IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 20, Issue 7 Ser.8 (July. 2021), PP 55-67
www.iosrjournals.org

Comparative Study between Bleomycin and Ethanol-amine Oleate Sclerotherapy in Management of Pediatric Maxillofacial Venous Malformations: A Randomized Clinical Trial

Sarah Arafat [1], Abdelbadia Abdallah Abdelmabood [2], Wesam Mohamed[3], Gamal El-Tagy [4], Amr El-Swify [5]

[1] *(Assistant Lecturer, Oral and maxillofacial Surgery Department, Faculty of Dentistry / Misr University for Science and Technology, Egypt)*

[2] *(Associate Professor, Oral and Maxillofacial Surgery Department, Faculty of Dental Medicine /Al-Zagazig University, Al-Zagazig, Egypt)*

[3] *(Associate Professor, Pediatric Surgery Department, Cairo University Specialized Pediatric Hospital (CUSPH), Faculty of Medicine / Cairo University, Cairo, Egypt)*

[4] *(Professor, Pediatric Surgery Department, Cairo University Specialized Pediatric Hospital (CUSPH), Faculty of Medicine / Cairo University, Cairo, Egypt)*

[5] *(Professor, Oral and Maxillofacial Surgery Department, Faculty of Dentistry / Suez Canal University, Ismailia, Egypt)*

Abstract:
Background*: Venous malformations in the maxillofacial region cause multiple functional and esthetic problems in pediatric patients. Intralesional sclerotherapy is their mail line of treatment; many sclerosing agents are available with various advantages and disadvantages. Many studies compared Ethanol-amine Oleate or Bleomycin with ethanol, or with other sclerosing agents. The present study compares between Bleomycin and Ethanolamine Oleate sclerotherapy of pediatric maxillofacial venous formations to decide which can achieve better therapeutic results.*
Materials and Methods*: 30 pediatric patients, of both sexes, having maxillofacial venous malformations; were randomly divided into 2 equal groups of 15 patients. Group I was treated with Bleomycin at 4 weeks interval, and group II was treated with Ethanol-amine Oleate, at 2 weeks interval. All cases were injected by the same operator, and the 2 groups were compared over 12 months.*
Results*: Bleomycin group I: Clinical response: complete response in 12\15 patients, marked improvement in 3\15 patients. The treatment duration ranged from 2 to 8 months. Ethanol-amine Oleate group II: Clinical response: complete response in 7\15 patients, marked improvement in 4\15 patients, moderate improvement in 3\15 patients, and no response in 1\15 patient. The treatment duration ranged from 1 to 3 months. All Patients suffered post-operative pain, swelling and mild elevation of body temperature, 2 patients had ulceration and scarring. The difference between the 2 groups was non-significant in clinical response, post-operative swelling, ulceration, scarring, and recurrence was non-significant. Bleomycin had significantly less local anaesthesia and less post-operative pain, but it required significantly longer treatment duration than Ethanol-amine Oleate.*
Conclusion: *Bleomycin is better tolerated by maxillofacial tissues and has lower complications than Ethanol-amine Oleate; however, Bleomycin requires more treatment time. Ethanol-amine Oleate should be limited to intra-oral VMs, and should be performed with GA to avoid the risk of local anesthesia toxicity.*
Key Word*: Bleomycin, Ethanolamine Oleate, Sclerotherapy, Pediatric, Maxillofacial, Venous Malformations*

Date of Submission: 02-07-2021 Date of Acceptance: 16-07-2021

I. Introduction

Vascular malformations are congenital localized defects of blood or lymphatic vessels. [1] Venous malformations (VMs) are the most common type of vascular malformations. [2]

Sclerotherapy is the main treatment line of 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 were conducted on EO alone, or BLM alone, comparing each-one with ethanol or with other sclerosing agents, but, no study compared between these two sclerosing agents. This prospective study compares BLM and EO sclerotherapy in management of maxillofacial VMs in Egyptian pediatric patients, in order to decide which sclerosing agent can achieve better therapeutic results.

II. Material And Methods

This prospective study was approved by the Research Ethics Committee (No. 157 /2018) in Suez Canal University in Egypt. Informed written consents were obtained from all parents of children to participate in this research. Verbal consents were obtained for publication of this research. Confidentiality of data was confirmed that patient's names and personal data will never be mentioned.

Study Design: Prospective Study (Randomized Clinical Trial)

Study Location: Faculty of Dentistry, Suez Canal University, Egypt

Sample size: 30 patients, based on Bajpai and Bajpai [4] study; total sample size = 26 patients + 4 (10% to compensate for drop outs) = 30 patients; which were randomly divided into 2 equal groups: group I treated by BLM and group II treated by EO.

Subjects & selection method: The study population was selected from pediatric patients in vascular anomalies clinic of pediatric surgery department in Cairo University Specialized Pediatric Hospital (Abu EL-Reesh hospital), in Egypt.

Inclusion criteria:

1. Age up to 12 years
2. Both sexes
3. Patients with maxillofacial venous malformations

Exclusion criteria:

1. lung, liver and\or kidney disease
2. Klippel-Trenaunay syndrome
3. Physical or mental disabilities

Pre-operative Assessment:

Medical History included previous medications and allergies. The diagnosis was established as VMs by taking clinical examination, ultrasonography (USG), and Magnetic resonance imaging (MRI). Colored photographs were taken with a standardized digital camera (Samsung camera resolution 5312 x 2988, pixel resolution 2560 x 1440, and pixel size 1.12 µm) on first visit, throughout treatment and after treatment. Demographic data for each patient was documented in the patient file and in the follow-up card; including: name, sex, date of birth, address, telephone number, and clinical data of the lesion including; anatomical site and size, sclerosing agent, dose according to child weight and timing of each injection, clinical response, and complications.

Sclerotherapy Procedure

Vital signs were checked before sclerotherapy on each session. The procedure was postponed in case of fever, recent immunization, coughing, signs of central cyanosis, local infection or ulceration [5] Body weight of each patient and vascular lesion size were measured to determine the dose to be injected. Expiry date of the sclerosing agent was checked. The required dose was calculated according to each patient weight and lesion size on each visit.

Topical Anaesthesia was applied 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 lesions related to the airway and for uncooperative patients.

All procedures were done by the same operator under complete aseptic conditions. **Fig. 1** The syringe needle was inserted 2-3 mm beyond the vascular lesion to avoid bleeding, then, it was moved within the lesion in different directions to distribute the sclerosing agent homogenously. Sclerotherapy was done on 4 weeks interval for BLM and 2 weeks interval for EO. Intralesional injections were performed according to each lesion response to treatment, until no more intervention was needed.

Group I:

Bleomycin is available from its manufacturer in 15 IU vials (Bleocel®, CELON Labs, Ltd, India). BLM was freshly prepared; 15 mg powdered BLM was dissolved in 15 ml of normal saline (each 1 IU BLM becomes equivalent to 1mg/ml BLM). **Fig. 2** The safe pediatric dose is 0.5 IU\kg; the maximum dose is 15 IU\session, and intralesional sclerotherapy was performed at 4 weeks interval. [7]

Group II:

Ethanol-amine Oleate 5% is available from its manufacturer in 5 mL ampules (Ethanolamine Oleate, EPICO, Egypt). EO was diluted with sterile normal saline 0.9 %, in a ratio 1:4; 1mL of EO 5% diluted in 4 mL saline (each 1 mL of the EO 5% ampule becomes 1.25% concentration). **Fig. 3** The safe dose of EO is 0.4 mL /Kg

body weight; and the maximum dose is 20 mL\session, and intralesional sclerotherapy was performed at 2 weeks interval. [8]

Post-operative Phase

Paracetamol 100 mg/ml as 250 mg/5ml as CETAL® suspension (EPICO, Egypt), prescribed for 1-3 days, and B.B.C® mouth and throat topical spray (AMOUN, Egypt) prescribed 1-2 applications. Parents were instructed to apply cold fomentations on the first day after intralesional injection. Colored photographs, MRI were obtained after the last intralesional injection to evaluate each lesion response to treatment.

Clinical response by **Sainsbury et al** [9] was categorized as: complete response (complete disappearance > 90% reduction of vascular lesion), marked improvement (>70% reduction of vascular lesion), moderate improvement (40 – 70% reduction of vascular lesion), slight improvement (< 40% reduction of vascular lesion), and no response (< 10% reduction of vascular lesion). [9]

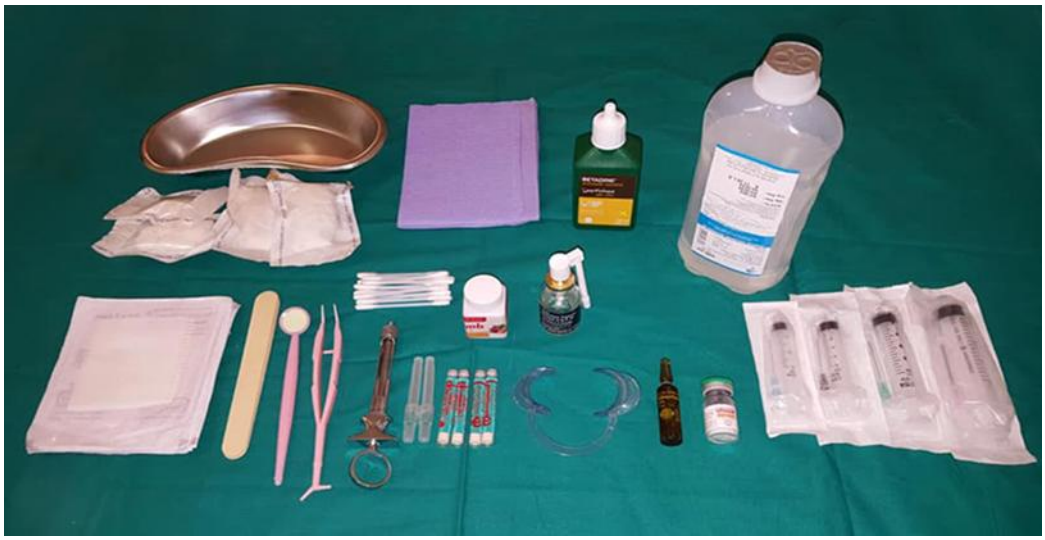


Fig. 1: Armamentarium used in the procedure

Fig. 2: BLM Sclerotherapy Procedure

Fig. 3: EO Sclerotherapy Procedure

III. Results

Group I: BLM

Fifteen patients were included in this group, 8 males and 7 females, their mean age was 5.1 years (age range: 2-months to 11-years old).

Regarding anaesthesia, 11 patients (73.3%) had sclerotherapy under topical local anaesthesia, and 4 patients (26.7%) had regional local anaesthesia. Regarding complications: there was no ulceration in any patient. There was no weight loss or alopecia (hair loss) throughout the follow up time in any patient. Recurrence occurred only in 2 patients (13.3%). Parents of the 15 patients (100%) reported post-operative swelling and lasted for 3-5 days, but they did not report any post-operative pain or elevation of body temperature.

The mean treatment duration was 6.3 months (range: 2 – 8). Patients required between 2 and 8 sessions; at 4 weeks interval; 6 patients required 8 sessions (8 months), 6 patients required 6 sessions (6 months), and 2 patients required 4 sessions (4 months), and 1 patient required 2 sessions (2 months)

Regarding clinical response, 12 patients (80%) had complete response, and 3 patients (20%) had marked improvement. **Fig. 4** shows BLM sclerotherapy VM in the tongue of a 10 years old girl, and **Fig. 5** shows VM in the left side of lower Lip in an 8 years old boy. **Table 1** shows demographics & clinical response of BLM.

Group II: EO

Fifteen patients in this group included 7 males and 8 females, the mean age was 6.1 years (age range: 8-months to 11-years old)

Regarding anaesthesia, only 3 patients (20%) had topical anaesthesia, 11 patients (73.3%) had regional anaesthesia, and one patient (6.7%) required GA; the lesion was in the parapharyngeal region and the child age was 3 years old. Regarding clinical response, 7 patients (46.7%) had complete response, 4 patients (26.7%) showed marked improvement, 3 patients (20%) showed moderate improvement, and 1 patient (6.7%) showed no response. **Fig.6** shows EO sclerotherapy of VM in the tongue in a 5 years old boy, and **Fig. 7** shows VM in VM in the lower Lip in a 2 years old girl. **Table 2** shows Demographics and Clinical Response of EO.

Regarding complications: ulceration and scarring occurred in 2 cases (13.3%) in the lower lip. Fig.9-B, C Recurrence occurred in 3 cases (20%). Parents of the 15 patients (100%) reported post-operative swelling on the 1st day and lasted for 3-5 days. In addition, all parents reported post-operative pain, and mild elevation of body temperature on the 1st day. This was managed by Paracetamol analgesic and antipyretic

Regarding treatment sessions and duration; the mean treatment duration was 2.1 months (range: 1 – 3). Patients required between 1 and 6 sessions; at 2 weeks interval; 6 patients required 6 sessions (3 months), 4 patients required 4 sessions (2 months), and 5 patients required 2 sessions (1 month).

Statistical Analysis:

Data were analyzed using IBM® SPSS® Statistics 20 and Microsoft® Excel® 2013 (15.0.4420.1017) 32-bit software. Comparisons between groups for categorical variables were assessed using Chi-square test (Fisher's exact test). Mann Whitney test was used to compare between two groups for not normally distributed quantitative variables. The obtained results were judged at 5% level of significance. There was no dropout.

Table 3 and **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.

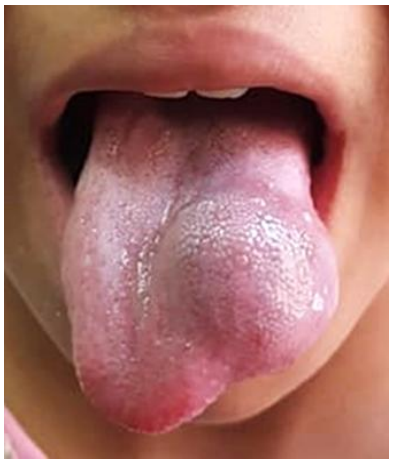


Fig. 4-A: VM in Lt side of tongue in middle third in a 10 years old girl

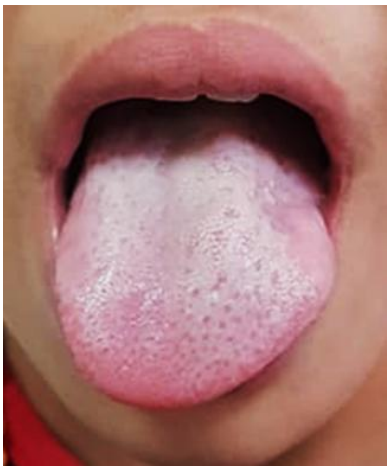


Fig. 4-B: complete response after 4 intralesional BLM injections

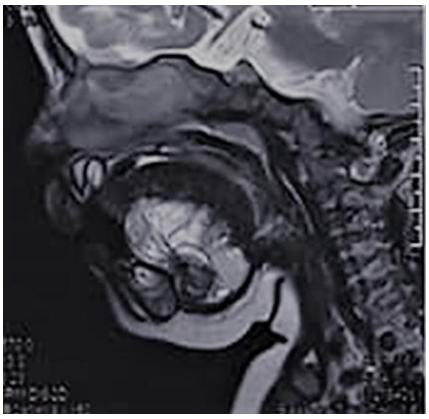


Fig. 4-C: MRI sagittal cut showing VM in middle third of the tongue

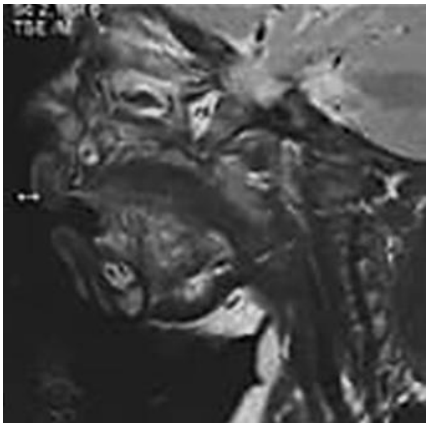


Fig. 4-D: MRI sagittal cut after 4 intralesional BLM injections

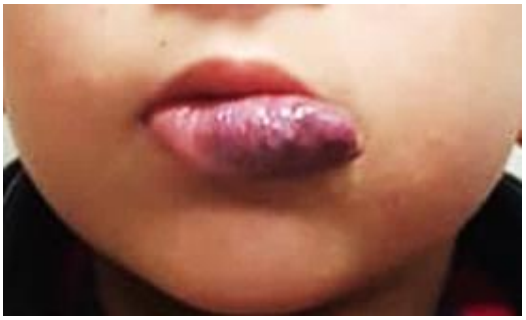


Fig. 5-A: VM in Lt side of Lower Lip in an 8 years old boy

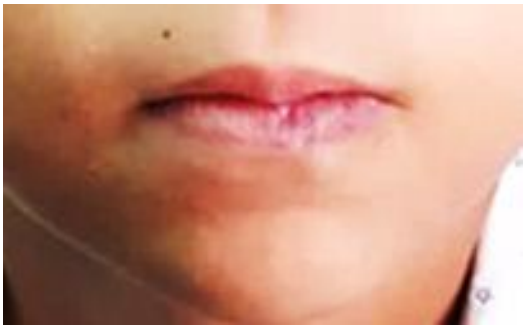


Fig. 5-B: complete response after 8 BLM intralesional injections

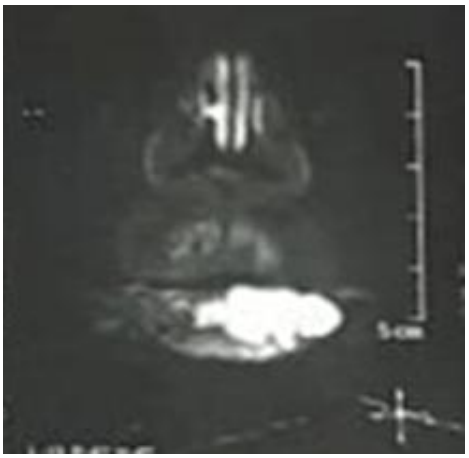


Fig. 5-C: MRI coronal cut showing ill-defined VM in lower lip

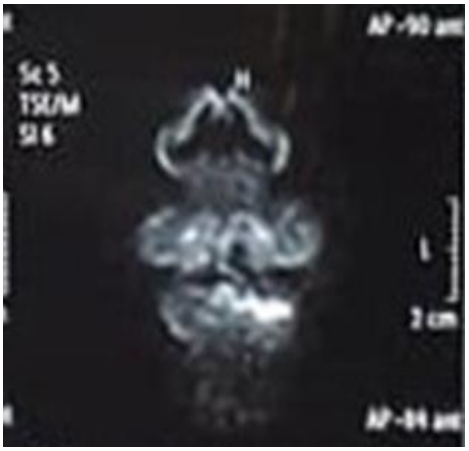


Fig. 5-D: MRI coronal cut after 8 BLM injections

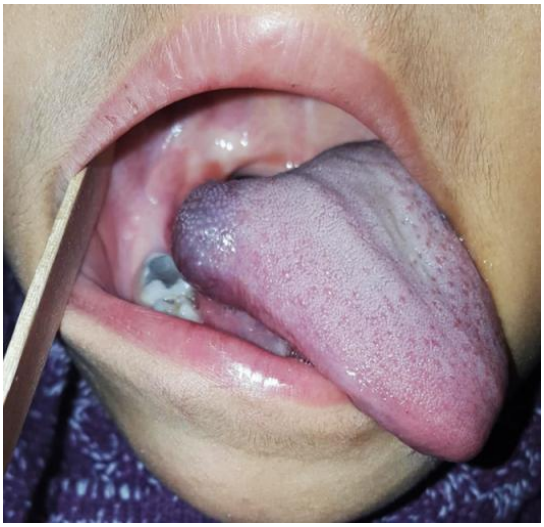


Fig. 6-A: VM in Rt side of posterior third of tongue in a 5 years old boy

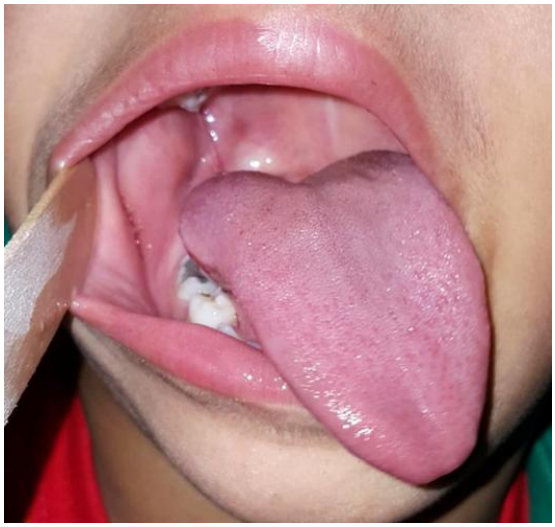


Fig. 6-B: complete resolution after 6 intralesional EO injections

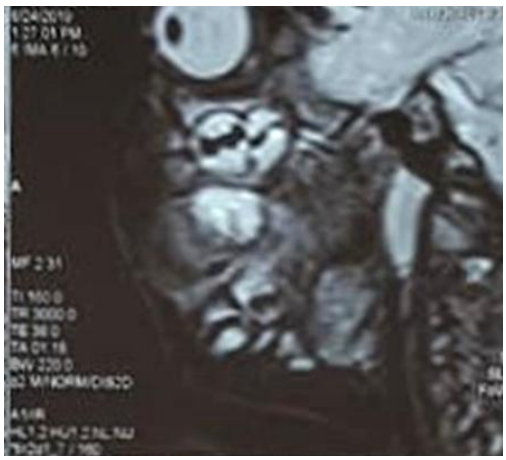


Fig. 6-C: sagittal MRI cut showing VM in Rt side of the tongue

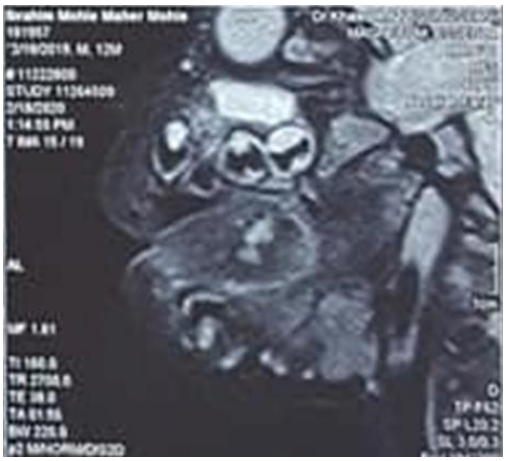


Fig. 6-D: sagittal MRI cut after 6 intralesional EO injections

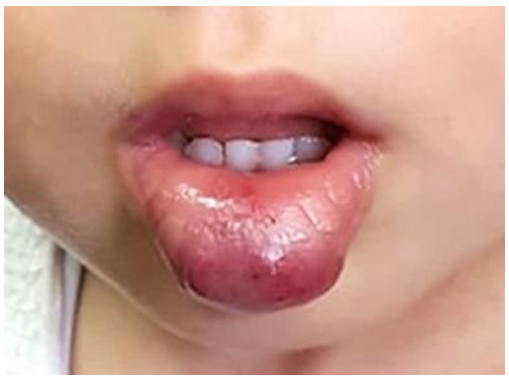


Fig. 7-A: VM in Lower Lip in a 2 years old girl

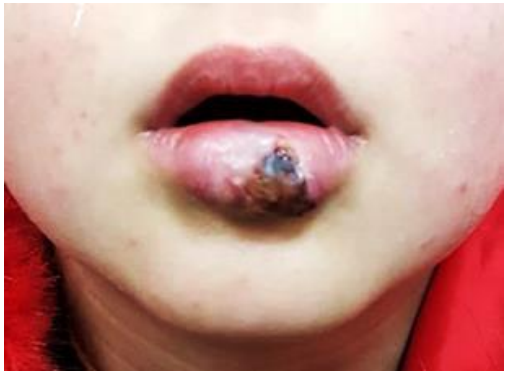


Fig. 7-B: VM in Lower Lip in a 2 years old girl

Fig. 7-C: Healing with atrophic scarring after 2nd EO injection

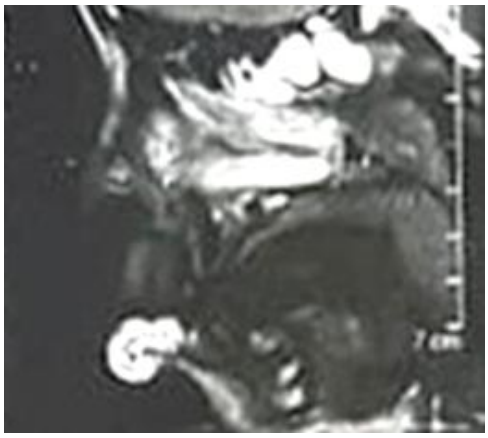


Fig. 7-D: MRI sagittal cut showing VM in the lower lip

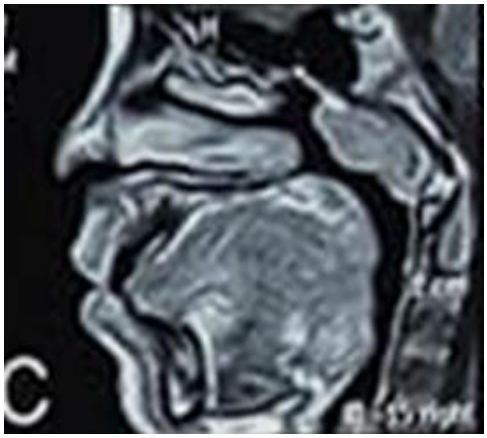


Fig. 7-E: MRI sagittal cut after 2 EO intralesional injections

Table 1: Demographics & Clinical Response of BLM Group

Case No	Site	Age	Sex	Size (cm)	Anaesthesia	No of Sessions	Treatment Duration	Clinical Outcome
1	Tongue	10 yrs	M	3.3 × 2.2 × 1.3	Nerve Block	8	8 m	Complete
2	Rt Cheek	11yrs	M	4.1 × 4.7 × 2.3	Topical	6	6 m	Complete
3	Lt Cheek	1 yr	F	4.8 × 3.2 × 4.6	Topical	8	8 m	Complete
4	Rt Cheek	8 m	F	7.5 × 7.3 × 6.8	Topical	8	8 m	Complete
5	Lower Lip	8 yrs	M	2.9 × 1.3× 2	Nerve Block	8	8 m	Complete
6	Upper Lip	9 m	F	1.7 × 1.3 × 1.5	Topical	6	6 m	Marked
7	Lt Temporal	2 m	M	3 × 6.2 × 2	Topical	5	6 m	Complete
8	Rt Temporal	4 m	M	3.7 × 3 × 1.2	Topical	8	8 m	Complete

9	Lower Lip	8 yrs	F	5.4 × 3.4 × 2.4	Topical	6	6 m	Marked
10	Rt Para-pharyngeal	8 yrs	F	2.4 × 2.2 × 1.4	Topical	4	4 m	Marked
11	Rt Cheek	4 m	F	6 × 4.6 × 2.6	Topical	8	8 m	Complete
12	Lt Cheek	3 yrs	M	10.4 × 7.4 × 4.3	Nerve Block	6	6 m	Complete
13	Tongue	10 yrs	F	7.8 × 8.4 × 5.7	Nerve Block	4	4 m	Complete
14	Chin	7 yrs	M	1.8 × 7.2 × 3.1	Topical	3	6 m	Complete
15	Rt side of Nose	8 yrs	M	4 × 2.6 × 2	Topical	2	2 m	Complete
Abbreviations (Lt) left, (Rt) right, (m) months, (yrs) years, (M) male, (F) female, (cm) centimeter								

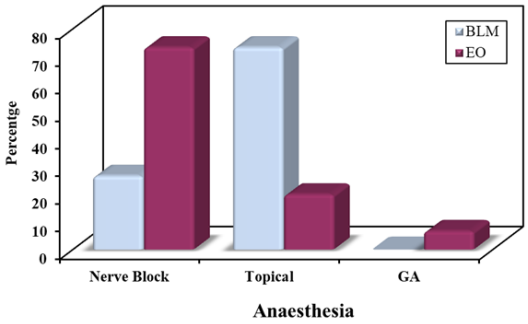
Table 2: Demographics & Clinical Response of EO Group

Case No.	Site	Age	Sex	Size (cm)	Anaesthesia	No. of Sessions	Treatment Duration	Clinical Outcome
1	Tongue	5 yrs	M	3 × 2 × 1.5	Nerve Block	6	3 m	Complete
2	Lower Lip	4 yrs	M	2.3 × 2 × 1.5	Nerve Block	6	3 m	Complete
3	Lt Cheek	8 yrs	F	2.1 × 1.8 × 2	Nerve Block	2	1 m	Complete
4	Rt Cheek	11yrs	F	1.3 × 1 × 1.8	Nerve Block	4	2 m	Complete
5	Upper Lip	10 yrs	F	4.5 × 1.7 × 2.8	Nerve Block	6	3 m	Marked
6	Lt Cheek	9 yrs	F	4 × 3.4 × 2.4	Nerve Block	4	2 m	Marked
7	Upper Lip	8 m	M	3 × 2 × 2	Nerve Block	6	3 m	Marked
8	Lower Lip	2 yrs	F	9.2 × 2.2 × 1.8	Nerve Block	2	1 m	Marked
9	Upper Lip	10 yrs	F	4.5 × 3.5 × 2.5	Nerve Block	2	1 m	No
10	Tongue	9 m	M	4.3 × 2 × 3.3	Nerve Block	6	3 m	Moderate
11	Rt Post-auricular	7 yrs	M	3 × 1.9 × 1	Topical	2	1 m	Complete
12	Submental	9 yrs	F	4.3 × 2 × 4	Topical	4	2 m	Complete
13	Lt Para-Pharyngeal	3 yrs	M	7.4 × 8.4 × 5.3	General Anaesthesia	6	3 m	Moderate
14	Submental	6 yrs	M	1.8 × 7.2 × 3.1	Topical	2	1 m	Complete
15	Lower Lip	5 yrs	F	0.7 × 2 × 1	Nerve Block	4	2 m	Moderate
Abbreviations (Lt) left, (Rt) right, (m) months, (yrs) years, (M) male, (F) female, (cm) centimeter								

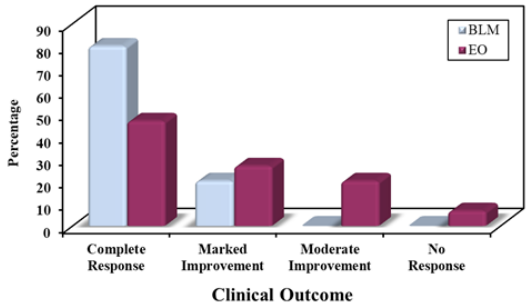
Table 3: Comparison according to different Parameters & Complications

	BLM (n = 15)	**EO (n = 15)**	**Test of Sig.**	**p**
Sex				
Male	8 (53.3%)	7 (46.7%)	$\chi2$= 0.133	0.715 NS
Female	7 (46.7%)	8 (53.3%)		
Age (years)				
Mean ± SD.	5.1 ± 4.2	6.2 ± 3.7	U= 90.50	0.367 NS
Median (Min. – Max.)	7 (0.16 – 11)	6 (0.66 – 11)		
Size (max. dim.) (cm)				
Mean ± SD.	5.2 ± 2.4	4.4 ± 2.6	U= 82.50	0.217 NS
Median (Min. – Max.)	4.7 (1.7 – 10.4)	4 (1.8 – 10.4)		
Size (volume)(cm3)				
Mean ± SD.	96.4 ± 137.8	40.9 ± 81.4	U= 72.0	0.098 NS
Median (Min. – Max.)	40.2 (3.3 – 373.5)	21.4 (1.4 – 330.9)		
Anesthesia				
Nerve Block	4 (26.7%)	11 (73.3%)	$\chi2$= 8.638	MCp= 0.011* S
Topical	11 (73.3%)	3 (20%)		
GA	0 (0%)	1 (6.7%)		
No. of Sessions				
Mean ± SD.	5.9 ± 2.1	4.1 ± 1.8	U= 58.50*	0.023* S
Median (Min. – Max.)	6 (2 – 8)	4 (2 – 6)		
Treatment Duration				
Mean ± SD.	6.3 ± 1.8	2.1 ± 0.88	U= 8.0*	<0.001* S
Median (Min. – Max.)	6 (2 – 8)	2 (1 – 3)		
	6 cases = 8 months 6 cases = 6 months 2 cases = 4 months 1 cases = 2 months	6 cases = 3 months 4 cases = 2 months 5 cases = 1 month		
Treatment Outcome				
Complete Response	12 (80%)	7 (46.7%)	$\chi2$=3.589	0.058 NS
Marked Improvement	3 (20%)	4 (26.7%)	$\chi2$=0.186	FEp=1.000 NS
Moderate Improvement	0 (0%)	3 (20%)	$\chi2$=3.333	FEp=0.224 NS
No Response	0 (0%)	1 (6.7%)	$\chi2$=1.034	FEp=1.000 NS
Complications				
Ulceration & Scarring	0 (0%)	2 (13.3%)	$\chi2$=2.143	FEp=0.483 NS
Recurrence	2 (13.3%)	3 (20%)	$\chi2$=0.240	FEp=1.000 NS
Post-op Pain	0 (0%)	15 (100%)	$\chi2$=30.0*	<0.001* S
Post-op Swelling	15 (100%)	15 (100%)	–	–
Post-op Elevation of Temp	0 (0%)	15 (100%)	$\chi2$=30.0*	<0.001* S

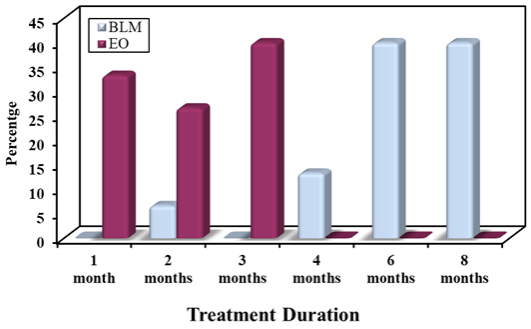
χ2: Chi square test, MC: Monte Carlo, FE: Fisher Exact, U: Mann Whitney test
p: p value for comparing between the studied groups
NS: Non significant, S: Significant



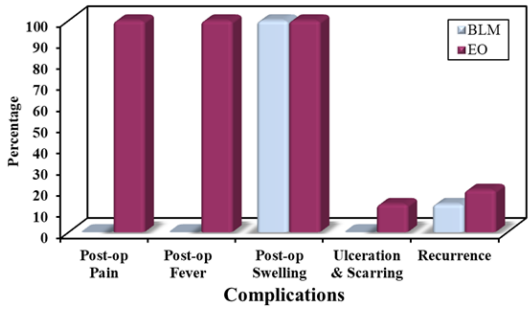
Graph 1
Comparison according to Anesthesia



Graph 2
Comparison according to Clinical outcome



Graph 3
Comparison according to Treatment Duration



Graph 4
Comparison according to Complications

IV. Discussion

Classical surgical excision of VMs is not recommended as a treatment option, due the high risk of intra-operative life-threatening hemorrhage, and injuring important structures in the face, resulting in functional and cosmetic complications. Currently, Sclerotherapy is the gold standard treatment of VMs; various sclerosing agents are mentioned in the literature; with different 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]

Effectiveness and safety of each sclerosing agent, vascular lesion type, size and its anatomical site, and patient age remain the deciding factors in selection of the proper sclerosing agent.[11] After ethanol 95% was discouraged due to its severe complications, EO 5% became the main sclerosing agent used for treatment of VMs, in addition to its low cost compared to other sclerosing agents. [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]

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, we decided to dilute EO 5% in a ratio 1: 4, as recommended by **De Carvalho** [8] for facial vascular malformations to reduce the risk of injury to the facial nerve, ulceration, and scarring. However, despite EO was diluted, it was significantly more painful during injection and required more local anaesthesia than BLM. Patients in BLM group required significantly less local anaesthesia than patients in the EO group. In the BLM group, only 4\15 patients had nerve block anaesthesia, and 11\15 patients had topical anaesthesia only during intralesional injection. On the other hand, in EO group, 11\15 patients required nerve block anaesthesia; and 3\15 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.

In the present study, ulceration and scarring did not occur with BLM, but occurred in only in 2 cases treated by EO, who had VMs in the lower lip. EO did not cause ulceration or scarring of intra-oral VMs. This confirms the findings in the study conducted by **Zeevi et al** [17], who explained the greater safety of EO for intra-

oral vascular malformations than in the facial skin and lip tissue, due to the higher vascularity of the oral mucosa that reduce the harmful effect of EO and promote quicker healing.

In the BLM group, all patients did not feel pain during or after intralesional injections and there was no elevation of body temperature. These clinical findings are in accordance with **Mack et al** [18], who confirmed that the main benefit of BLM over other sclerosing agents is its reduced inflammatory response. Similarly, Helal and **Mahmoud et al** [19] in their study concluded that BLM injections can be done without GA, and it does not result in ulceration, or nerve injury, making it especially recommended for facial VMs.

Also, **Sindel et al** [20] recommended BLM for sclerotherapy of vascular malformations in vulnerable areas related to facial nerve, eyes, and airway (tongue and oro-pharynx).

The greater complications of EO can be explained as EO acts by inducing endothelial injury and thrombosis [21], on the other hand, BLM works by inducing of breakage of DNA strands of cells and promoting sclerosis and fibrosis of vascular malformations. [22]

V. Conclusion

Bleomycin is recommended over EO for sclerotherapy of maxillofacial VMs; BLM is better tolerated by oro-facial tissues; no pain during injection, less need for anaesthesia, less risk of local anaesthesia toxicity, less post-operative pain and swelling, and no risk of ulceration or scarring. EO sclerotherapy achieves faster results, but, it should be limited to intra-oral VMs to avoid local tissue injury and performed under GA to avoid the risk of local anaesthesia toxicity. However, BLM requires more treatment time and it is more expensive than EO.

Declaration

This research is included in the PhD thesis of the first author (Sarah Arafat), in Oral and Maxillofacial Surgery Department, Faculty of Dentistry, Suez Canal University in Egypt, entitled "Comparative Study between Bleomycin and Ethanol-amine Oleate Sclerotherapy in Management of Pediatric Maxillofacial Low Flow Vascular Malformations: A Randomized Clinical Trial"

Operator: Sarah Arafat

Funding: No funding

Conflicts of Interest: The authors declare that they have no conflict of interest

References

[1]. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. Plast Reconstr Surg. 1982 Mar; 69(3):412-22. doi: 10.1097/00006534-198203000-00002. PMID: 7063565.

[2]. Kaban LB, Mulliken JB. Vascular anomalies of the maxillofacial region. J Oral Maxillofac Surg. 1986 Mar; 44(3):203-13. doi: 10.1016/0278-2391(86)90109-6. PMID: 3456442.

[3]. Horbach SE, Lokhorst MM, Saeed P, de Goüyon Matignon de Pontouraude CM, Rothová A, van der Horst CM. Sclerotherapy for low-flow vascular malformations of the head and neck: A systematic review of sclerosing agents. J Plast Reconstr Aesthet Surg. 2016 Mar; 69(3):295-304. doi: 10.1016/j.bjps.2015.10.045. Epub 2015 Nov 18. PMID: 26723834.

[4]. Bajpai H, Bajpai S. Comparative analysis of intralesional sclerotherapy with sodium tetradecyl sulfate versus bleomycin in the management of low flow craniofacial soft tissue vascular lesions. J Maxillofac Oral Surg. 2012 Mar; 11(1):13-20. doi: 10.1007/s12663-011-0325-7. Epub 2011 Dec 28. PMID: 23449774; PMCID: PMC3319813.

[5]. Rabe E, Breu FX, Cavezzi A, Coleridge Smith P, Frullini A, Gillet JL, Guex JJ, Hamel-Desnos C, Kern P, Partsch B, Ramelet AA, Tessari L, Pannier F; Guideline Group. European guidelines for sclerotherapy in chronic venous disorders. Phlebology. 2014 Jul; 29(6):338-54. doi: 10.1177/0268355513483280. Epub 2013 May 3. PMID: 23559590.

[6]. Orlando JL, Caldas JG, Campos HG, Nishinari K, Wolosker N. Outpatient percutaneous treatment of deep venous malformations using pure ethanol at low doses under local anesthesia. Clinics (Sao Paulo). 2010; 65(9):837-40. doi: 10.1590/s1807-59322010000900004. PMID: 21049209; PMCID: PMC2954733.

[7]. Mohan AT, Adams S, Adams K, Hudson DA. Intralesional bleomycin injection in management of low flow vascular malformations in children. J Plast Surg Hand Surg. 2015 Apr; 49(2):116-20. doi: 10.3109/2000656X.2014.951051. Epub 2014 Sep 10. PMID: 25204206.

[8]. De Carvalho MF, Kaline N, Duailibi E. et al. Extensive arteriovenous malformation in the face of a pediatric patient – Case report. Rev Port Estomatol Med Dent Cir Maxilofac. 2014; 55 (4): 250 – 255

[9]. Sainsbury DCG, Kessell G, Fall AJ, Hampton FJ, Guhan A, Muir T. Intralesional bleomycin injection treatment for vascular birthmarks: a 5-year experience at a single United Kingdom unit. Plast Reconstr Surg. 2011 May; 127(5):2031-2044. doi: 10.1097/PRS.0b013e31820e923c. PMID: 21532430.

[10]. Fowell C, Verea Linares C, Jones R, Nishikawa H, Monaghan A. Venous malformations of the head and neck: current concepts in management. Br J Oral Maxillofac Surg. 2017 Jan; 55(1):3-9. doi: 10.1016/j.bjoms.2016.10.023. Epub 2016 Nov 25. PMID: 27894790.

[11]. Zheng JW, Mai HM, Zhang L, Wang YA, Fan XD, Su LX, Qin ZP, Yang YW, Jiang YH, Zhao YF, Suen JY. Guidelines for the treatment of head and neck venous malformations. Int J Clin Exp Med. 2013 May 22; 6(5):377-89. PMID: 23724158; PMCID: PMC3664006.

[12]. Kaji N, Kurita M, Ozaki M, Takushima A, Harii K, Narushima M, Wakita S. Experience of sclerotherapy and embolosclerotherapy using ethanolamine oleate for vascular malformations of the head and neck. Scand J Plast Reconstr Surg Hand Surg. 2009; 43(3):126-36. doi: 10.1080/02844310902840296. PMID: 19401940.

[13]. Kong J, Yi L, Xiong Y, Huang Y, Yang D, Yan X, Shen B, Duan Y, Zhu X. The discovery and development of microbial bleomycin analogues. Appl Microbiol Biotechnol. 2018 Aug; 102(16):6791-6798. doi: 10.1007/s00253-018-9129-8. Epub 2018 Jun 6. PMID: 29876605.
[14]. Muir T, Kirsten M, Fourie P, Dippenaar N, Ionescu GO. Intralesional bleomycin injection (IBI) treatment for haemangiomas and congenital vascular malformations. Pediatr Surg Int. 2004 Jan; 19(12):766-73. doi: 10.1007/s00383-003-1058-6. Epub 2004 Jan 22. PMID: 14740248.
[15]. Chin KL, Yagiela JA, Quinn CL, Henderson KR, Duperon DF. Serum mepivacaine concentrations after intraoral injection in young children. J Calif Dent Assoc. 2003 Oct; 31(10):757-64. PMID: 14626871.
[16]. Duffy DM. Ethanolamine oleate: a dangerous and outmoded sclerosant. Dermatol Surg. 2011 Mar; 37(3):402. doi: 10.1111/j.1524-4725.2011.01897.x. PMID: 21410823.
[17]. Zeevi I, Chaushu G, Alterman M, Chaushu L. Sclerotherapy of Vascular Malformations in the Oral Cavity-Minimizing Postoperative Morbidity. Medicina (Kaunas). 2020 May 22; 56(5):254. doi: 10.3390/medicina56050254. PMID: 32456057; PMCID: PMC7279465.
[18]. Mack JM, Richter GT, Becton D, Salem O, Hill SEM, Crary SE. Short-term side effects and patient-reported outcomes of bleomycin sclerotherapy in vascular malformations. Pediatr Blood Cancer. 2018 Jun; 65(6):e27008. doi: 10.1002/pbc.27008. Epub 2018 Feb 12. PMID: 29431255.
[19]. Helal HA, Mahmoud NA. Effect of foam and liquid bleomycin in the management of venous malformations in head and neck region: A comparative study. J Plast Reconstr Aesthet Surg. 2020 Jan; 73(1):90-97. doi: 10.1016/j.bjps.2019.05.034. Epub 2019 May 22. PMID: 31201109.
[20]. Sindel A, Sayan A, Özgür Ö, Sindel T, Ilankovan V. Percutaneous treatment of orofacial vascular malformations. Br J Oral Maxillofac Surg. 2018 Apr; 56(3):206-211. doi: 10.1016/j.bjoms.2018.01.013. PMID: 29422307.
[21]. Masaki M, Obara K, Suzuki S, Orikasa K, Mitsuhashi H, Iwasaki K, Sakamoto H, Morito T, Kasukawa R. The destructive effects of sclerosant ethanolamine oleate on mammalian vessel endothelium. Gastroenterol Jpn. 1990 Apr; 25(2):230-5. doi: 10.1007/BF02776821. PMID: 2347476.
[22]. López-Larraza D, De Luca JC, Bianchi NO. The kinetics of DNA damage by bleomycin in mammalian cells. Mutat Res. 1990 Sep; 232(1):57-61. doi: 10.1016/0027-5107(90)90110-p. PMID: 1697038.