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Comparison between Bleomycin and Ethanol-amine Oleate Intralesional Injection Sclerotherapy of Maxillofacial Low Flow Venous Malformations in Pediatric Patients

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Abstract

Background: Venous malformations (VMs) are the most common type of vascular malformations; maxillofacial VMs result in functional and esthetic problems. Sclerotherapy is their main treatment.

Aim of Study: to compare between Bleomycin (BLM) and Ethanolamine Oleate (EO) sclerosing agents in treatment of maxillofacial VMs to decide which can achieve better therapeutic results, with fewer complications.

Materials and Methods: 30 children having maxillofacial VMs were divided into two equal groups. BLM was injected at 4 weeks interval, and EO was injected at 2 weeks interval. Clinical response was classified into: complete resolution, marked improvement, moderate improvement, or no improvement. Results were compared after 12 months.

Results: BLM Group: complete resolution in 12\15 patients, marked improvement in 3\15 patients. Treatment duration ranged from 2 to 8 months. EO Group: complete resolution in 7\15 patients, marked improvement in 4\15 patients, moderate improvement in 3\15 patients, and no response in one patient. Treatment duration ranged from 1 to 3 months. Difference between 2 groups was non-significant in clinical response and recurrence. BLM required significantly less local anaesthesia and had significantly less pain, but required significantly longer treatment duration than EO.

Conclusion: BLM has fewer complications than EO; however, BLM requires longer treatment duration. EO is effective and safe only for intra-oral VMs and should be performed under GA to avoid local anesthesia systemic toxicity.

.**Key Words:** Bleomycin, Ethanol-amine Oleate, Pediatric, Maxillofacial, Vascular Malformations

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Introduction

Vascular malformations are congenital localized defects of blood vessels or lymphatic vessels or both. [1] Vascular malformations are classified according to blood flow within their vessels and their abnormal vessel type into low-flow and high-flow malformations. Low-flow vascular malformations include venous, lymphatic, capillary, and combined malformations. Venous malformations (VMs) are the most common type of low flow vascular malformations. VMs may be sporadic, inherited or syndromic; VMs are bluish\purple in color, gravity dependent; their growth proportional to child growth rate, and they are triggered by trauma, infection, surgery, hormonal changes during puberty. **[2]**

There are various treatment options for VMs; such as, surgery, sclerotherapy, Laser, gamma knife radiotherapy, sirolimus, systemic targeted drugs, or combination therapy for complex cases. Sclerotherapy remains the first treatment line for VMs; for years ethanol-amine oleate (EO) has been the most commonly used sclerosing agent. Later, Bleomycin (BLM), an antibiotic and anti-cancer agent, was used as a sclerosing agent. **[3]**

Many studies evaluated EO alone, BLM alone, or comparing EO or BLM with ethanol or with other sclerosing agents, but, up to our knowledge no study compared these two sclerosing agents. This prospective study compares BLM and EO intralesional injections in management of maxillofacial low-flow venous malformations in pediatric patients in Egypt. This study's primary objective was to decide which sclerosing agent can achieve better therapeutic results with least complications.

Material and Methods

This study (Randomized Controlled Trial) was approved (No. 2018\157) by Research Ethics Committee in Suez Canal University (SCU), Ismailia, Egypt. The study was performed according to ethical standards of the responsible committee on human experimentation (institutional and national) and according to the 1975 Helsinki Declarations, as revised in 2013. Informed written consents were obtained from all parents of children to participate in this research, and verbal consents were obtained for presentation of the cases within this present scientific paper. Confidentiality of data was confirmed that patient's names and personal data will never be mentioned. The study included 30 pediatric patients of both sexes, which were divided into 2 equal groups: group I treated by BLM and group II treated by EO.

PICO Criteria: Population (P): pediatric patients of age up to 12 years suffering from oral and maxillofacial low flow venous malformations; Intervention (I): intralesional injection sclerotherapy; Comparison (C): BLM and EO; Outcome (O): clinical response of vascular lesion, with a follow-up of at least 12 months

Inclusion Criteria:

1. Pediatric patients of age up to 12 years
2. Patients with oral and maxillofacial low flow venous malformations

Exclusion Criteria:

3. Lung, kidney and\or liver disease
4. Klippel-Trenaunay syndrome

Pre-operative Assessment:

Medical History included previous medications, allergies, intra-lesional injections or laser therapy. CBC, coagulation profile, ECG were obtained for all patients. The diagnosis was established as low flow VMs by taking history, clinical examination (lesion present at birth & lesion growth rate is proportional to the child body growth rate & lesion become obviously enlarged in size, congested with venous blood, and its color darkens, during physical exercise, lowering the head, or crying), and imaging including ultrasonography (USG) superficial linear transducer (probe) used to evaluate vascular lesion size, depth, and blood flow to exclude high flow vascular malformations (AVMs) and magnetic resonance imaging (MRI): for deep vascular malformations to demonstrate vascular lesion size, and proximity to vital anatomical structures

Colored photographs were taken with a standardized Samsung digital camera on first visit, throughout treatment and after last injection. Demographic data for each patient, and clinical data of vascular lesion including; lesion anatomical site and size, sclerosing agent used, dose and timing of each injection, and clinical response to treatment were documented in each patient file.

Intra-lesional Injection Procedure:

Vital signs were monitored for each child on each session before intralesional injection. In case of infection or ulceration at site of injection, fever, recent immunization, coughing, and\or signs of central cyanosis, the procedure was postponed, [5] Body weights of each child and vascular lesion size were measured on each session to determine the dose required.

Regarding anaesthesia, topical Anaesthesia was used for superficial lesions, nerve block local anaesthesia for deep lesions with 3% Mepivacaine hydrochloride 1.8 mL without vasoconstrictor [6], and General anesthesia (GA) for uncooperative patients or lesions related to the airway. All procedures were done under complete aseptic conditions by the same operator. The needle was inserted 2-3 mm beyond the vascular lesion to avoid hemorrhage, then, it was moved within the lesion in different directions to distribute the sclerosing agent homogenously. Patients were kept under observation for 30 minutes post-injection. Intralesional injections were performed according to each lesion response to treatment, until no more intervention was needed.

Bleomycin Group: Bleomycin is available in 15 IU vials (Bleocel®, CELON Labs, Ltd, India). BLM was freshly prepared; 15 mg BLM powder was dissolved in 15 ml of sterile normal saline. **S**afe pediatric dose of BLM is 0.5 IU\kg; the maximum dose is 15 IU\session, and injections were performed at 4 weeks interval. [7]

Ethanol-amine Oleate Group: Ethanol-amine Oleate 5% is available in 5 mL ampules (Ethanolamine Oleate, EPICO, Egypt). EO was diluted with sterile normal saline, in a ratio 1:4; 1mL of EO 5% diluted in 4 mL saline (1.25% concentration). Safe dose of EO is 0.4 mL /Kg body weight; and the maximum dose is 20 mL\session, and injections were performed at 2 weeks interval. [8]

Post-operative Phase:

Acetaminophen 100 mg/ml as 250 mg/5ml as CETAL® (EPICO, Egypt) was prescribed for 2-3 days, and B.B.C® mouth topical spray (AMOUN, Egypt). Parents were instructed to apply ice fomentations on the first day after injection. Colored photographs were obtained after the last injection to evaluate clinical response of each vascular lesion.

Clinical response was measured according to Sainsbury et al [9]; classified as: complete resolution (> 90% reduction of vascular lesion size), marked improvement (> 70% reduction of vascular lesion size), moderate improvement (40 – 70% reduction of vascular lesion size), slight improvement (< 40% reduction of vascular lesion size), and no response (< 10% reduction of vascular lesion size). [9]

Results

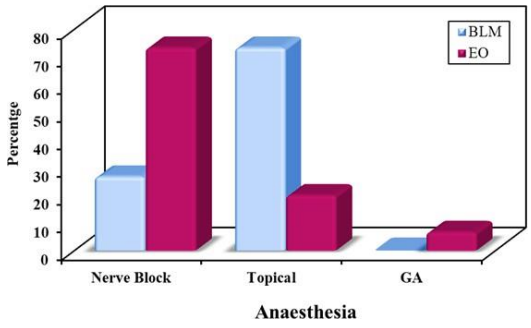
Bleomycin Group: Fifteen patients were included in this group, 7 females and 8 males, age range: 2-months to 11-years old. Regarding anaesthesia, 11\15 patients were injected with topical anaesthesia only, and 4\15 patients had nerve block anaesthesia. Regarding common complications of BLM, there was no alopecia or weight loss or hyperpigmentation throughout the follow up time in any patient and no ulceration at injection site. Recurrence happened in 2 patients only. Parents of all patients reported post-operative swelling that lasted for 3-5 days, without any post-operative pain or elevation of body temperature. The mean duration of treatment was 6.3 months. Patients required 2 to 8 sessions (range: 2 – 8 months); with 4 weeks interval; 6\15 patients required 8 treatment sessions (8 months), 6\15 patients required 6 sessions (6 months), 2\15 patients required 4 treatment sessions (4 months), and one patient required 2 treatment sessions (2 months). Regarding clinical response, 12\15 patients had complete resolution, and 3\15 patients had marked improvement. Fig. 1 shows BLM injection of VM in the tongue of a 10 years patient, Fig. 2 shows VM in left side of lower Lip in an 8 years old boy, Fig. 3 shows VM in lower lip in 8 years old girl

Ethanol-amine Oleate Group: Fifteen patients in this group included 8 females and 7 males, with age range: 8-months to 11-years old. Regarding anaesthesia, only 3\15 patients were injected under topical anaesthesia, 11\15 patients under regional anaesthesia, and only one patient required GA; the child age was 3 years old and the vascular lesion was in the parapharyngeal region. Regarding clinical response, 7\15 patients had complete resolution, 4\15 patients had marked improvement, 3\15 patients had moderate improvement, and one\15 patient had no response. Figure 4 shows VM in the lower Lip in a 2 years old girl, Fig. 5 shows VM in upper lip in 10 years old girl, Figure 6 shows immediate alarming swelling after EO injection VM in upper lip in 10 years old boy; swelling lasted for 7 days. Ulceration and scarring happened only in 2 cases (13.3%) in the lower lip. Fig.9-B, C Recurrence occurred in 3 cases (20%). Parents of all patients reported post-operative pain, post-operative swelling that lasted for 3-5 days and mild elevation of body temperature on the first day. These complications were managed by Paracetamol analgesic and antipyretic. Regarding duration of treatment; the mean duration was 2.1 months. Treatment required between 1 and 6 sessions (range: 1 – 3); with 2 weeks interval; 6\15 patients required 6 treatment sessions (3 months), 4\15 patients required 4 treatment sessions (2 months), and 5\15 patients required 2 treatment sessions (1 month).

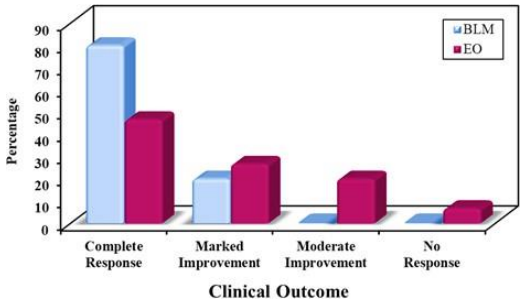
During this study, all parents of participating children insisted to know the sclerosing agent being injected. Moreover, parents were asking doctors of different specialties, exploring Google search engine and social media for data about different sclerosing agents used in treatment of vascular anomalies.

Graphs 1-4 show comparison between BLM and EO according to different parameters and complications. There was no dropout. EO group had significantly more local anaesthesia, post-operative pain and mild elevation of body temperature, and significantly less treatment duration than BLM. The post-operative swelling was the same (75%) in BLM and EO groups. The difference between BLM and EO groups in clinical outcome was non-significant.

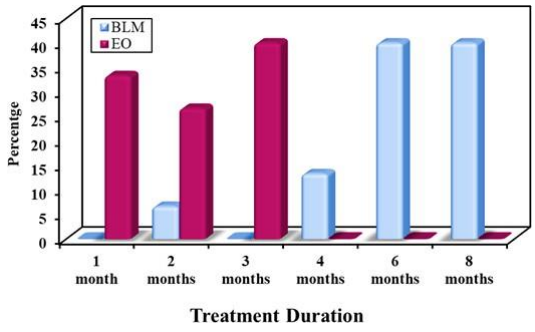
Statistical Analysis: Results were analyzed using IBM® SPSS® Statistics 20 and Microsoft® Excel® 2013 software. Chi-square test (Fisher's exact test) was used to assess comparisons for categorical variables. Mann Whitney test was used for not normally distributed quantitative variables. Research results were judged at 5% level of significance.



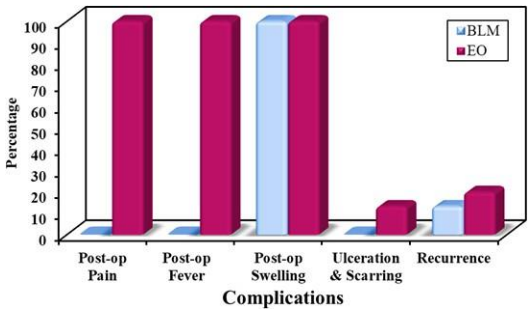
Graph 1
Comparison according to Anesthesia



Graph 2
Comparison according to Clinical outcome



Graph 3
Comparison according to Treatment Duration



Graph 4
Comparison according to Complications

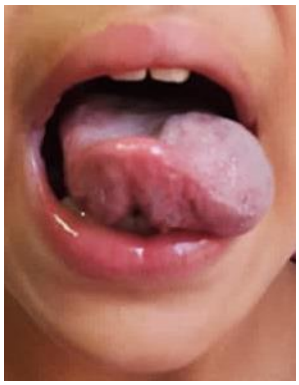


Fig. 1-A: VM in tongue in a 10 yrs old girl

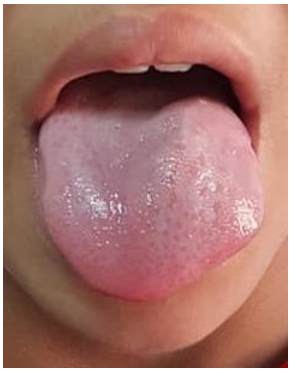


Fig. 1-B: reduction in size after 2 injections of BLM

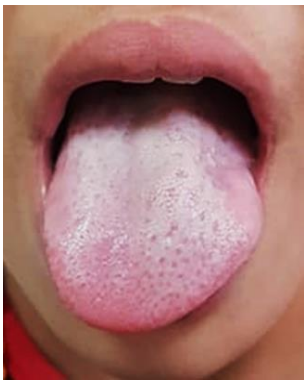


Fig. 1-C: complete response after 4 injections of BLM

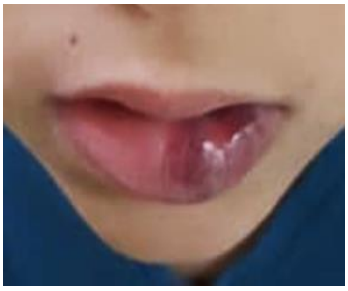


Fig. 2-A: VM in Lower Lip in 8 yrs old child

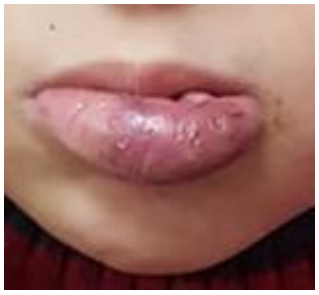


Fig. 2-B: after 5th BLM injection

Fig. 2-C: complete response after 8 injections of BLM

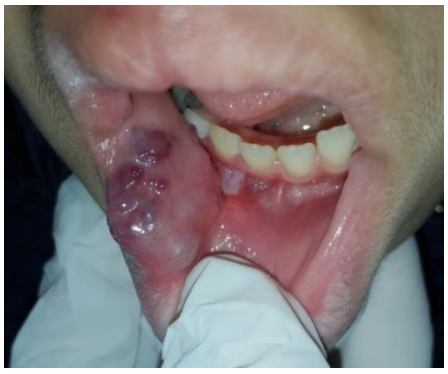


Fig.3-A VM in lower lip in 8 yrs old girl

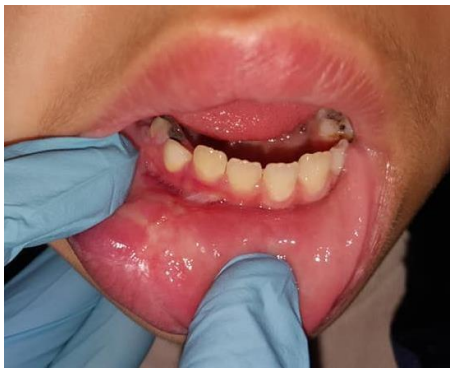


Fig. 3-C: Complete resolution after 6 injections of BLM

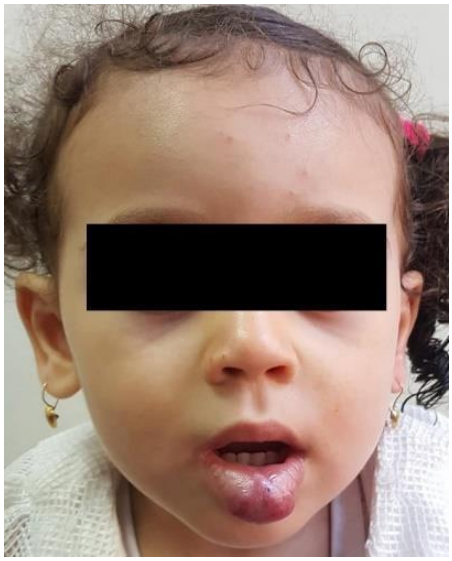


Fig. 4-A: VM in Lower Lip in a 2 yrs old girl

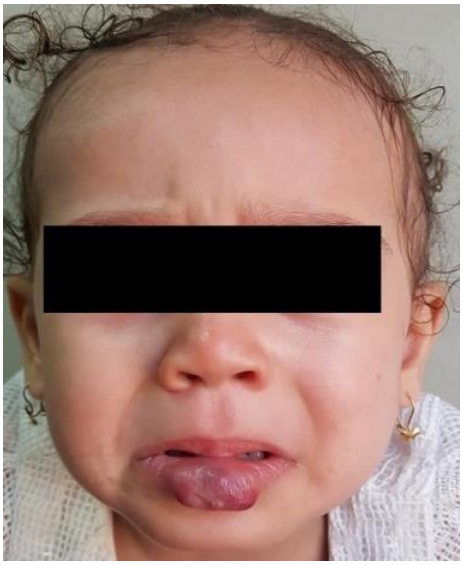


Fig. 4-C: reduction in size after 1st injection

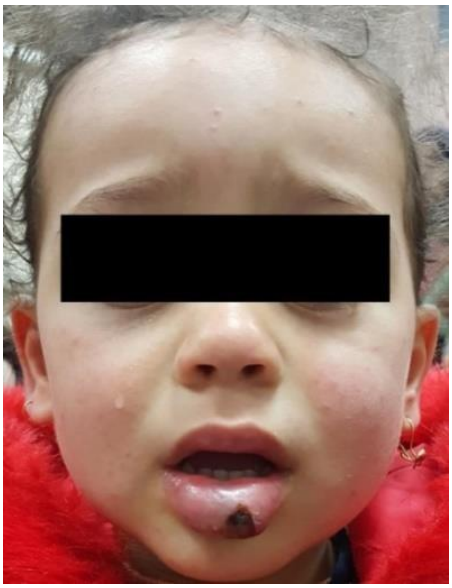


Fig. 4-D: necrosis at injection site 2 days after 2nd injection of EO

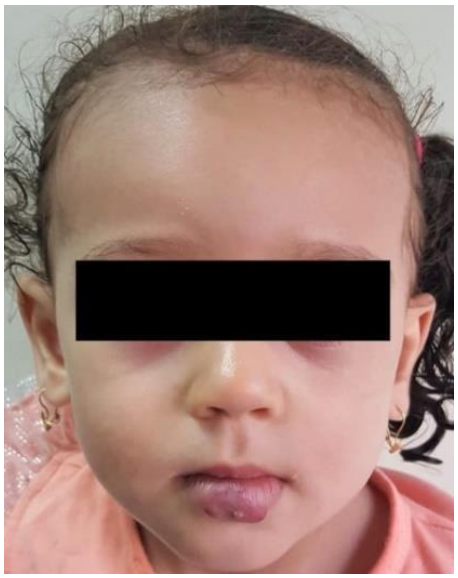
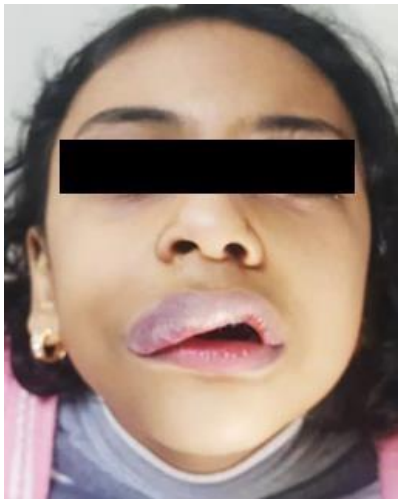


Fig. 4-E: Atrophic scar after 4 weeks



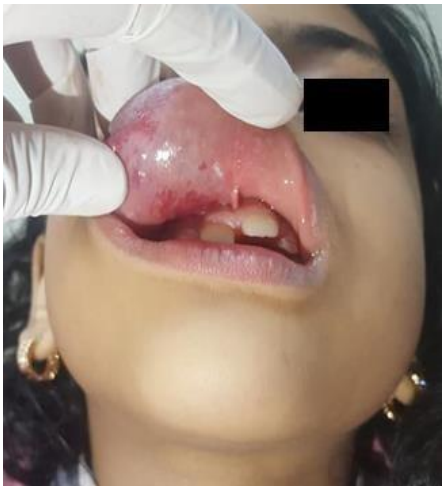


Fig. 5-A: VM in upper lip in 10 yrs old girl

Fig. 5-B: EO intralesional injection

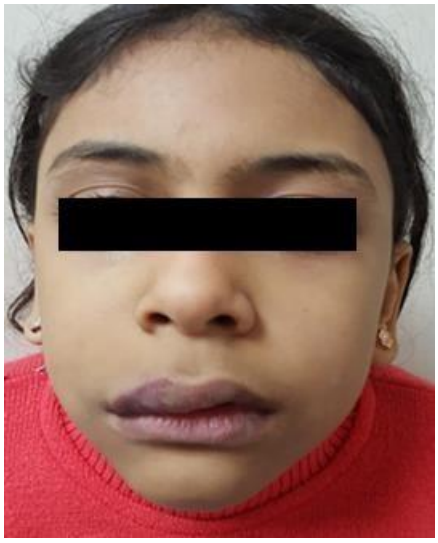


Fig. 5-C: Resolution after 6 injections of EO

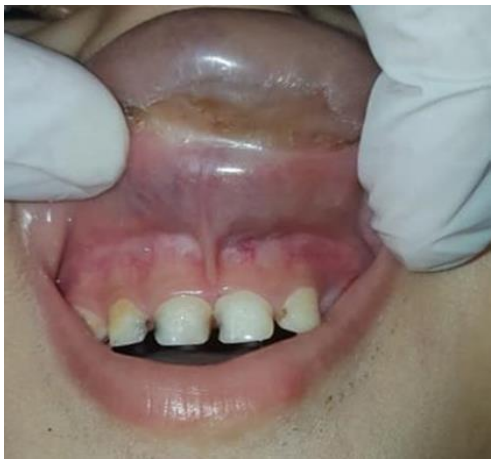


Fig.6-A: VM in upper lip in 10 yrs old boy

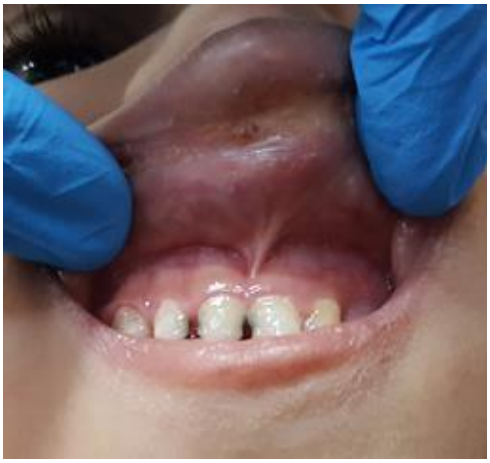


Fig. 6-B: complete resolution after 6 injections of EO

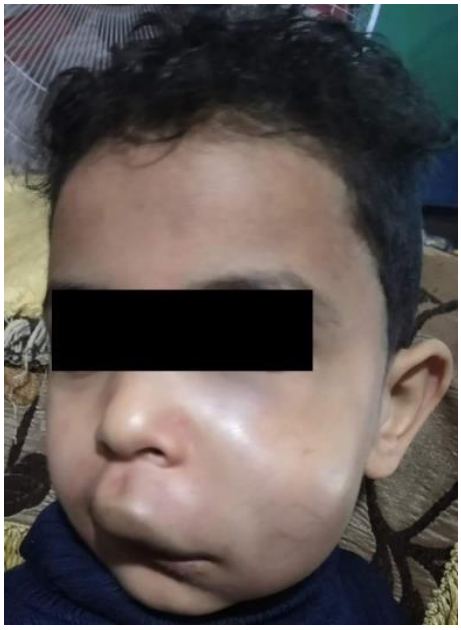


Fig.6-C: Alarming immediate swelling after EO injection

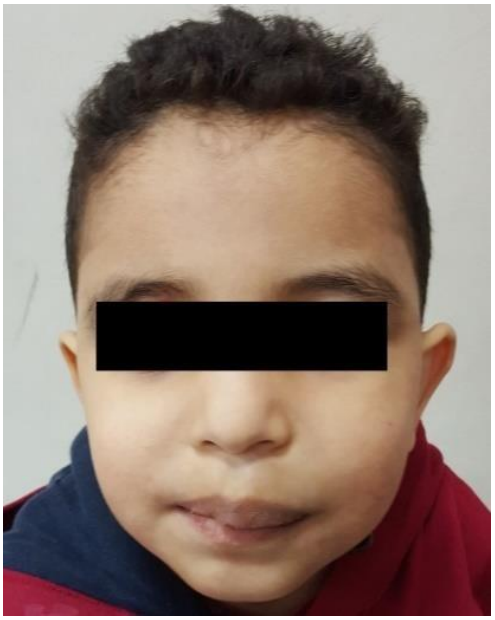


Fig. 6-D: Resolution of swelling after one week

Discussion

Surgical excision is not recommended as a treatment option of facial low flow venous malformations, due to intra-operative hemorrhage, and post-operative scarring in the face, resulting in functional and cosmetic complications. Intralesional sclerotherapy is the gold standard treatment option. There are many sclerosing agents; with various advantages and disadvantages. Although sclerotherapy is a minimally invasive procedure, complications may occur during or soon after treatment, ranging from skin discoloration to nerve injuries, ulceration, scarring, blood coagulation problems, and lethal pulmonary fibrosis. [10]

Selection of the proper sclerosing agent depends on vascular lesion type, size and its anatomical site, effectiveness and safety of each sclerosing agent, and patient age.[11]

Ethanol 95% was the first sclerosing agent used, however, due to its severe complications; EO 5% became the main sclerosing agent. [12]

BLM is a cytotoxic and anti-neoplastic antibiotic that has been used as a chemotherapeutic drug to treat various malignancies. Recently, BLM has been introduced as sclerosing agent to treat vascular malformations. [13, 14]

Numerous articles in the literature have evaluated the effectiveness of EO alone or BLM alone or compared each with ethanol. To the best of author's knowledge, the present study was the first of its kind in the field of maxillofacial surgery to compare between these two sclerosing agents.

Regarding the clinical outcome in this study, the difference between BLM and EO was non-significant. However, BLM required significantly longer treatment duration than EO. BLM required between 2 and 8 months, while, EO required between 1 and 3 months; this significant difference is due to the 4 weeks interval in BLM group and 2 weeks interval in EO group.

Because this study was conducted on maxillofacial VMs, the authors decided to dilute EO 5% in a ratio 1: 4, as recommended by De Carvalho [8] for facial lesions to reduce risk of ulceration\scarring or injury to the facial nerve. However, despite EO was diluted, it was significantly more painful during injection and required more amount local anaesthesia than BLM group.

Patients in BLM group required significantly less local anaesthesia than patients in the EO group. In the BLM group, 11 patients were injected with topical anaesthesia during intralesional injection, only 4 patients had nerve block anaesthesia, parents did not report any post-operative pain and children did not need any analgesics. On the other hand, in EO group, 11 patients required nerve block anaesthesia; and 3 patients had topical anaesthesia and 1\15 patient required GA. The significantly higher amount of local anaesthesia required with EO increases the risk of toxicity, because the maximum recommended dose of local anesthesia is based on the child body weight. **[15]** The significantly higher pain with EO compared to BLM was explained by Duffy et al **[16]** due to the high alkaline pH of EO, which results in pain, inflammation, and ulceration.

Mashaly et al **[17]** in a recent study conducted on 16 patients compared injection of EO alone in 8 patients with injection of EO with lidocaine in oral venous malformations in 8 patients, and documented a significant decrease in post-operative pain reaching an (87.5%) when EO injected with lidocaine local anaesthetic, however, in this study EO was injected in oral lesions only.

In the present study, ulceration and scarring occurred only in 2 patients injected with EO, who had VMs in the lower lip; whereas EO did not cause any ulceration or scarring of intra-oral VMs. This coincide with the study conducted by Zeevi et al [18], who confirmed safety of EO for intra-oral VMs more than in facial VMs because oral mucosa has higher vascularity and more growth factors than the skin; which reduce the destructive effect of alkaline EO and enhance faster tissue healing.

Although according to available studies in literature suggest that EO can be used safely in case of intralesional injections below its safe dose of 0.5ml/kg; the manufacturer [Glaxo Pharmaceuticals] had reported anaphylactic shock in 3 patients after EO injection of varicose veins, with a dose less than 0.5 ml/kg. , this fatal complication of EO must be considered during intralesional injections of VMs; and it is managed by intra-muscular injection of Epinephrine (00.25 mg for pediatrics & 0.5 mg for adults of 1:10,000 Epinephrine) into Vastus Lateralis muscle of thigh; Epinephrine should not injected IV; as it can stimulate the myocardium and can cause ventricular fibrillation. **[19]**

In the BLM group, all children did not feel pain during or after intralesional injections and there was no elevation of body temperature. These clinical findings confirm results of Mack et al [20] study, who confirmed that the principle advantage of BLM as a sclerosing agent is its reduced inflammatory response and it does not cause nerve injury, or ulceration; moreover, it can be injected without need for general anaesthesia. Sindel et al [21] recommended BLM for vascular malformations in areas related to eyes, facial nerve, and oropharyngeal airway (tongue and oro-pharynx), which makes it safe for facial VMs.

Regarding mechanism of action of both sclerosing agents, EO induces vascular endothelial inflammation and thrombosis [22], whereas, BLM induces breakage of DNA strands of cells and promoting fibrosis of vascular malformations. [23]

An observation that worth mentioning that in this study all parents of participating children were asking many doctors of different specialties and exploring Google search engine and social media for data about different sclerosing agents, and insisted to know the sclerosing agent being injected in their child. Parents were worried that BLM is a chemotherapeutic agent; asking whether this vascular lesions is cancer. This observation has been confirmed by Gibson et al, [24] who emphasized that there are key differences between adult and pediatric patients during treatment of vascular anomalies; because parents have concerns if there is any harmful effect of the sclerosing agent on their child physical growth and mental development. Therefore, explaining the pathologic nature of vascular anomalies and all treatment options to the families and children in a simple language, and the need for their repeated interventions is very important to ensure their compliance throughout treatment.

Finally, the difficulty of randomization when comparing BLM and EO sclerosing agents in pediatric population has to be mentioned; because after ulceration and scarring in 2 patients; for ethical reasons the operator has decided that EO should not be injected into VMs in vulnerable anatomical sites because of its potential destructive effect on tissues and nerves. In other words, the 30 patients were divided into two equal groups but not randomly to avoid functional and esthetic harm to children for ethical reasons.

The main drawback of this study was the small sample size and follow up period of 12 months only. There is still uncertainty regarding the future recurrence of these vascular lesions, which is expected when children grow up due to angiogenesis by hormonal effect during puberty. Parents were informed that there is possibility of recurrence in the future when their child reaches approach puberty and were instructed to recall if there is recurrence after 12 months. Studies of larger populations and follow-up of 5 years are recommended.

Conclusion

Despite the limitation of this study, Bleomycin is safer sclerosing agent than EO as for maxillofacial VMs; BLM can be injected with topical anaesthesia, causes less post-operative pain and swelling, and no risk of ulceration or scarring in the face. EO is effective and safe sclerosing agent for intra-oral VMs and should be performed under GA to avoid the risk of local anaesthesia systemic toxicity. However, BLM requires longer treatment duration than EO.

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Conflicts of Interest: The authors undersign, certificate that they do not have any financial or personal relationships that might bias the content of this work

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