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Research Paper

Comparison between Bleomycin Foam and Liquid Injection in Treatment of Maxillofacial Low Flow Vascular Malformations

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ABSTRACT:

BACKGROUND:

Vascular anomalies represent a wide range of vascular pathology classified by flow velocity. Venous malformations are the most frequent kind of head and neck vascular malformation that cause functional and cosmetic disturbances. Injection sclerotherapy is the initial therapeutic choice for venous abnormalities.

OBJECTIVE:

To compare the effects of bleomycin foam and liquid in treatment of maxillofacial venous malformation regarding the dose, size of the lesion and number of treatment sessions.

PATIENTS AND METHODS:

This study involved 20 patients (11 females, 9 males) with an age range (9-47) years, had venous malformation in the head and neck region presented to the Maxillofacial Surgical department in Alwasity hospital / Baghdad, from January 2021 to April 2022.

Patients were divided into two equal groups randomly. The odd number of patients (group A) were treated by bleomycin foam injection while the even number group (B) were injected by bleomycin liquid.

RESULTS:

The results showed in group (A), 6 patients were in scale 4 with an excellent response and 4 patients were in scale 3 with good responses. In group (B) group, 3 patients were in scale 4 (excellent response),6 patients were in scale 3 (good response) and one patient was in scale 2 (fair response).

CONCLUSION:

Bleomycin liquid and foam injections are effective sclerosing agent for vascular malformation treatment. Bleomycin foam sclerotherapy was an effective with a decreasing number of treatment sessions and less dose of bleomycin medication. Data from the present study suggested more effective treatment outcomes in females than males.

KEYWORDS: Bleomycin foam, Sclerotherapy, Vascular malformations.

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INTRODUCTION:

Vascular anomalies are birthmarks or growths made up of abnormally formed blood vessels, or a diverse group of disorders involving vascular tumors characterized by increased endothelial cell proliferation and vascular malformations that represent underlying mesenchyme and angiogenesis disorders.[1-3] Vascular malformations are always present at birth (even if asymptomatic) and never spontaneously regress in size; instead, they tend to enlarge as the patient ages with normal endothelial turnover, with no gender predilection. [4] Mulliken and Glowacki's publication of the initial classification marked a turning point in our understanding of the diseases connected to the underlying vasculogenesis and angiogenesis abnormalities. [1,5,6] Vascular abnormalities can be classified into two main groups [6-9]:

1- Hemangiomas, proliferative of endothelial cells that are vascular tumors
2- Vascular malformations, which are abnormalities in the embryonic development of lymphatic, capillary, venous, or arterial vessels. [1,3]

Vascular malformations are the result of abnormal vascular development during embryogenesis.

Errors in morphogenesis of human embryonic life, when venous and arterial channels appear on either side of the capillary network. The International Society for the Study of Vascular Anomalies (ISSVA) updated the existing classification during the May 2018 ISSCA meeting in Amsterdam. Further classification of vascular malformation is based on the major channel type (single vessel type, mixed) and flow (into high-flow or low-flow lesions classification system). [10,11]

Different modalities were used for treatment of these lesions includes medical and surgical procedures. Sclerotherapies like bleomycin antitumor antibiotic, intercalates with DNA in the presence of a redox reaction, causing free radicals to be released and, as a result DNA degradation. In addition, bleomycin considered as an effective agent but it has many complications like pulmonary fibrosis. [11]

This prospective study aims to compare the effects of intralesional injection of bleomycin foam and liquid in the treatment of maxillofacial low flow venous malformation regarding size (detected by doppler ultrasound), number of treatment sessions and the dose of bleomycin in foam and liquid type.

PATIENTS AND METHODS:

A prospective study was conducted in the maxillofacial surgery department in Al-Wasity specialized surgical center, Baghdad, from January 2021 to April 2022.

The study involved 20 patients (11 females, 9 males) with an age range from 9-47 years, who sustained with vascular venous malformation in the head and neck region.

Patients were divided into two groups randomly. The odd number of patients was selected for the bleomycin foam injection (group A) and the even number for the liquid injection (group B). Each group included 10 patients for the study.

Preoperative evaluation:

The patient's complete history was taken, registered, and data were collected using a standardized case sheet for each patient included patient's details, site, size of the lesion, bleomycin injection and follow up of the patient. An informed consent was considered for each patient and an ethical approval for this study was confirmed by the research ethical committee of the Scientific Council of Maxillofacial Surgery of the Iraqi Board for Medical Specializations.

The diagnosis accomplished by clinical examination of low flow venous malformations and the use of doppler ultrasound. Patients with pulmonary diseases, history of allergic reaction, kidney or liver diseases were excluded from the study in addition to history of any previous treatment modalities of vascular malformations.

Operative procedure:

The procedure was performed in the operative theatre and the patients were placed in supine position. Neither general anesthesia nor local anesthesia was utilized except 2 patients were treated under sedation. The injection site was prepared and all patients received the same standard treatment for each group. The surgical trolley was prepared with materials and equipment as shown in (Figure 1).

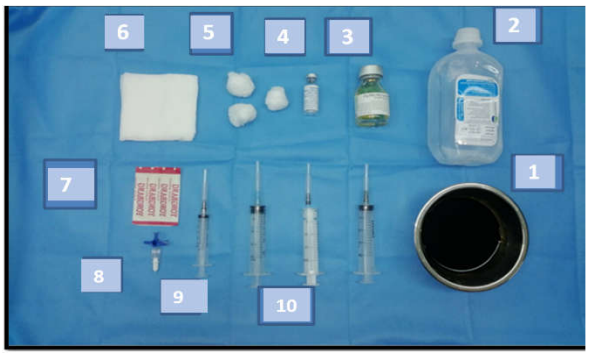


Figure 1: Items of surgical trolley contain:1-Povidone iodine, 2-Normal saline 0.9% solution, 3-Human serum albumin (HSA) 20%, 4- Bleomycin powder (vial of 15 mg), 5- Cotton, 6- Gauze, 7- Strip bandage plaster, 8-Three-way cannula, 9- Syringe 5ml, 10- Syringes 20ml.

Preparation of the sclerotic agent injection:

A. Liquid formula: bleomycin powder (15 mg) diluted in 15 mL normal saline solution 0.9% (dilution 1 mg: 1mL).

B. Foam formula: consist of mixing bleomycin powder 1mg, ½ mL normal saline solution 0.9% and ½ mL human serum albumin 20% (HAS) mixed with 4 mL room air through a three-way cannula for about 20 times (Figure 2) .

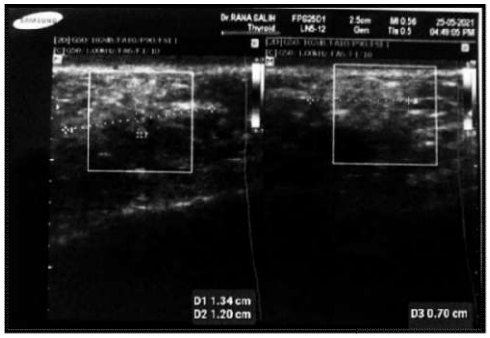
The maximum dose for each bleomycin injection is limited to (0.5 -1) mg/kg, or never be exceeded the single dose of 15 mg per session.

Figure 2: Mixing the room air using 3-way canula to prepare bleomycin foam.

The interventional procedure:

Percutaneous or permucosal intralesional bleomycin injection through the normal skin or normal mucosa (gauge of needle was 22) was performed, followed by aspiration to confirm the intralesional needle position then the bleomycin slowly infused into the lesion in all directions. The injection should be stopped if the covering mucosa or skin blanch or the patient received the maximum recommended dose of injected sclerosant as shown in figure (3). After the treatment session is over, a sterile gauze was applied with manual pressure for 2 to 5 minutes to stop any oozing with dressing of the injected site. The total injection dose and the number of sessions were recorded in the case sheet.

The patient was kept under supervision for checking: body temperature, pulse, respiratory rate, blood pressure, and oxygen saturation for an hour after injection of the sclerosant agent whether liquid or foam then the patient was discharged. All patients followed monthly for 3 months.



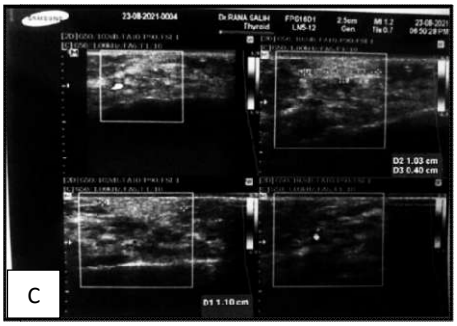


Figure 3: A 21-year-old female patient presented with venous malformation in the right side of the cheek, treated by bleomycin foam type (A) administration of bleomycin foam type (B) preoperative doppler ultrasonography showed the size of the lesion, (C) postoperative doppler ultrasonography showed reduction in the size.

All patients evaluated according to the size of the lesion, healing of the injection sites, using Achauer et al proposal which involved (4) grade scale based on improvement in volume, color, and texture of the lesion as follow scales: 1, poor (0 to 25 %); 2, fair (26 to 50 %); 3, good (51 to 75 %); and 4, excellent (76 to 100 %). [12] The data analyzed using Statistical Package for Social Sciences (SPSS) version 25.

RESULTS:

Demographic and clinical characteristics

A total number of 20 patients were involved in this study with age ranged from 9 to 47 years with a mean of 20.80. There were 6 females and 4 males in the foam group (A), while the patients in the liquid group (B) were distributed equally (5 females and 5 males). Table 1 show the distribution of the lesions according to the site, sex of the patient and number of treatment sessions.

Table 1: Distribution of the study groups by clinical characteristics.

Clinical characteristic	Study Groups		Total n= 20
	Foam Group n= 10	Liquid Group n= 10	
Sex of the patients			
Male	4	5	9
Female	6	5	11
Site of lesion			
Cheek	6	5	11
Chin	1	0	1
Tongue	1	4	5
Upper Lip	1	0	1
Lower Lip	1	1	2
Number of sessions			
One	4	0	4
Two	4	4	8
Three	2	6	8

Comparison of bleomycin doses and number of sessions

In the present study, there was a statistically significant difference in the P- value of bleomycin doses and the number of sessions between the two groups (Table 2).

Table 2: Comparison of bleomycin doses and number of sessions between study groups.

Clinical Characteristics	Study Groups		P - Value
	Foam Group Mean ± SD	Liquid Group Mean ± SD	
Bleomycin Dose (mg)	3.25 ± 2.22	15.03 ± 7.37	0.001
Number of Sessions	1.80 ± 0.78	2. 60 ± 0.51	0.037

The outcome of bleomycin therapy

Results of bleomycin sclerotherapy were as follows: In the foam group, 6 patients were on scale 4 with an excellent response and 4 patients were on scale 3 with good response. In the liquid group, 3 patients were in scale 4 (excellent response), 6 patients were in scale 3 (good response) and one patient was in scale 2 (fair response), and no one of each groups have scale: 1 (poor results) as shown in Figure 4.

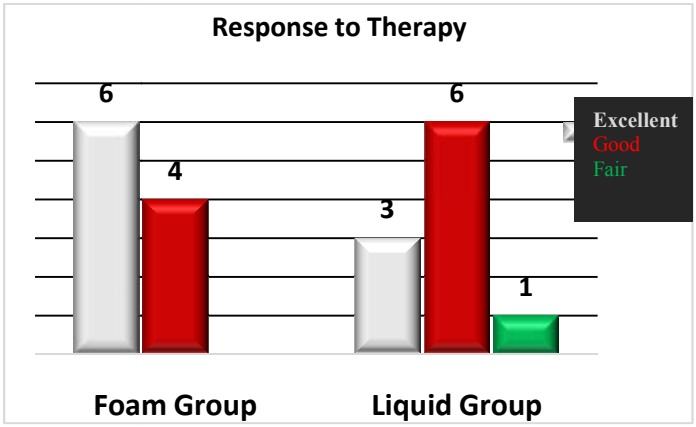


Figure 4: Response to bleomycin therapy among the study groups.

Percentage of size change

The results showed that the mean percentage of size change was significantly different between the study groups. Patients in the foam group had significantly higher mean percentage of size change than those in the liquid group (78.60 versus 60.00, P= 0.017) (Table 4).

Table 4: Comparison between the study groups by percentage of size change

Clinical Characteristic	Study Groups		P- Value
	Foam Group Mean ± SD	**Liquid Group Mean ± SD**	
% Size Change	78.60 ± 12.13	60.00 ± 14.18	0.017

DISCUSSION:

The most frequent vascular anomalies in the head and neck area are venous malformations. Typically, they impact a variety of anatomical areas, including the skin, mucosa, neuromuscular tissues, and bones. The venous malformation, which can be localized, diffuse infiltrating, or complex combined, frequently causes symptoms due to compression of surrounding structures such as muscles and nerves. If left untreated, they usually grow in proportion to the body's normal growth, eventually causing disfigurement and organ dysfunction in some cases. [1-3]

Sclerotherapy is currently considered the gold standard for treating venous malformations. Several sclerosant agents had been used to treat these lesions, but none were deemed the best. bleomycin is considered as a promising vascular sclerosant agent. [3,4]

In the current study, 20 patients with maxillofacial venous malformations were recruited their age ranged from 9 to 47 years the mean and standard deviation (SD) of age was 20.80 ± 11.33 years, regarding the sex, there were females as represented the largest number (55%) of study patients which agrees with Helal et al. were females about (53.3%). [13]

The results of this study showed that the low flow venous malformation affected younger age group which agree with other studies. [13,14]

In this study the distribution of lesions in the cheek was the most affected site 55% of patients while each of tongue 25%, lower lips 10%, chin 5%, upper lip 5% were affected in patient due to the prevalence of venous malformations about 1-5 in 10,000 births with the head and neck region having the highest prevalence of vascular anomalies about 60 percent or more of venous abnormalities. [1-3]

In the (group A) patients, the mean of bleomycin dose and mean number of sessions were significantly lower than liquid group P= 0.001 and 0.037 respectively. This may be attributed to air-containing bubbles and large surface area compared to the liquid form that's prolongs contact with the endothelial lining making it more effective on vascular lesions. Additionally, the bleomycin foam offers greater drug volume per dose, lower cumulative doses, and lower costs. Also foaming may reduce systemic concentration and the risk of toxicity by slowing the rate of absorption and less complications.

The current study revealed that the mean percentage of size was significantly different between the study groups, patients in foam group (A) had significantly higher mean percentage of size (78.60±12.13) than those in liquid group (B) preoperatively size of lesion (60.00±41.18) (P= 0.017), which coincide with other authors. [14-16]

The results of many studies used bleomycin as a sclerotherapy showed it was a simple technique and very effective in the management of venous malformations. Bleomycin has a double effect on human tissue as a cytotoxic and antitumor which can induce DNA degradation in strand regions. It has a specific sclerosing effect on vascular endothelium via a nonspecific inflammatory reaction, which can result in endothelial cell injury and detachment, discontinuation of the tunica intima, thickening of the vessel wall, lumen narrowing, or occlusion which leads to gradual fibrous degeneration and lesion regression. [17,18]

The use of (Human Serum albumin) HSA as a foaming agent as protein solution with higher surface activity forms a film which then surrounds the air and forms bubbles as viscous colloidal solution, which consists of small molecular compounds had a short peptide chain with strong hydrophilic groups and hydrophobic groups with higher surface activity to promote the development of the foam. It is a simple method by the proportion of human serum albumin (HSA), saline solution and the proportion of air-liquid, as previously mentioned, to produce larger quantities of more stable bleomycin foam.

The variations in response may be seen between many studies and can be attributed to a variety of variables, some of which are statistical in nature, such as study design or sample size, or which are related to the patients themselves, such as their age and comorbid conditions, or which are related to the lesion itself, such as duration, location, type, and size variations, which may also have an impact on outcomes. [19]

CONCLUSION:

Bleomycin liquid and foam are effective sclerosing agents for vascular malformation treatment. Foam form sclerotherapy is a promising treatment due to decreased number of visits, less concentration of sclerosing material and less complications

CONFLICT OF INTERSET

None to declare

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