Values (no=18)**	
	No.	**%**
Head and neck	14	77.8
Back	2	11.1
Chest wall	1	5.6
Other: **Abdomen and lumbar region and extending to the groin**	1	5.6

Our results showed that most cases were cystic hygroma 14 cases (77.8%), two cases were venous malformation (11.1%) and two cases were hemangiomas (11.1%) **(Table 2).**

Table (2) pathological reports of postoperative patients:

Items	**Values (no=18)** **No.** **%**
Cystic hygroma	**14** **77.8**
Venous malformation	**2** **11.1**
Hemangioma	**2** **11.1**

This table shows that there were 14 cases of cystic hygroma, 13 cases were in the head and neck and one case was in the Abdomen and lumbar region and extending to the groin. Two cases of venous malformations, one case was in the head and neck (involving lower lip, left cheek, nasopharynx, and vocal cords) and another case was in the back. Two cases of hemangiomas, one case was in the scalp and another one was in the chest wall.

Table (3) Distribution of vascular anomalies in the body:

Items	**Values (no=18)** **No.** **%**
Cystic hygroma (14 cases)	**14** **77.8**
Head and neck	12/14
Back	1/14
Abdomen and lumbar region and extending to the groin	1/14
Venous malformation (2 cases)	2 11.1
Head and neck (involving lower lip, left cheek, nasopharynx and vocal cords)	1/2
Back	½
Hemangioma (2 cases)	**2** **11.1**
Head and neck (scalp)	1/2
Chest wall	½

There were eleven cases (61.1%) underwent intraoperative dilution of bleomycin (15 units/20 ml) on 15 ml normal saline due to large volume of the lesions, while seven cases (38.9%) underwent the intervention with dilution of bleomycin on 10 ml normal saline (Each vial of bleomycin having 15 units, i.e., equivalent to 15 mg).

There were no cases of acquired nerve injury, visceral injury, vascular injury, solid organ injury or mortality intraoperative, there was one case (5.6%) who underwent incomplete excision of the lesion and bleeding occurred intraoperative. The source of bleeding was venous malformation after

that the patient had many sessions of bleomycin injection, with partial regression of the lesion that is involving lower lip, left cheek, nasopharynx and vocal cords. The other early and postoperative complications were mentioned in **Table 4.**

Table (4) Intraoperative complications in the studied patients:

Items	**Values (no=18)**	
	No.	**%**
Intraoperative complications		
Respiratory problems	1	5.6
Bleeding	1	5.6
Nerve injury	0	0
Visceral injury	0	0
Vascular injury	0	0
Solid Organ injury	0	0
Mortality	0	0
Short term complications		
Edema	9	50
Nerve affection	2	11.1
Respiratory affection	1	5.6
Infection	0	0
Bleeding	0	0
Stiffness	0	0
Reaction to bleomycin	0	0
Wound dehiscence	0	0
Mortality	0	0
Long term complications		
Partial recurrence	6	33.3
Cosmetic disfigurement as: scar, keloid, hypertrophy and adherent scar	3	16.7
Nerve affection	0	0
Stiffness	0	0
Lymphedema	0	0
Interstitial lung fibrosis	0	0
Turning into malignant	0	0
Total recurrence	0	0

N:B short term complications postoperative denoted immediately postoperative and for two weeks and long term complications denoted from 2 weeks postoperative till six months. There were 11 cases had good response at 1st attack with complete regression of the lesion postoperative (61.1%) and till period of 6 months of follow up , while six cases had satisfactory response with >50%

regression of the lesion(incomplete regression but has good results as regarding respiration and feeding) (33.3%) and one case had poor response with <50% regression of the lesion (5.6%) (venous malformation, invading lips, left cheek , tongue, nasopharynx with extension to vocal cords) Figure 1.

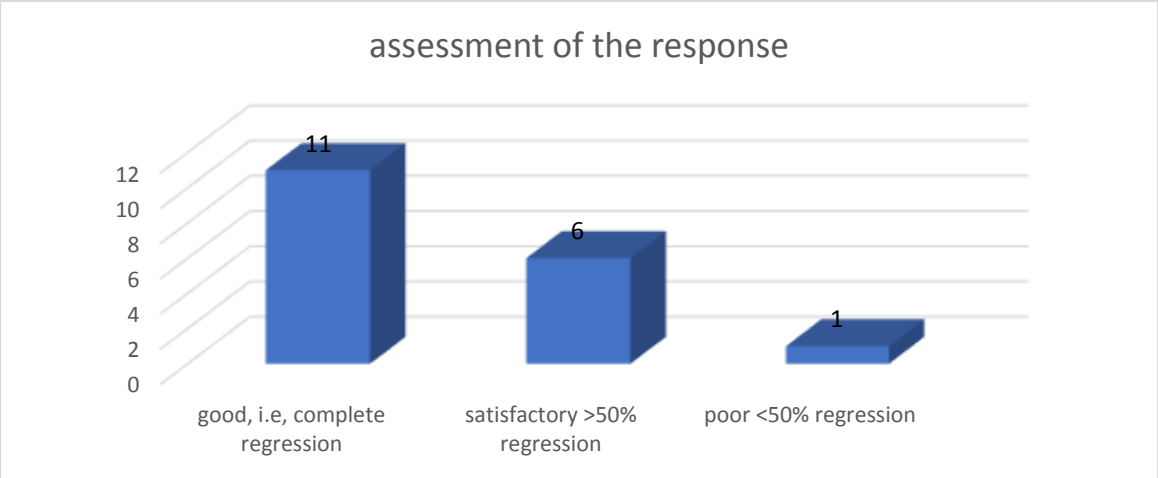


Figure (1) assessment of the response in the studied patients

Regarding the number of injections, 15 cases (83.3%) needed a single injection with excision of the lesion intraoperative, two cases (11.1%) needed 2 injections. One intraoperative and the second time percutaneously under sedation. One case (5.6%) had venous malformation and needed 7 injections of bleomycin, one injection intraoperative & Six injections thereafter.

This table shows that 14 parents (77.8%) were completely satisfied, 3 parents (16.7%) were moderately satisfied, and one parent was unsatisfied (5.6%). Six months after the initial operation, another Questionnaire was taken and showed 15 parents were completely satisfied (83.3%) and 2 parents (11.1%) were moderately satisfied and one parent (5.6%) was unsatisfied **Table 5.**

Table (5) Parents satisfaction one month and 6 months after initial operation of surgical excision with bleomycin injection in the studied groups:

Parent satisfaction	**At one month**		**At 6 month**	
	No.	**%**	**No.**	**%**
Completely satisfied	14	77.8	15	83.3
Moderately satisfied	3	16.7	2	11.1
Unsatisfied	1	5.6	1	5.6

4. Discussion:

There are several ways to treat lymphatic abnormalities, such as excision, sclerotherapy, medication, and monitoring; however, choosing one might be challenging. Since these masses usually include many head and neck regions, determining the appropriate course of therapy for them is challenging **[12].** So, we conducted at the General Surgery Department, Faculty of Medicine, Beni-Suef University to assess the efficacy of surgical excision of vascular lesions combined with intralesional injection of bleomycin. The median age of patients managed with surgical excision combined with injection of bleomycin was 3.5 years and half of them were males (50%).

Near results were reported by the study of Thorburn & Price, 2022 who investigated the expectant management of pediatric lymphatic malformations and reported that (50%) of patients were males. Near to our results, they reported the median age of management was 3 years **[13].**

As regards the complications, recurrence was observed in only 6 (33.3%) patients while cosmetic disfigurement was seen 16.7% in the studied group. Intraoperative bleeding was reported in one case, respiratory affection was seen in one case in our study group. Postoperative edema was seen in 50% of cases, 11.1% had nerve affection, 5.6% had respiratory affection.

Prat et al. (2020), who assessed low-dose bleomycin injections for ocular lymphatic and lymphatic-venous abnormalities, concurred with our findings. Due to recurrence or inadequate improvement, eight patients (38%) required a second surgery, and two patients (9.5%) needed a third **[14].**

According to Thorburn & Price's 2022 study on the treatment of juvenile lymphatic anomalies, recurrence occurred in 21% of the surgical group, which was the primary surgical consequence **[13].** Furthermore, a retrospective case analysis of 128 patients was conducted by Okazaki et al. (2007) in order to compare sclerotherapy with surgical excision. Although surgical excision was shown to be more successful than sclerotherapy, it came with a significant risk of complications (12–33%) and recurrence (15–53%) **[15].** This recurrence rate could explain the effective role of surgical excision in management of lymphatic malformations. The lower rate in our study could be due to the additive effect of bleomycin injection as a sclerotherapy in reducing the recurrence rate.

The introduction of a sclerosant into a vascular abnormality, which causes inflammation and damage to endothelium.

Inflammation causes thrombosis, fibrosis, and ultimately the lymphatic malformation's lumen to be completely destroyed. Only 20 to 40 percent of surgical excisions result in recurrence, regardless of how thorough or partial the excision was. The development of the residual lymphatic malformation in the apparently normal tissue is the cause of the high "recurrence" rate, or rather, re-expansion, after a complete excision **[16].**

Regarding further consequences, Li et al. (2020) found that patients received treatment with bleomycin-based interventional sclerotherapy, surgery, or surgery in conjunction with interventional therapy. The research focused on cervical lymphatic malformation in pediatric patients. Of the 84 patients (26.25 percent) who encountered complications, 64 (20 percent) had bleeding, 10 (3.12 percent) had infections, 7 (2.19 percent) had both hemorrhage and infection at the same time, and 3 (0.94 percent) had calcification. Every lesion eventually disappeared **[17].**

In research on bleomycin sclerosing treatment in enormous macrocystic lymphatic malformation, Bhatnagar et al. (2020) found no significant side effects. None of the individuals needed to be hospitalized, while a couple of them had slight discomfort, either with or without fever **[10].**

For extracervical cystic lymphatic malformations in children, Ardıçlı et al. (2016) compared sclerotherapy with bleomycin versus surgical excision. They discovered that complications manifested in eight (15%) of the patients treated by surgery, including wound infection in 2 cases, hematoma was seen in 2 cases, bleeding was reported in 1 case, sepsis was seen in 1 case, damage to major vessels was seen 1 case, and intussusception was seen in 1. However, two (5%) of the patients who had sclerotherapy experienced side effects, including hematoma was seen in 1 case and infection in one 1 case **[18].**

As regards parent satisfaction, 14 (77.8%) were satisfied, 3 (16.7%) showed neutral, and 1 (5.6%) showed dissatisfaction with the intervention after 1 month. While after 6 months, 15(83.3%) were satisfied, 2(11.1%) showed neutral, and 1 (5.6%) showed dissatisfaction with the intervention.

Wang et al. (2020), who looked into the safety and effectiveness of surgery combined with bleomycin irrigation for complex cervical–facial lymphatic malformations in children, found that 90.5 percent of patients (57 of 63) showed an excellent response, and 9.5 percent (6 of 63) showed a satisfactory

response. These findings are consistent with our research. Three patients in the sclerotherapy group had an outstanding reaction, and six had a decent one.

Additionally, Sheng et al. (2021) assessed the effectiveness of bleomycin sclerotherapy for large diffuse microcystic lymphatic malformations. Based on clinical manifestations and MR findings, they found that 32 patients (69.6%) had an excellent outcome, 11 patients (23.9%) had a moderate decrease, and 3 patients had a mild outcome (6.5 percent) **[19].**

Lerat et al. (2016) looked into head and neck lymphatic malformations and their treatment with surgical excision plus sclerotherapy. They discovered that in 20 cases (86.96 percent), the aesthetic outcome was satisfactory, and in 3 cases (13.14%), there were aesthetic sequelae: 2 deformities and 1 inferior facial palsy that were all related to suprahyoid mixed lesions that needed to be treated **[20].**

For extracervical cystic lymphatic malformations in children, Ardıçlı et al. (2016) compared sclerotherapy with bleomycin versus surgical excision. They found that 53 patients underwent surgery, with excellent response rates of 75%, good response rates of 8%, and no response rates of 17%, correspondingly. Thirteen individuals had ST, with ninety-one percent experiencing no reaction and ninety-one percent experiencing an outstanding response **[18].**

Given that surgical excision has long been the mainstay of LMs therapy, the remarkable response obtained from the combination of surgery and bleomycin may be explained. Conversely, significant rates of recurrence after surgery have been linked to the procedure; these rates may range from 0% to 25% following full excision and from 35% to 100% following partial excision. After surgical excision, combination with sclerotherapy might prevent recurrence **[21].**

5. Conclusion and recommendation:

Surgical excision combined with intralesional injection of Bleomycin as a sclerosing agent is highly effective in management of vascular malformation with better aesthetic outcomes as demonstrated by parents' and surgeons' satisfaction associated with low recurrence rates and minimal complications easily managed. Surgical excision combined with intralesional injection of bleomycin is recommended for management of vascular malformation in children. However, patients should be assessed preoperatively for the best plan of management. We recommend further studies performance on a larger sample size to

confirm the results of this study for long-term follow up of patients for the possible complications or recurrence is recommended in further studies. Also, comparison between different sclerosing agents should be evaluated to reach the optimum agents with the suitable dose and minimal adverse effects.

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