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Complications of Ethanol-amine Oleate Intralesional Sclerotherapy Injections of Pediatric Maxillofacial Venous Malformations

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

[1] Assistant Lecturer, Oral and maxillofacial Surgery Department, Faculty of Dentistry, Misr University for Science and Technology, Cairo, 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

Correspondence author: Sarah Arafat, MSc, Assistant Lecturer of Oral and Maxillofacial Surgery, Faculty of Dentistry, Misr University for Science and Technology, Egypt. Tel: +201227143700
ORCID 0000-0003-4786-1695
Email: sarah2000arafat@gmail.com

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ABSTRACT

BACKGROUND: Maxillofacial Venous malformations cause many functional and esthetic complications in children, intralesional sclerotherapy is currently their best treatment choice; and Ethanol-amine Oleate is the most commonly used sclerosing agent. **OBJECTIVES**: In this study we focus on the complications of Ethanol-amine Oleate in order to avoid those complications to ensure patient safety. **METHODS:** In this study, 15 pediatric patients, 7 males and 8 females, of age 8 months to 11 years who presented with maxillofacial venous malformation were treated with intralesional injections of Ethanol-amine Oleate 5% diluted with normal saline in a ratio 1:4, at 2 weeks interval. All cases were injected by the same operator, and were followed up over a period of 12 months to assess clinical response and complications. **RESULTS:** Clinical response: 7 patients had complete response, 4 patients showed marked improvement, 3 patients showed moderate improvement, and 1 patient showed no response. The treatment duration range was 1 to 3 months. All Patients experienced post-operative pain; swelling and mild elevation of body temperature, 2 patients had ulceration and scarring in the lower lip. **CONCLUSION:** Ethanol-amine Oleate is a safe sclerosing agent only for intra-oral venous malformations to avoid face and lip tissue ulceration and scarring. In addition, it is better performed under general anesthesia to reduce the high risk of local anesthesia toxicity, and to monitor all vital signs during the procedure.

Keywords: Complications, Ethanolamine Oleate, Intralesional, Sclerotherapy, Pediatric, Maxillofacial, Venous Malformations

INTRODUCTION

Venous malformations (VMs) are congenital lesions formed of abnormally dilated tortuous venous channels lined with normal endothelium. They are the most common form of vascular malformations encountered in clinical practice, and about 40 % of VMs are located in the head and neck (Behravesh et al., 2016). Without treatment, VMs will increase in size throughout life, causing significant esthetic and functional complications. Treatment options for VMs include surgery, sclerotherapy, Laser, or combination therapy for complex cases. Historically, classical surgical excision had been the main treatment; nowadays, surgery is not recommended, because of the life-threatening intra-operative hemorrhage, due to disturbed blood coagulation, caused by stagnation of the venous blood within the VMs, resulting in a continuous intralesional thrombosis and thrombolysis and

consumption of blood platelets and coagulation factors (Dompmartin et al., 2010). Therefore, sclerotherapy had become the first-line treatment for VMs. Many sclerosing agents have been used for facial VMs; such as ethanol 95%, ethanol-amine oleate (EO) 5%, bleomycin (BLM), doxycycline, and 3% sodium tetradecyl sulfate (STS) (Zheng et al., 2013). Ethanol-amine Oleate (EO) 5% is an organic chemical compound formed of Ethanol-amine as a basic substance, with oleic acid and benzyl alcohol 2% as a preservative. It had been used for many years in the treatment of oesophageal varices (Kiripolsky, 2010).

Masaki et al. (1990) conducted their study to understand the pharmacological effect of EO on vascular endothelium in animals. The authors concluded that EO causes an acute inflammatory reaction of the vascular endothelium, leading to sclerosis of blood vessels, and eventually collapse of oesophageal varices or varicose veins. Later, Johann et al. (2005) conducted the first clinical trial to assess the effectiveness of EO sclerotherapy of oral vascular anomalies. The authors reported that all lesions responded with total clinical resolution. In their study, Ribeiro et al. (2018) confirmed the safety and effectiveness **of** EO 5% intralesional injections of VMs in the head and neck. According to the available studies, EO 5% is safe and effective for intralesional sclerotherapy of VMs, because of its availability and reasonable price compared to other sclerosing agents. Furthermore, while Ethanol 95% sclerosing agent causes severe tissue damage if extravasated, EO 5% is a mild sclerosing agent that does not invade tissues deeply; thereby, reducing potential damage to adjacent soft tissues and nerves in the face. The safe dose of EO is 0.4 mL\Kg, and the maximum dose is 20 mL\ session, given at 1 or 2 weeks intervals (Alexander et al., 2014).

This study presents our experience with EO 5% intralesional injections of VMs in Egyptian pediatric patients, focusing on complications in the maxillofacial region since no studies have been conducted on this topic.

I. METHODOLOGY

his prospective study was approved by the Research Ethics Committee (157\2018) at Suez Canal University in Egypt. Informed written consent was obtained from all parents of pediatric patients to participate in this research. Verbal consent was obtained from the parents of each pediatric patient for publication. Confidentiality of data was assured that participants' names and personal data would never be mentioned.

Study Design: Prospective Study

Study Location: Vascular Anomalies Clinic of pediatric surgery department in Cairo University Specialized Pediatric Hospital (Abu EL-Reesh hospital), in Egypt.

Sample size: 15 patients.

Subjects & selection method: The study population was drawn from pediatric patients presented in the Vascular Anomalies Clinic of the pediatric surgery department in Cairo University Specialized Pediatric Hospital (Abu EL-Reesh hospital), in Egypt.

Inclusion criteria:
1. Age < 12 years
2. Both sexes
3. Patients with venous malformations in the maxillofacial region

Exclusion criteria:
1. Liver and\or kidney disease
2. Mental or physical disabilities
3. Klippel-Trenaunay syndrome
4.

PROCEDURE METHODOLOGY

Pre-operative Assessment:

Medical history included previous illness, medications, allergies, and clinical history of the vascular lesion. The diagnosis was established as VMs by history taking, clinical examination, and ultrasonography (USG). Clinical examination included determining anatomical lesion site, color, its proximity or extension to adjacent vital anatomical structures, and palpation to determine sensitivity to compression, pulsation, and lesion size measured with a sterile millimeter ruler **Fig. 1.**

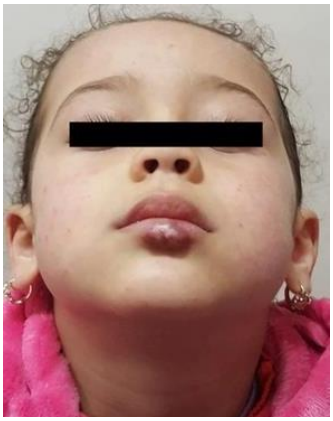

Fig. 1-A: VM in lower lip of a 2-yrs old girl

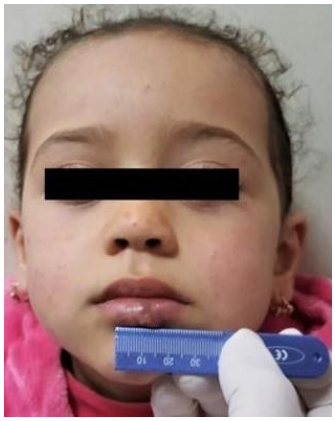

Fig. 1-B: lesion width

Fig. 1-C: lesion height

Lesion size measured with a sterile millimeter ruler

Colored photographs were taken of each patient with a standardized digital camera. Ultrasonography was used to evaluate the vascular lesion size, depth and blood flow to exclude high flow vascular malformations. Fig.2 A standardized set of demographic data for each patient was recorded, including patient name, age, sex, lesion anatomical site and size, a sclerosing agent used, dosage and timing of each session, clinical response, complications, and follow-up visits..

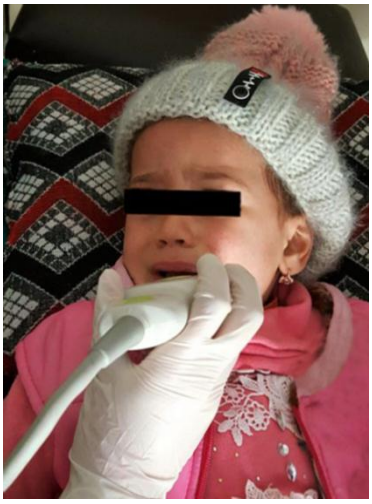

Fig. 2-A: US transducer (probe) on the lower lip of a 2-yrs old girl

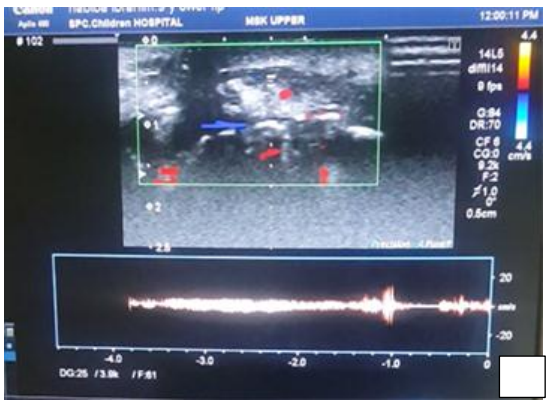

Fig. 2-B: Lesion Vascularity

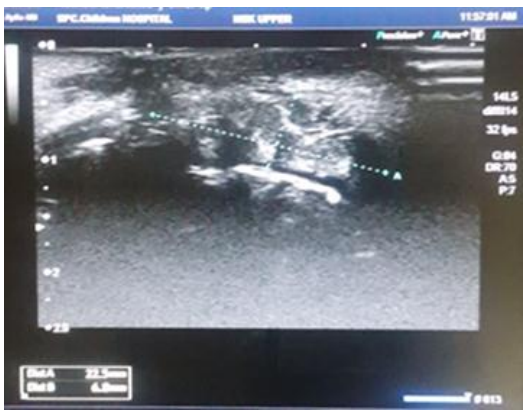

Fig. 2-C: Lesion Size & Depth

Surgical Technique

Patient body weight and lesion size were measured on each session to determine the amount of EO sclerosing agent injected. Each patient's vital signs were checked on each visit; the procedure was postponed in case of signs of central cyanosis, recent immunization, elevated body temperature, coughing, local ulceration, or infection in the vascular lesion (Rabe et al., 2014).

The same operator performed all treatment procedures under aseptic conditions. Topical Anaesthesia was used for superficial lesions, and nerve block local anaesthesia was used for deep lesions, 3% Mepivacaine hydrochloride, without vasoconstrictor (Orlando et al., 2010). General anaesthesia (GA) was used for lesions in inaccessible sites related to the airway and uncooperative pediatric patients. First, induction of GA by Sevoflurane inhalational anaesthetic, then, Atropine (0.01mg\kg) was given to compensate for bradycardia that may occur with inhalational anaesthesia, maintenance of GA by Sevoflurane, and the patient was spontaneously breathing till the end of the procedure.

Ethanol-amine Oleate 5% is available from its manufacturer in 5 mL ampules (EPICO, Egypt), EO 5% was diluted with sterile normal saline, in a ratio 1:4; 1mL of EO 5% was diluted in 4 mL saline. **Fig. 3** The safe dose of EO is 0.4 mL /Kg, and the maximum dose is 20 mL\ session. The required dose was calculated according to each patient body weight and lesion size. Intralesional injections were performed at 2 weeks intervals; the number of sessions was decided according to the clinical response of each lesion (De Carvalho et al., 2014).

Fig. 3-A EO 5% ampules – EPICO

Fig. 3-B: 16 mL normal saline aspirated with 20 mL syringe

Fig.3 -C: 4 mL EO 5% solution mixed with 16 mL normal saline (ratio 1:4)

The syringe needle was inserted 2-3 mm before the vascular lesion to avoid bleeding, then moved in different directions to distribute the sclerosing agent inside the vascular lesion **Fig. 4.**

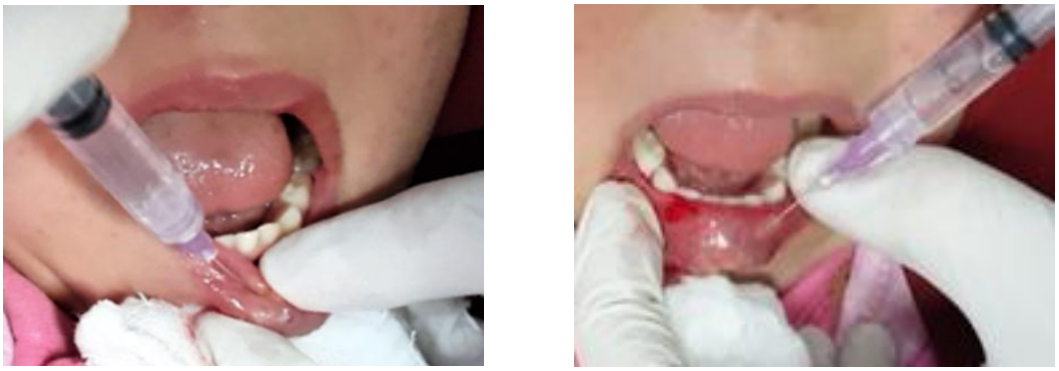

Fig. 4– A **Fig. 4 – B**

Multiple needle punctures from different directions in the lower lip

Post-operative Phase

Paracetamol 100 mg/ml as CETAL® drops for age ≤ 6 years, or 250 mg/5ml as CETAL® suspension (EPICO, Egypt) for age > 6 years, and B.B.C® topical spray (AMOUN Pharmaceutical Co, Egypt) were prescribed for 1-3 days. Parents were instructed to do cold fomentations on the first post-operative day.

Colored photographs and USG were obtained after the last intralesional injection to evaluate each lesion response to treatment. Clinical response of vascular lesion was categorized as recommended by Sainsbury et al (2011): complete response \resolution (complete disappearance > 90% reduction of vascular lesion), marked improvement (>70% reduction), moderate improvement (40 – 70% reduction of vascular lesion), slight improvement (< 40% reduction of vascular lesion), and no response (< 10% reduction of vascular lesion).

II. RESULTS

In the present study 15 patients were treated by EO; including 7 males and 8 females, and their age range was 8 months - 11years. There was no dropout. Regarding the anatomical site of lesions, 6 cases were facial lesions and 9 cases were intra-oral lesions; 2 in the lower lip, 1 in the upper lip, 2 in the submental region, 1 in the post-auricular region, 2 in the tongue, 1 in para-pharyngeal region, 1 in lower lip mucosa, 2 in upper lip mucosa, 2 in cheek mucosa. Regarding anaesthesia, 11 patients (73.3%) required nerve block anaesthesia, 3 patients (20%) were injected with topical anaesthesia, and one child (6.7%) with para-pharyngeal VM required GA in the first injection, then, topical anaesthesia. Regarding clinical response, 7 patients (46.7%) had a complete response, 4 patients (26.7%) showed marked improvement, 3 patients (20%) showed moderate improvement, and 1 patient (6.7%) showed no response. **Fig. 5** shows ulceration and scarring in the lower lip.

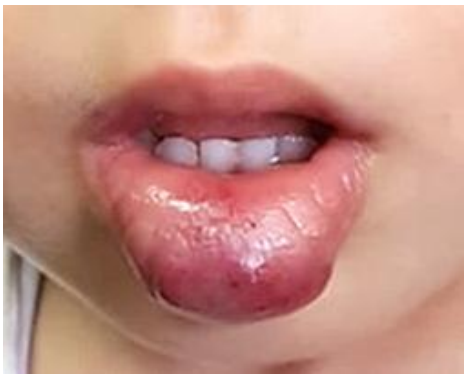

Fig. 5-A: VM in Lower Lip in a 2 years old girl

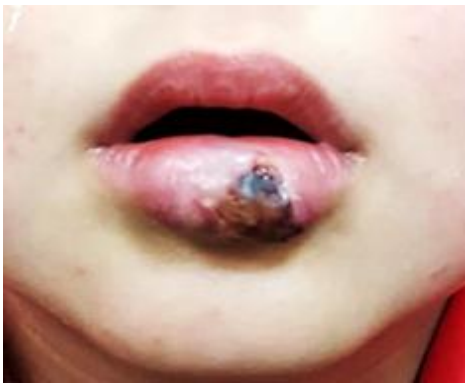

Fig. 5-B: tissue necrosis at the site of injection 2 days after 2nd EO injection

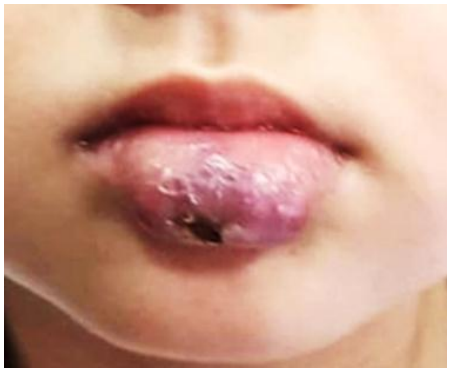

Fig.5-C: Healing after 2 weeks

Fig. 5-D: Healing after 6 months

All parents (100%) reported alarming post-operative swelling on the first day, immediately after injections, which lasted for 5-7 days. **Fig. 6**

In addition, all parents (100%) reported post-operative pain and mild elevation of body temperature on the first post-operative day; which was managed by Paracetamol medication. Scarring occurred in 2 cases (13.3%) in the lower lip. Recurrence occurred in 3 cases (20%).

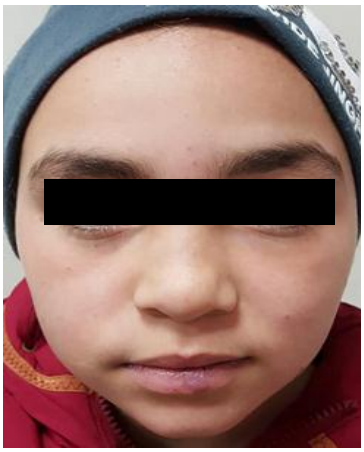

Fig. 6-A: VM in Rt cheek of an 11-yrs old girl

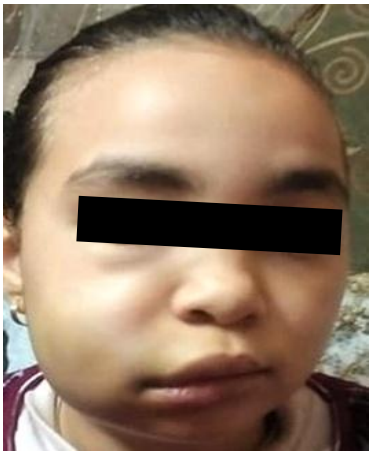

Fig. 6-B: Immediate post-op swelling after EO injection

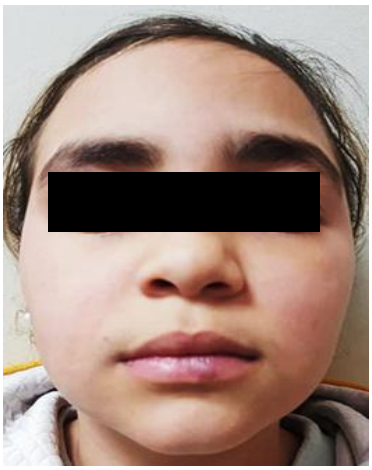

Fig. 6-C: Resolution of swelling after 5 days

Regarding treatment sessions and duration, patients required between 1 and 6 sessions, with 2 weeks interval; the average number of sessions was 4.1 ± 1.8 and the mean treatment duration was 2.1 months (range:1 - 3 months). Thus, six patients required 6 sessions (3 months), 4 patients required 4 sessions (2 months), and 5 patients required 2 sessions (1 month). **Table 1** shows Demographics & Clinical Response of EO Sclerotherapy.

Table no 1: Shows patients demographics and clinical responses of Ethanol-amine Oleate

Case No.	Anatomical Site		Age (yrs)	Sex	Size (cm)	Anaesthesia	No. of Sessions	Rx Duration	Clinical Outcome	Local Complications
1	Tongue	Intra-oral	5 yrs	M	3 × 2 × 1.5	Nerve Block	6	3 m	Complete	None
2	Lower Lip	Facial	4 yrs	M	2.3 × 2 × 1.5	Nerve Block	6	3 m	Complete	Ulceration
3	Lt Cheek mucosa	Intra-oral	8 yrs	F	2.1 × 1.8 × 2	Nerve Block	2	1 m	Complete	None
4	Rt Cheek mucosa	Intra-oral	11 yrs	F	1.3 × 1 × 1.8	Nerve Block	4	2 m	Complete	None
5	Upper Lip mucosa	Intra-oral	10 yrs	F	4.5 × 1.7 × 2.8	Nerve Block	6	3 m	Marked	None
6	Lt Cheek mucosa	Intra-oral	9 yrs	F	4 × 3.4 × 2.4	Nerve Block	4	2 m	Marked	None
7	Upper Lip mucosa	Intra-oral	8 m	M	3 × 2 × 2	Nerve Block	6	3 m	Marked	None
8	Lower Lip	Facial	2 yrs	F	9.2 × 2.2 × 1.8	Nerve Block	2	1 m	Marked	Ulceration
9	Upper Lip	Facial	10 yrs	F	4.5× 3.5 × 2.5	Nerve Block	2	1 m	No Response	None
10	Tongue	Intra-oral	9 m	M	4.3 × 2 × 3.3	Nerve Block	6	3 m	Moderate	None
11	Rt Post-auricular	Facial	7 yrs	M	3 × 1.9 × 1	Topical	2	1 m	Complete	None
12	Submental	Facial	9 yrs	F	4.3 × 2 × 4	Topical	4	2 m	Complete	None
13	Lt Para-Pharyngeal	Intra-oral	3 yrs	M	7.4 × 8.4 × 5.3	GA (1^{st} session) Topical (5 sessions)	6	3 m	Moderate	None
14	Submental	Facial	6 yrs	M	1.8 × 7.2 × 3.1	Topical	2	1 m	Complete	None
15	Lower Lip mucosa	Facial	5 yrs	F	0.7 × 2 × 1	Nerve Block	4	2 m	Moderate	None

Abbreviations
(Lt) left, (Rt) right, (m) months, (yrs) years, (M) male, (F) female, (cm) centimeter, (GA) general anaesthesia,(Rx) treatment
Clinical Outcome: complete response (complete disappearance > 90% reduction), marked improvement (>70% reduction), moderate improvement (40 – 70% reduction of vascular lesion), slight improvement (< 40% reduction), and no response (< 10% reduction)

III. DISCUSSION

Facial VMs commonly cause facial disfigurement and functional impairment, affecting the infant\child quality of life. Sclerotherapy is the first-line treatment of VMs to avoid complications of traditional surgery. EO 5% is the most commonly used sclerosing agent for VMs; after ethanol, 95% was discouraged due to its severe complications.[16] However, EO concentration for intralesional sclerotherapy was not standardized in all studies. (Fowell et al., 2017).

Kato et al. (2020) compared 3 different concentrations of EO; 1.25%, 2.5%, and undiluted EO 5% for the treatment of vascular anomalies of size ≤ 2 cm. The authors reported that only 1 - 2 treatment sessions were required for complete resolution of vascular lesions with undiluted 5% EO, and 1-4 sessions were required with EO concentrations of 1.25% and 2.5%. Therefore, the authors concluded that the undiluted EO 5% is the preferred concentration to provide faster treatment. However, in the mentioned study, the lesions were of size smaller than 2 cm in adult patients. Therefore, intralesional injection of lesions larger than 2 cm will necessitate a larger dose of EO and a larger dose of local anaesthesia, which would result in toxicity in pediatric patients, because of their less body weight.

De Carvalho et al (2014) in their study conducted on EO sclerotherapy of facial VMs in pediatric patients; diluted 1mL of EO 5% in 4 mL distilled water; in a ratio 1:4 (concentration of 1.25%) to reduce EO harmful esthetic and functional complications in the face; such as, injury to the facial nerve, ulceration, scarring, and pain during and after intralesional injections. Because the present study was conducted on orofacial VMs in pediatric patients, we diluted EO 5% in a ratio 1: 4 to ensure patient safety. However, all patients (100%) had alarming post-operative pain, swelling and mild elevation of body temperature. This coincides with Queiroz et al. (2016), who reported severe post-operative edema after EO intralesional injection of upper lip hemangioma in a child; the authors explained this as a severe allergic reaction to EO in children.

Regarding the need for anaesthesia, 11 patients (73.3%) had nerve block anaesthesia, 3 patients (20%) had topical anaesthesia, and one patient (6.7%) required GA. These results coincide with Choi et al. (2002), who reported burning sensation during intralesional injection of EO even with administration of local anesthetic; this implies that EO sclerosing agent itself

caused pain. Similarly, Ribeiro et al. (2018) in their study reported immediate post-operative pain after EO intralesional injections of VMs in the head and neck region in all patients.

Duffy et al (2011) explained that EO complications are due to its high alkaline PH (range: 8 – 9). In addition, the high amount of local anaesthesia required with EO sclerosing agent increases the risk of toxicity due to the anatomic and physiologic differences between children and adults. Baring in mind that the maximum recommended dose is based on the child body weight, the safe pediatric dose of Mepivecaine is 4.4 mg\kg, which limits the amount of local anaesthesia in young children (Chin et al., 2003). Therefore, we recommend performing EO intralesional sclerotherapy in children under GA to reduce pain, avoid risk of toxicity of local anaesthesia, and monitor all vital signs during the procedure.

In the present study, EO caused oedema and scarring in 2 cases with VMs in the lower lip; and did not cause ulceration in any intra-oral lesions. This coincides with Zeevi et al. (2020), who confirmed that EO is safer for intra-oral vascular malformations than the facial skin and lip tissue due to the higher blood supply and growth factors in oral mucosa that reduces the inflammatory effect of EO and subsequent quicker healing of oral mucosa.

IV. CONCLUSION

Based on this study, EO is an effective and quick treatment for VMs; however, it is recommended only for intra-oral VMs to avoid face and lip tissue ulceration and scarring. In addition, GA is recommended with intralesional EO injections to avoid pain during intralesional injection, the potential risk of toxicity of excessive local anaesthesia that would be required, and to allow monitoring of all vital signs during intralesional injections.

OPERATOR:

Sarah Arafat

SOURCE OF FUNDING

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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