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Efficacy of Direct Ethanol Sclerotherapy in Management of Low Flow Congenital Vascular Malformations

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Abstract: Background: Congenital vascular malformations (CVMs) may contain venous, capillary, lymphatic, or arterial components in any combination and have been associated with various dysmorphic syndromes. CVMs appear at birth, persist through life and have slowly progressive course and some of them may be temporary hidden due to their deep location. **Aim of the Work:** to evaluate the efficacy of ethanol sclerotherapy in management of low flow congenital vascular malformations and to report any possible adverse events related to this modality of treatment. **Patients and Methods:** This case series prospective study was conducted on 40 patients having low flow CVMs at the department of Vascular Surgery at the International Medical Center (IMC), Cairo Egypt, during the period from April 2017 to April 2019. **Results:** all patients showed good response as regard clinical improvement which was represented in patient's satisfaction, as 87.5% were satisfied and 12.5% were very satisfied. All patients showed good radiological response which was obvious in comparison of pre and post procedure MRI, as 5% were completely cured and 95% were markedly improved. All patients had no major complications, but 42.5% of patients had one or more minor complications which were subsided spontaneously or with nominal therapy without consequences or hospital admission. **Conclusion:** Ethanol sclerotherapy is highly efficient method in treatment of low flow CVMs, but accompanied with many local complications which could be minimized when management was done by multidisciplinary team.
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Key words: Ethanol Sclerotherapy, Low flow congenital vascular malformations

1. Introduction

The blood vascular system develops in two distinct, consecutive stages vasculogenesis & angiogenesis both of them are regulated by biomechanical factors. When any defect is happened to them, it will lead to vascular malformations. When defective development occurs in the early stage of embryonic development, it will produce an extra truncular malformation, but if it happens in later stage it will produce a truncular malformation [(1)].

Congenital vascular malformations (CVMs) may contain venous, capillary, lymphatic, or arterial components in any combination and have been associated with various dysmorphic syndromes. CVMs appear at birth, persist through life and have slowly progressive course and some of them may be temporary hidden due to their deep location [(2)].

The incidence and prevalence of the CVMs were confused through the previous decades due to so much confusing definitions and classifications, the extra truncular venous malformation (VM) is the most frequent type of CVMs [(3)].

Difference between hemangioma and CVM according to previous several classifications was not clear until Judah Volkman in 1982 demonstrated that hemangioma is a lesion that has endothelial hyperplasia while CVMs have normal endothelial. 'Biological' classification divided CVMs into high-flow and low-flow lesions according to hemodynamics adding syndromes of complex cases in a group of combined complex defects. Stevan Belov in 1988 proposed 'Hamburg' classification influenced by 'Biological' classification based on morphology as well but adding more criteria. He divided CVMs into 'truncular' group which are defects related to main vessels and 'extratruncular' group which are peripheral defects that could be present into diffuse and infiltrating forms of the single type [(3)].

The International Society for the Study of Vascular Anomalies (ISSVA) published 'ISSVA' classification in 1996. Several updates were published in the last years and the most recent one -Updated ISSVA- was published in 2018 adding several subgroups to include all new discoveries [(4)].

Low flow CVMs are extremely variable in type, site, extension and secondary effects so, their diagnosis should be done by multi-disciplinary team, taking detailed history, making good clinical

examinations and doing necessary images under standard protocols via radiologists who have good experience about CVMs [5].

Unfortunately there are no widely used standard methods or protocols in treatment of CVMs. There are so many different methods in treatment of CVMs; either surgical, endo-venous laser ablation, sclerotherapy using different substances or conservative treatment according to personal experience and facilities [5].

Occlusion of vessels could be achieved by injecting different substances in the vessels like ethanol, bleomycin, particles, coils, glue and others. Ethanol is an excellent sclerotherapy agent for all varieties of the extratruncular CVMs. In experienced hands ethanol sclerotherapy is associated with minimum morbidity. Patients injected with ethanol require close perioperative monitoring to manage its adverse events. The most of ethanol sclerotherapy complications could be managed by conservative measures [6,7].

Aim of the work

The aim of this study is to evaluate the efficacy of ethanol sclerotherapy in management of low flow congenital vascular malformations and to report any possible adverse events related to this modality of treatment.

2. Patients & Methods

Our study was a case series prospective study conducted on 40 patients having low flow CVMs at the department of Vascular Surgery at the International Medical Center (IMC), Cairo Egypt, during the period from April 2017 to April 2019.

Pre procedure assessment:

Full history was taken from all patients/parents; age, gender, past medical history including Known allergy to ethanol or contrast materials and bleeding tendency.

Main presenting symptom (s): cosmoses was mostly the main presenting symptom in head and neck lesions, while painful swelling was presented in patients with extremities lesions, patients were complaining from difficulty of swallowing or breathing when the lesion was affecting the tongue or airway, abnormal gait was detected when the lesion was affecting the lower limb joints, rarely the patients presented by bleeding from the lesion after subjecting to trauma or erosion of the skin over the lesion.

Lesion: We asked the patients/parents about site of the lesion, shape of the lesion, the course of the lesion, the time of lesion appearance and previous treatment by other sclerosant materials.

- Clinical examination was performed on all patients.
- Laboratory investigations in the form of complete blood count (CBC), serum creatinine, PT and PTT were done to all patients to assess general condition, kidney function and bleeding tendency.
- MRI without contrast (T1, T2, Fat suppression & STIR) with or without DUS to determine morphology, extension, measurements and flow through the lesions.

The study included patients >2 years age diagnosed with low flow CVMs, extratruncular venous, lymphatic or mixed low flow malformations, and patients who were symptomatically, cosmetically or functionally affected.

While truncular venous or lymphatic malformations, pure capillary malformations, patients who were previously managed by injection of another sclerosants, patients who had contraindications for contrast or alcohol injection as renal impairment (S. Creatinine >1.5 mg/dl) or known allergy to contrast material or alcohol, patients who were unfit for general anesthesia and pregnant female patients were excluded from the study.

All patients/ parents included in the study have given a written informed consent.

Procedure:

All selected patients / parents accepted the procedure and the steps were,

1- pre-procedure preparation: all patients had been examined by vascular surgery consultant and anesthetist in a pre-procedure assessment clinic few days before the procedure.

All patients admitted to the hospital on the same day of the procedure as a day case treatment session.

Intensive care unit (ICU) bed was booked for patients liable for major complications.

2- Anesthesia: all patients received general anesthesia.

3- Patient position on the table:

Positioning the patient supine or in lateral position according to the lesion site.

4- Anti septic lotion & drapes:

Skin sterilization was done using povidone-iodine and covering the patient with sterile disposable drapes.

5- Ethanol sclerotherapy steps

- Under general anesthesia all patients were subjected to fluoroscopy guided absolute ethanol injection through direct puncture of the vascular malformation using butterfly needle 23 or 21 gauge for superficial lesions and 18-gauge long needle for deep lesions. Previously obtained MRI was used to determine the location and the extent of the lesion.
- After obtaining blood from VMs channels or lymphatic aspiration from lymphatic malformation spaces, the contrast material was injected into the lesion to exclude arterial cannulation or

extravasations, also to assess the nature of the lesion, its drainage and to determine the lesion accessibility (Fig. 1).

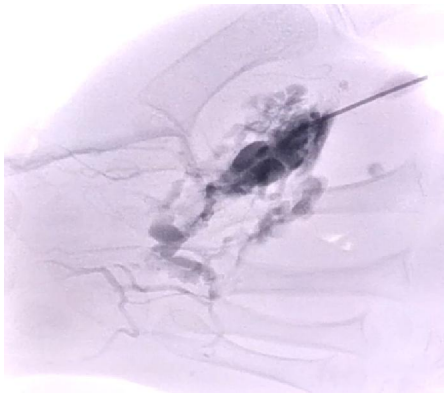


Figure (1): Contrast injection (Direct puncture venography)

- When the lesion was close to main venous drainage that vein was occluded by local external manual compression to avoid systemic spread, direct puncture venography could confirm the efficacy of the compression.
- The initial volume of the injected ethanol was less than the amount of contrast material required to opacify the drainage vein. Ethanol replaced the previously injected contrast material and appeared as negative contrast (white) on digital subtraction angiography (Fig. 2).

Figure (2): Ethanol sclerotherapy

- Repeated injections of contrast and ethanol were done until the lesion was completely filled as shown by Fluoroscopy, in large lesions different compartments were injected at the same session.
- The total volume of ethanol injected was less than 0.5 ml/kg body weight per session and never exceeding 0.1 ml/kg body weight every ten minutes which are the standard dose to avoid pulmonary hypertension, which was monitored during injection via end-tidal carbon dioxide volume which equals normally (35:45 mm hg) drop of its value during the sclerotherapy session from the base line indicates pulmonary hypertension.
- Any bleeding through puncture sites was managed by putting saline socked gauze with no compression.

6- Post-procedure medications and protocols:

- Immediate;

Post-operative parenteral NSAIDs (Diclofenacs), H2 receptors antagonists (Ranitidine) and steroids (Dexamethazone) were administrated to all patients according to their body weights. All patients were followed up at least six hours post-operative monitoring their vital signs.

If there were minor ethanol sclerotherapy adverse events they could be managed on bed, e.g. bleeding from the lesion post-procedure could be managed by putting saline socked gauze.

On suspicion of any major complication patient would be transferred to ICU to be under close observation.

Late;

All patients were discharged after being sure that they were well, prescribing to them oral NSAIDs, H2 receptors antagonists and tapering steroids for ten days.

7- All patients were scheduled to repeat the session of ethanol sclerotherapy every 3-4 months.

Follow up protocol:

- All patients were followed up monthly to assess primary & secondary endpoints.
- MRI was done to every patient two months after the third ethanol sclerotherapy session for follow up and measuring radiological improvement.

To evaluate the clinical improvement we have adopted a standard self-assessment questionnaire which was reported by Van Der Vleuten et al., 2014. The questionnaire contained items assessing symptoms and satisfaction levels. Patients (In pediatric patients, parents were asked to complete the questionnaire) were asked for specific symptoms (e.g. pain, swelling, functional limitations, and cosmetic disfigurements), and a four-point scale was used to rate the degree of symptom improvement as follows: markedly improved, moderately improved, no change, and worsening. Similarly, patients were asked about their satisfaction with sclerotherapy as follows: very satisfied, satisfied, dissatisfied, or neither. “Markedly improved” and “moderately improved” were defined as a “good response”, and “very satisfied” and “satisfied” were defined as “satisfaction” [8].

To assess radiological improvements of low flow CVMs, we used post procedure MRI. Pre- and post-treatment images MRI were compared. Maximal malformations diameters in coronal, sagittal and

transverse section were measured. Marked improvement by imaging was defined as 30% decrease in maximal MRI diameter of the low flow CVMs compared to pretreatment images [9].

All adverse events that happened to patients were recorded.

All patients that had adverse events were followed up more frequent every week.

- All data were recorded, calculated and statistically described in terms of mean ± standard deviation (SD), median and range, or frequencies (number of cases) and percentages when appropriate, using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 25 for Microsoft Windows.

3. Results

Our study was conducted on 40 patients that attended the outpatient clinic having low flow CVMs at the department of Vascular Surgery at IMC, Cairo Egypt.

I. Demographic data:

A) Age

The age of the patients included in the study was in between (3 & 46) years with mean ± SD equal 19±12.6 [median (range) equal 16(43)]. The median age was 16 years in patients having VMs and 12.5 years in patients having VLMs.

B) Gender: Sixteen patients were males and twenty four patients were females.

II. Type of malformation:

Thirty four (85%) patients had VM, four (10%) patients had VLM, one (2.5%) patient had LM and one (2.5%) patient had CVM.

III. Malformation distribution

Distribution of the malformations in our cohort of patients was as following: head & neck: Fifteen patients (37.5%), lower limbs: Fifteen patients (37.5%), upper limb: five patients (12.5%), pelvis & lower limb: four patients (10%) and chest & abdomen: one patient (2.5%).

IV. Main presenting symptom (s)

The most common presenting symptom for ethanol sclerotherapy was cosmetic in seventeen (42.5%) patients, followed by cosmetic with pain together in eleven (27.5%) patients, then pain alone in four (10%) patients, other indications were presented in a little extent as shown in (Fig. 3).

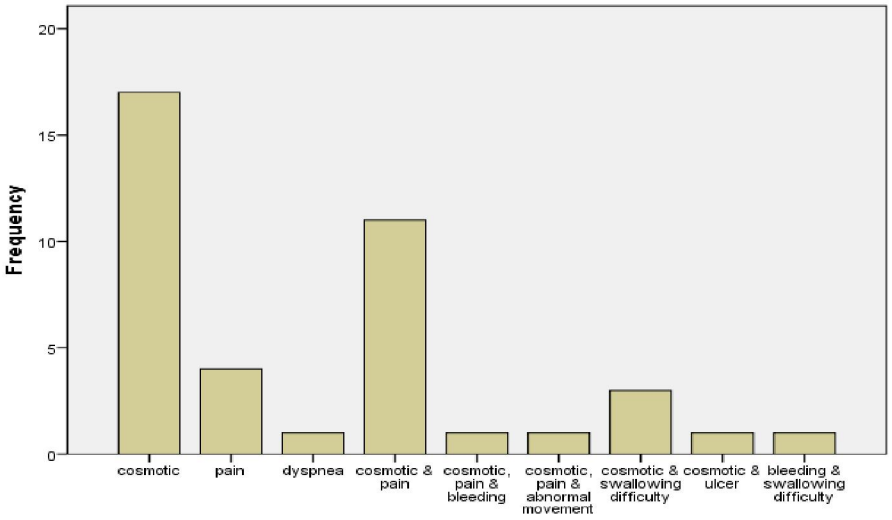


Figure (3): Mean presenting symptoms

V. Primary end points:

Our primary endpoints were improvement in clinical and radiological findings after three ethanol injection sessions.

1) Clinical improvement (Satisfaction)

All patients showed good response to ethanol sclerotherapy which is defined as very satisfied or satisfied. Five (12.5%) were very satisfied, thirty five (87.5%) were satisfied, no patient was dissatisfied or neither (Table 1).

2) Radiological improvement

Lesions measurements were calculated via measuring maximum coronal, transverse and sagittal diameters pre and post three ethanol sclerotherapy sessions. We found that pre ethanol sclerotherapy median of measures in coronal dimension was 30 cm^2 and markedly decreased to 4.5 cm^2 after ethanol sclerotherapy, median of pre transverse measures was 20 cm^2 and markedly decreased to 3 cm^2 post sclerotherapy, also median of measures in sagittal dimension was markedly decreased from 31 cm^2 to 5.5 cm^2 after three ethanol sclerotherapy sessions (Table 2).

Table (1): Patient satisfaction

Satisfaction	Frequency (Percent)	P value
Dissatisfied	0(0%)	
Neither	0(0%)	
Satisfied	35(87.5%)	<0.001
Very satisfied	5(12.5%)	
Total	40(100%)	

Chi-square test

Table (2): Radiological changes in comparison between pre & post-procedure MRI diameters in three dimensions

MRI measurements		Mean	Std. Deviation	Median	Range	P value*
Pair 1	Pre-procedure coronal diameter	39.7	29.8	30	122	
	Post-procedure coronal diameter	6.6	5.9	4.5	21	<0.001
Pair 2	Pre-procedure transverse diameter	21.8	12.8	20	68	
	Post-procedure transverse diameter	4.5	3.5	3	13	<0.001
Pair 3	Pre-procedure sagittal diameter	46.5	35.7	31	137	
	Post-procedure sagittal diameter	8.4	6.8	5.5	23	<0.001

*** Wilcoxon Signed Ranks Test**

All patients showed good response to treatment, as two (5%) patients had cured, as one of these patients had a small size lesion (8 cm^2, 10 cm^2 & 20 cm^2 in coronal, sagittal & transverse diameters respectively) and the second patient had VM type I according to venous angiographic classification. This type of VM is known to have no venous drainage showing good response to sclerotherapy. Thirty eight (95%) patients showed marked improvement which is defined as decrease in maximum MRI diameter more than 30% when comparing pre and post images (Table. 3).

Table. (3): Radiological improvement

Radiological improvement	Frequency (Percent)	P value
Worsen	0(0%)	
No change	0(0%)	
Moderate improved	0(0%)	<0.001
Marked improved	38(95%)	
Cured	2(5%)	
Total	40(100%)	

Chi-square test

VI. Secondary endpoint

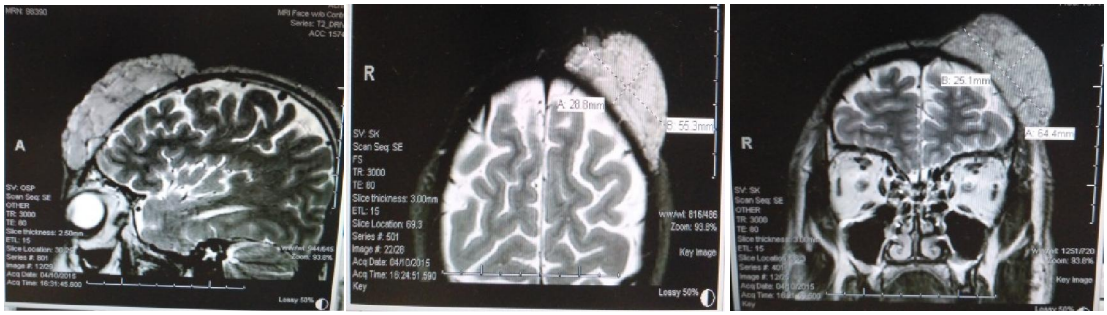
Our secondary end point was appearance of ethanol sclerotherapy adverse events. All our cohort of patients did not experience any major complications. As regard minor complications, 57.5% of our patients did not develop any minor complications, while 15% of patients had ulcer alone, 12.5% of patients had ulcer & minor bleeding and other complications had been occurred to a little extent as shown in (Table. 4).

Table (4): Ethanol sclerotherapy complications

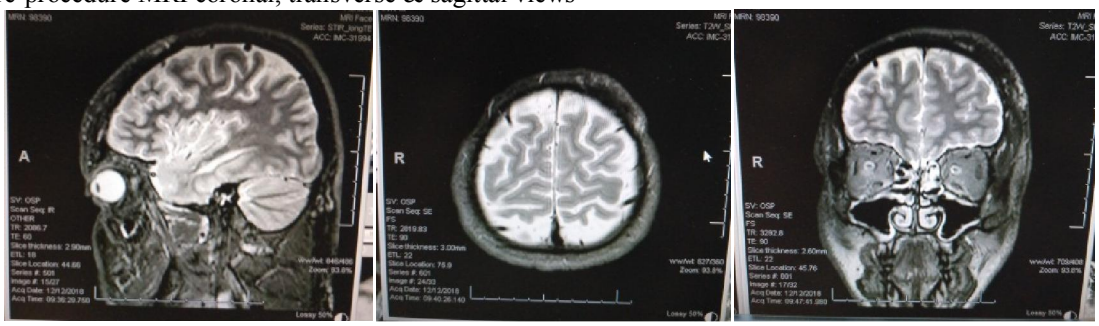
Complications	Frequency (Percent)
No complications	23(57.5%)
Ulcer	6(15%)
Minor bleeding	1(2.5%)
Neuropathy	3(7.5%)
Ulcer & minor bleeding	5(12.5%)
Minor bleeding & neuropathy	1(2.5%)
Ulcer, minor bleeding & neuropathy	1(2.5%)
Total	40(100%)

It was found that ulcers appeared with patients who had superficially injected lesions. Neuropathy had occurred when the injected lesions were in very close relation to the neighboring nerve. Bleeding usually was happened after occurrence of deep ulceration. All complications were transient and subsided spontaneously or with nominal therapy without consequences or hospital admission.

Comparison between pre and post MRIs of some cases

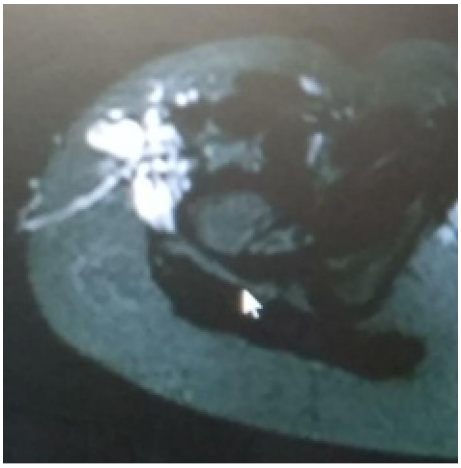


Pre-procedure MRI coronal, transverse & sagittal views

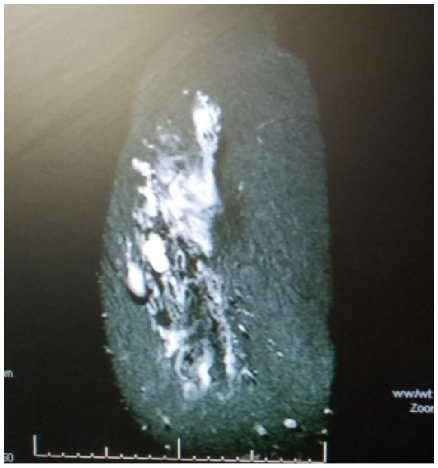


MRI 2 months post-procedure coronal, transverse & sagittal views

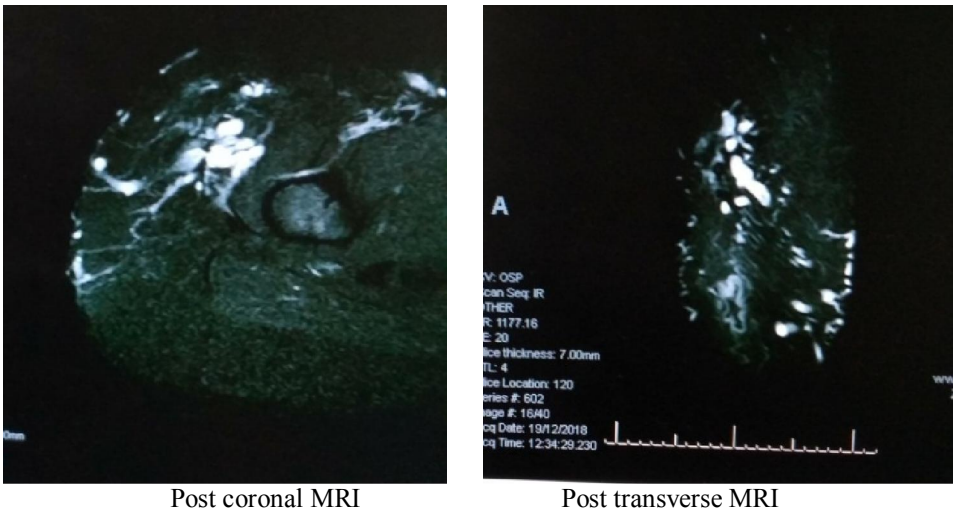
Fig. 4a Forehead VM treated by ethanol sclerotherapy



Pre coronal MRI

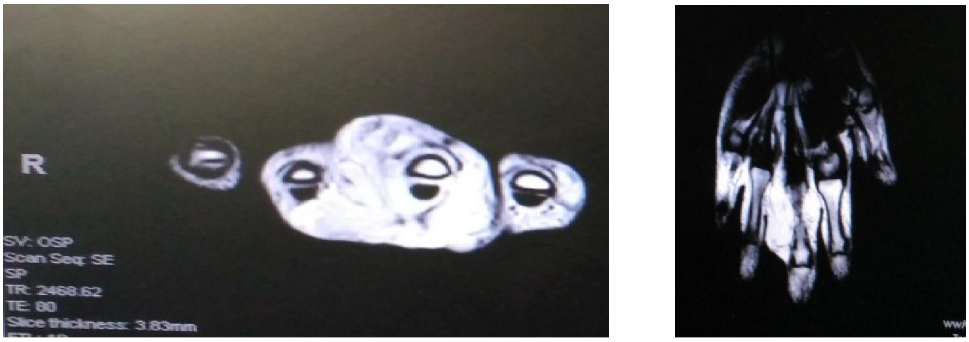


Pre transverse MRI

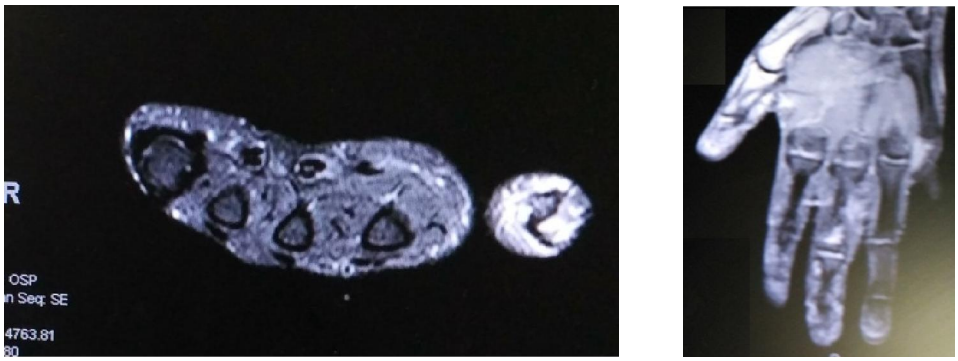


Post coronal MRI Post transverse MRI

Fig. 4b. VM anterior lateral aspects of right thigh treated by ethanol sclerotherapy



Pre coronal MRI Pre transverse MRI



Post coronal MRI Post transverse MRI

Fig. 4c. Hand VM treated by ethanol sclerotherapy

4. Discussion

CVMs were detected in 0.03% of births. Among various types of CVMs, VM was reported as the most common type of CVMs, which has been reported to occur in 0.01-0.02% of births [10].

There are numerous endovascular techniques to treat symptomatic CVMs; most of these are effective in relieving symptoms. Techniques with the highest efficacy and lowest chance of complications should be chosen. Ethanol sclerotherapy was found to be an efficient method to relieve the subjective symptoms and to produce significant radiological improvements of patients with low flow CVMs [7]. Ethanol sclerotherapy can produce many local or systemic adverse events. These adverse events could be minimized when management is done by multidisciplinary experienced team following standard protocols [11].

In our study that was done on forty patients all of them showed good response as regard clinical

improvement which was represented in patient's satisfaction, as 87.5% were satisfied and 12.5% were very satisfied. All patients showed good radiological response which was obvious in comparison of pre and post procedure MRI, as 5% were completely cured and 95% were markedly improved.

Regarding patient's demographic data in this study we found that the patient's age was ranging from 3 to 46 years.

Comparing other studies demographic data we found that, in a study done by Schumacher M, 2011 in Germany on seventy five patients their age was ranging from 4 to 46 years, but in the study done by Su L, 2010 in China on sixty patients their age was ranging from 8 months to 64 years. The age group was ranging from 1 to 58 years in a study done by Yun et al., 2009 in South Korea [9,12,13].

So, the range of age was nearly similar to Schumacher M et al., 2011 study this is may be due to study design as this study was a case series prospective study like our study. Minimum age in Su le et al., 2010 and Yun et al., 2009 was 8 months and 1 year respectively but in our study we excluded patients <2 years in a trial to minimize general anesthesia adverse effects.

In our study it was found that the female gender was represented more than the male gender as females represented sixty percent of patients. If we will compare to Yun et al., 2009 we will find that the females represented fifty eight percent of patients, which is closely similar to our study ratio [9].

As regard vascular malformations types included in this study the VMs had the larger percentage as they represented in 85% of patients, VLMs were represented in 10%, LM & CVM each of them were represented in one case only 2.5% for each type.

Highlighting Yun et al., 2009 we found that VMs represented also the larger percentage 77% of patients; VLMs were the same as in our study 10%, CVMs were11% represented more than our study, CVLMs were 2% which not be founded in our study, lastly no LM was represented but in our study we had 2.5% with pure LM as we included all low flow CVMs [9].

The distributions of malformations in our study were presented all over the body in different ratios as follow; 37.5% of patients at head & neck, 37.5% of patients at lower limbs, 12.5% of patients at upper limb, 10% of patients at pelvis & lower limb together and 2.5% of patients at chest & abdomen.

When comparing to Yun et al., 2009 they reported that distribution of the lesions in their cohort of patients to be 42% of patients at head & neck, 37% of patients at lower limbs, 9% of patients at upper limb, 12% of patients at pelvis, chest & abdomen together "trunk". In a comparison with our study the distribution was nearly similar with very little difference in ratios, also Yun et al., classified chest, abdomen and pelvis in one group "trunk" but we classified them in two separate groups their percentage's sum equals the trunk group [9].

In our study the most common main presenting symptom for ethanol sclerotherapy was cosmetic alone in 42.5% of patients, followed by cosmetic with pain together in 27.5% of patients, then pain alone in 10% of patients, dyspnea in 2.5% of patients, bleeding & swallowing difficulty together in 2.5% of patients, the remaining 15% of patients were suffering from cosmetic effect plus one or more of the following symptoms (ulcer, bleeding, abnormal movement, pain and swallowing difficulty), so 85% of patients were suffering from cosmetic effect and 42.5% of patients were suffering from pain.

In Yun et al., 2009 study they mentioned that 57% of patients suffered from cosmetic effects in the form of (varicosities, lateral embryonic vein and limb length discrepancy >2 cm), 60% of patients suffered from pain, 59% of patients were complaining from Swelling or mass and 2% were suffering from skin discharge. When we compare this with our study the most common complaints were cosmetic effects and pain in both studies but, the cosmetic effects were more in our study may be due to our society social habits [9].

The primary endpoints of our study were clinical and radiological improvements and the secondary endpoint was ethanol sclerotherapy complications which were similar to other studies endpoints using the same methods in evaluation of primary endpoints and recording of secondary endpoint. The comparison between our study and other studies is shown in table 5.

In our study we did not experience any major or systemic complication, but other studies showed variable major complications rate. This might be due to that our anesthetic team who has much experience in dealing with CVMs cases had assessed the patients well in the pre-procedure assessment clinic. Using minimum standard doses of ethanol and using minimum standard rate of ethanol injections at the same session. Very close monitoring and observation done by well-trained experienced physician staff and nurses.

We recorded in our study local and minor complications more than most of other studies which was thought to be related to anatomical considerations and patho-physiological reactions. In our study we noticed that ulcers occur mainly after injecting very superficial lesions, neuropathy had occurred when injected lesions were in very close relation to nerves, as a normal sequence after ethanol sclerotherapy tissues inflammations and hyperemia will occur to

surrounding tissues, so tapering steroids and NSAIDs should be given to patients intra and post operatively to minimize these normal physiological reactions.

Table. (5): Comparison between ethanol sclerotherapy studies

Author, year & Country	Study design	Patient's number	Number of Sessions (mean)	Control group	Efficacy	Adverse events
Yun et al., [9] 2009 S. Korea	Retrospective	158	4.1	none	16%	27%
Su L et al., [13] 2010 China	Retrospective	60	2.6	none	93%	18%
Schumacher M et al., [12] 2011 Germany	Prospective	75	2.3	none	93%	28%
Spence J et al., [14] 2011 Canada	Retrospective	18	1.7	Bleomycin	100%	61%
Orlando JL et al., [15] 2014 Brazil	Retrospective	51	7	none	94%	18%
Our study, 2019 Egypt	Prospective	40	3	none	100%	42.5%

Our study showed better results as regard decreasing the systemic and major ethanol sclerortherapy complications through following standard protocols in management.

We had limitations in our study. The first limitation was in number of cases as the incidence of CVM is small and there is no good public awareness about this disease. The second limitation was the treatment cost as not all patients can afford intervention cost. Short follow up period was anther limitation that we had faced, as we followed the patients after the end of the third session for a time ranging from 4 months to 12 months with median 8 months. Clinical outcome assessment was a limitation as it was subjectively calculated due to absence of standard objective method, as some patients showed marked radiological improvement but without good satisfaction. Calculation of the CVM lesion diameter through the MRI was difficult, as diameters were not changed equally in all dimensions. Also the MRI intensity of the treated lesions may need months to be changed.

We have conclude that if we determine more inclusion and exclusion criteria as regard type of CVMs generally, angiographic type of VMs, size, site, depth of malformations, increasing number of cases, longer period of follow up and trying to standardize widely accepted methods to assess outcome these will make results more significant.

Conclusion

Ethanol sclerotherapy is highly efficient treatment modality in management of low flow CVMs, but it is dangerous modality can producing many local and systemic complications which could be minimized when it is used by multidisciplinary experienced team following standard protocol.

Recommendations

- Increasing public awareness about CVMs.
- Proper diagnosis, preoperative preparation and safe procedure can decrease ethanol sclerotherapy complications.

References:

1. LEE, B.-B. 2008. Changing concept on vascular malformation: no longer enigma. *Annals of vascular diseases,* 1**,** 11-19.
2. NORTH PE. 2010. Vascular tumors and malformations, in surgical pathology clinics, vol 3(3). *Elservier Saunders, Phladelphia,* p 455-494.
3. MATTASSI, R., LOOSE, DA., VAGHI, M. 2015. hemangioma and vascular malformations: An atlas of diagnosis and treatment, 2nd Ed 20: 165-168.
4. ADAMS, D. M. & RICCI, K. W. 2019. Vascular Anomalies: Diagnosis of Complicated Anomalies and New Medical Treatment Options. *Hematology/Oncology Clinics,* 33**,** 455-470.
5. LEE, B., BAUMGRTNER, I., BERLI, P., et al., 2014. Diagnosis and treatment of venous malformations consensus document of international union of phlebology: updated 2013. *Int Angiol.* [Epub ahead of print]
6. LEE, B., DO, Y., BYUN, H., et al., 2003. Advanced management of venous malformation with ethanol sclerotherapy: mid-term results. *Journal of vascular surgery,* 37**,** 533-538.
7. MENDONCA DA, MCCAFFERTY I, NISHIKAWA H, et al., 2010. Venous malformation of the limbs: the Birmingham excperience, comparisons and classification in

children. *J Plast Reconstr Aesthet Surg* 63(3), 383-389.
8. VAN DER VLEUTEN, C. J., KATER, A., WIJNEN, M. H., et al., 2014. Effectiveness of sclerotherapy, surgery, and laser therapy in patients with venous malformations: a systematic review. *Cardiovascular and interventional radiology,* 37, 977-989.
9. YUN, W.-S., KIM, Y.-W., LEE, K.-B., et al., 2009. Predictors of response to percutaneous ethanol sclerotherapy (PES) in patients with venous malformations: analysis of patient self-assessment and imaging. *Journal of vascular surgery,* 50, 581-589.
10. CORREA, C., MALLARINO, C., PEñA, R., et al., 2014. Congenital malformations of pediatric surgical interest: prevalence, risk factors, and prenatal diagnosis between 2005 and 2012 in the capital city of a developing country. Bogotá, Colombia. *Journal of pediatric surgery,* 49**,** 1099-1103.
11. STUART, S., BARNACLE, A. M., SMITH, G., et al., 2014. Neuropathy after sodium tetradecyl sulfate sclerotherapy of venous malformations in children. *Radiology,* 274**,** 897-905.
12. SCHUMACHER, M., DUPY. P., BARTOLI. J. M., et al., 2011. Treatment of venous malformation: first experience with a new sclerosing agent a multicenter study. *Eur J Radiol,* 80, 366-372.
13. SU, L., FAN, X., ZHENG, L., et al., 2010. Absolute ethanol sclerotherapy for venous malformations in the face and neck. *Journal of Oral and Maxillofacial Surgery,* 68**,** 1622-1627.
14. SPENCE, J., KRINGS, T., TERBRUGGE, K. G., et al., 2011. Percutaneous treatment of facial venous malformations: a matched comparison of alcohol and bleomycin sclerotherapy. *Head & neck,* 33**,** 125-130.
15. ORLANDO, J. L., CALDAS J. G., CAMPOS H. G., et al., 2014. Ethanol sclerotherapy of superficial venous malformation: a new procedure. *dermatology* 220(4), 376-380.

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