CLINICO-RADIOLOGICAL PREDICTORS OF FAVOURABLE OUTCOME AND QUALITY OF LIFE IN PATIENTS UNDERGOING PERCUTANEOUS SCLEROTHERAPY FOR SLOW FLOW VASCULAR MALFORMATIONS

Dissertation submitted in partial fulfilment of the requirement of the Tamil Nadu Dr. M. G. R. Medical University for the M.D Branch VIII (Radio Diagnosis)

Examination to be held in May 2019

CLINICO-RADIOLOGICAL PREDICTORS OF FAVOURABLE OUTCOME AND QUALITY OF LIFE IN PATIENTS UNDERGOING PERCUTANEOUS SCLEROTHERAPY FOR SLOW FLOW VASCULAR MALFORMATIONS

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CERTIFICATE

This is to certify that the dissertation entitled "Clinico-radiological predictors of favourable outcome and quality of life in patients undergoing percutaneous sclerotherapy for slow flow vascular malformations" is a bonafide original work of Dr. Seelam Joshua Anand, towards the M.D. Branch VIII (Radiodiagnosis) Degree examination of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, to be conducted in May 2019.

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DECLARATION CERTIFICATE

This is to certify that the dissertation entitled “Clinico-radiological predictors of favourable outcome and quality of life in patients undergoing percutaneous sclerotherapy for slow flow vascular malformations” is a bonafide original work done by me, towards the M.D. Branch VIII (Radiodiagnosis) Degree examination of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, to be conducted in May 2019.

This comprises only of my original work and due acknowledgement has been made in the text to all material used

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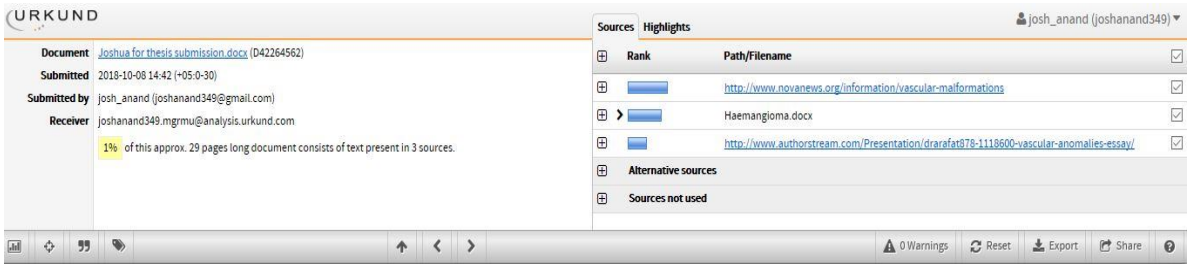
ANTI- PLAGIARISM CERTIFICATE



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ABSTRACT

Clinico-radiological predictors of favorable outcome and quality of life in patients undergoing percutaneous sclerotherapy for slow flow vascular malformations

BACKGROUND:

Slow flow vascular malformations are one of the commonest soft tissue lesions in children and young adults. They include venous malformations (VM) and lymphatic malformations (LM). They cause significant morbidity in terms of cosmesis and functional impairment. Surgical resection is often incomplete, and proximity to vital deeper structures are a common reason for incomplete resections. Sclerotherapy is a treatment method by which a sclerosant is injected into the cystic vascular spaces. Percutaneous sclerotherapy has become the standard of care for slow flow vascular malformations worldwide.

AIMS & OBJECTIVES:

The aim of this study was to objectively evaluate the improvement in symptoms and quality of life in patients receiving percutaneous sclerotherapy for slow flow vascular malformations. Additionally, the study attempted to identify clinical and radiological predictors of a favorable outcome in patients undergoing this procedure.

MATERIALS & METHODS:

Patients who were referred to the interventional radiology clinic for the first time were included in this study after informed consent. Sodium Tetradecyl Sulfate (STS) was injected into the venous malformations. STS and

bleomycin were injected into the lymphatic malformations. A modified form of a standardized questionnaire (SF-36) was used to assess the quality of health life. The questionnaire was administered to the patient prior to the sclerotherapy and at three-time points after sclerotherapy- day1, day 3 and day 7. The basic demographics of the patient as well as specific radiological features such as type and the extent of involvement was used for analysis.

RESULTS:

There were 53 patients, with age ranging from 2-47 years. There were 23 males and 30 females. There were 37 patients with VM and 16 with LM. There was a statistically significant difference in the means of the quality of life pre-sclerotherapy, and day 7 post sclerotherapy scores ($p<0.0001$). There was also a statistically significant association between the earlier age of presentation with better quality of life ($p=0.019$, Pearson coefficient of 0.320, suggesting moderate correlation). The analysis also revealed a transient worsening of the quality of life scores immediately following sclerotherapy (day 1) with improvement at day 7. The other parameters such as the plane of the malformation, type, pre-treatment size, number of needles did not have a statistically significant association with the quality of life. There was no significant difference in quality of life between the patients with VM or LM.

CONCLUSION

Sclerotherapy for slow flow vascular malformations is a safe and reliable way to treat patients. Earlier age of first session of sclerotherapy was associated with a significantly better outcome in terms of quality of life. There was a significant association between the volume of foam sclerosant

injected and better quality of life. The use of sclerosant should be limited in the head of neck region (lip and tongue) where there is high risk of tissue necrosis. Patients should be informed of the natural course of events, where there is a transient worsening of the symptoms immediately after sclerotherapy due to the local inflammatory response.

KEYWORDS:

Sclerotherapy, slow flow vascular malformations, venous malformation, lymphatic malformation, quality of life.

Table of Contents

INTRODUCTION

Slow flow vascular malformations are one of the most common soft tissue lesions in children, adolescents and young adults. They cause significant morbidity not only in terms of cosmesis and functional impairment, but can also be a cause for mortality, if in relation to vital structures. Surgical resection is often incomplete, and proximity to vital deeper structures can often impair complete resection. Hence, sclerotherapy or injection of sclerosant into these cystic vascular spaces has become the standard of care worldwide.

AIMS AND OBJECTIVES

This study had the following aims and objectives:

1. To objectively evaluate the improvement in symptoms and quality of health life in patients receiving percutaneous sclerotherapy treatment for slow flow vascular malformations.

2. To identify and evaluate radiological and clinical predictors of outcomes (favourable and unfavourable) in patients undergoing this treatment procedure.

LITERATURE REVIEW AND BACKGROUND

INTRODUCTION

Vascular malformations have often been misdiagnosed in the past and continue to be even today. A lot of confusion exists even on the nomenclature today.

Most of the vascular malformations can be diagnosed using a good history taking and thorough clinical examination with focussed imaging to plan or discern its uncertain deeper extension.

Ultrasound and colour doppler was considered as the primary modality for assessment of lesions or tumours of vascular origin because of its wide availability and ease of use. However it has inherent limitations such as limited field of view, reduced penetration for deep lesions and operator dependency (1).

This has been largely been replaced by MRI examination, along with gadolinium enhanced scans which have become the investigation of choice for most of these malformations, which has the advantages of imaging in three dimensions, which is useful in planning and also to know its relation to

vital deeper structures. The type of vascular malformation determines the type of treatment or therapy that is given (2).

The commonest term that continues to be used today among clinicians and other specialists is ‘haemangioma’, which is a non-specific term. Confusion about the nomenclature and the imaging guidelines is largely responsible for the faulty diagnosis and improper treatment which can cause significant morbidity to the patients (3).

Vascular malformations and tumours alike are comprised of a wide array of lesions that can involve any part of the body. The beginning of the classification of these vascular malformations began in 1983 in a landmark article by Mulliken et al which first described them in terms of histology of the type of the endothelial proliferation (4).

ETIOLOGY

The aetiology or causative factor for most of these vascular malformations remains largely unknown. A few of them have been associated with syndromic associations, associated with specific gene mutations which are primarily collagen or reticulin related, which have been earlier elucidated (5).

There are a few factors which aggravate these slow vascular malformations:

1. Infection
2. Trauma
3. Hormonal change
4. Radiation
5. Connective tissue disease

These specific etiological factors are known to aggravate the already existing lesions, because of which the patient might become symptomatic only after these events. Thus, in most of these patients they give a history of these prior aggravating factors and they associate these conditions as a causative agent for them.

PATHOPHYSIOLOGY OF VASCULAR MALFORMATIONS

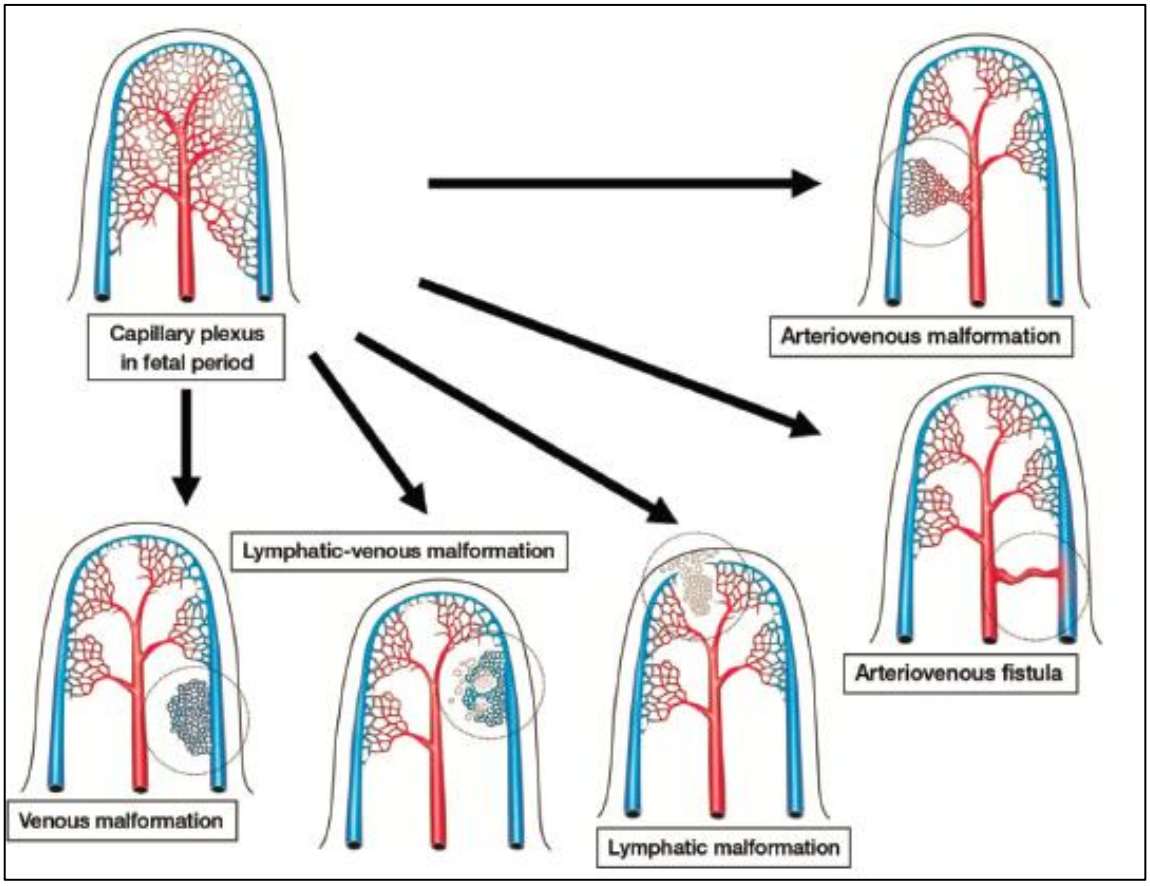


Figure 1

The above illustration describes (6) the pathophysiology of vascular malformations when arrest of development occurs in the different stages of vasculogenesis.

Abnormal regression of any one of those structures is responsible for various vascular malformations.

If there is an abnormal connection between the arterial and venous components – this leads to an arteriovenous fistula. If there is failure of regression of the venous, lymphatic or capillary components of the cancellous network of capillaries – leading to various malformations.

The knowledge of the basic pathophysiology of these vascular malformations is important as it guides in the management of them.

ISSVA CLASSIFICATION OF VASCULAR MALFORMATIONS (2017)

Two major classes had emerged from the Mulliken and Glowacki classification of vascular anomalies- haemangiomas and vascular malformations. However with the advent of advanced colour doppler and MRI examinations in the 1990s, there was new understanding of these vascular malformations (4).

The current classification that is accepted worldwide is International Society for Study of Vascular Malformations (ISSVA) in 2017, which is comprehensive and includes most of the malformations and tumours of vascular origin (5).

VASCULAR ANAMOLIES			
Vascular tumours	**Vascular malformations**		
	Simple	Combined	Syndromic association
Benign	Capillary Lymphatic Venous Arteriovenous malformations Arteriovenous fistulas	CVM CLM CAVM CLAVM LVM CLVM	Klippel Trenaunay Parkes weber Servelle martorelle Mafucci

Locally aggressive	Kaposiform hemangioendothelioma Kaposi sarcoma		
Malignant	Angiosarcoma		

The benign vascular tumours are further subclassified into (8):

BENIGN VASCULAR TUMOURS
Congenital haemangioma - Rapidly involuting - Non involuting - Partially involuting
Tufted angioma
Spindle cell haemangioma

Epithelioid haemangioma
Pyogenic granuloma
LOCALLY AGGRESSIVE OR BORDERLINE TUMOURS
Kaposiform haemangioendothelioma
Retiform haemangioendothelioma
Composite haemangioendothelioma
Kaposi sarcoma
Papillary intralymphatic angioendothelioma
MALIGNANT VASCULAR TUMOURS
Angiosarcoma
Epithelioid hemangioendothelioma

The simple vascular malformations are further classified into capillary, venous, lymphatic broadly which have distinct entities in each:

CUTANEOUS VASCULAR MALFORMATION
Cutaneous or mucosal with
-Soft tissue overgrowth
-With CNS or ocular anomalies
-with microcephaly capillary malformation

-Megalencephaly capillary malformation polymicrogyria
Hereditary haemorrhagic telangiectasia
Cutis marmorata congenital
Nevus simplex / Angel kiss / Stork bite

Lymphatic (8)

SIMPLE VASCULAR MALFORMATIONS
Lymphatic Malformations
Microcystic
Macrocystic
Mixed
Generalised Lymphatic anomaly
Gorham stout disease
Primary lymphedema

Simple vascular malformations – II
Lymphatic malformations
Common (cystic) lymphatic anomaly
- Macrocystic LM
- Microcystic LM
- Mixed LM
Generalised lymphatic anomaly
LM in Gorham stout disease
Primary Lymphedema
Chanel type LM

Lymphedema is further classified as:

PRIMARY LYMPHEDEMA
Nonne Milroy syndrome
Primary hereditary lymphedema
Hypotrichosis lymphedema telangiectasia
Primary lymphedema with myelodysplasia
Microcephaly with or without chorioretinopathy

Venous malformations (8)

Simple vascular malformations III
Venous malformations
Common VM
Familial VM cutaneous – mucosal (VMCM)
Blue rubber bleb nevus (bean) syndrome VM
Glomovenous malformation
Cerebral cavernous malformation
Others

Arterio-venous malformations with an arterial component in the malformation – which are a different entity – should be embolised with alcohol.

Simple vascular malformations IV
Arteriovenous malformations
Sporadic
In HHT
In CM – AVM
Arterio-venous fistula (congenital)
Sporadic
In HHT
Others

A combination of any of these can occur, whereby it is classified as combined vascular malformation (8).

Combined vascular malformations		
CM + VM	Capillary - venous malformation	CVM
CM + LM	Capillary - lymphatic malformation	CLM
CM + AVM	Capillary - arteriovenous malformation	CAVM
LM + VM	Venous – lymphatic	VLM
CM + LM + VM	Capillary - Lymphatic - venous malformation	CLVM
CM + LM + AVM	Capillary - Lymphatic - arteriovenous malformation	CLAVM
CM + VM + AVM	Capillary -venous - arteriovenous malformation	CVAVM
CM + LM + VM + AVM	Capillary -lymphatic - venous - arteriovenous malformation	CLAVM

There are syndromic associations which are associated with vascular malformations which are separately classified according to ISSVA guidelines (8).

Vascular malformations associated with other anomalies	
Klippel – Trenaunay	CM + VM + limb overgrowth
Parkes Weber	CM + AVF + limb overgrowth
Servelle – Martorell	Limb VM + bone undergrowth
Sturge- Weber	Facial + leptomeningeal CM + Eye anomalies + bone /soft tissue overgrowth
Mafucci	VM + spindle cell haemangioma + multiple enchondromas
CLOVES	LM + VM + CM + AVM + lipomatous overgrowth
Bannayan- Riley- Ruvalcaba	AVM + VM + macrocephaly + lipomatous overgrowth

A few of these vascular anomalies cannot be grouped under any of the categories and are grouped under unclassified category in the ISSVA classification (9).

Provisionally unclassified vascular anomalies
Verrucous hemangioma
Angiokeratoma
Kaposiform lymphangiomatosis (KLA)
PTEN (type) hamartoma of soft tissue
Multifocal lymphangioendotheliomatosis with thrombocytopenia

Thus, although the classification is extensive, a broad division of these vascular anomalies (other than tumours) for therapy is that determining if any of these lesions have an arterial or fast component associated in these specific conditions.

If any of them have an arterial component – which is determined by ultrasound and doppler study, then the management would primarily consist of embolization with alcohol (10).

Slow flow vascular malformations – lymphatic, capillary, venous and a combination of them is diagnosed by the absence of arterial component on ultrasound and doppler screening. Treatment for these slow flow malformations is primarily done by injecting a sclerosant into these vascular spaces. The sclerosant induces intimal fibrosis and induces an inflammatory response which causes near total obliteration of these vascular spaces (11).

Treatment of these various types of slow malformations requires a multidisciplinary approach with paediatric and plastic surgeons, anaesthetists, diagnostic and interventional radiologists , critical care and vascular surgery (12). Most of these vascular malformations should be managed in a tertiary level centre, as it requires expertise of all these specialists, and a combined decision regarding patient management is done.

HEMANGIOMAS

Haemangiomas are the commonest vascular tumours (13). The pathophysiology of these lesions is disorderly endothelial cell proliferation with abnormal angiogenesis.

These generally are not visualised at birth. Two types of haemangiomas are generally described – congenital and infantile types which are different in their clinical presentation (13).

Congenital haemangiomas are at maximal size at birth and have three types of behaviour:

1. Rapidly involuting haemangiomas – involute rapidly
2. Partially involuting – do not regress completely
3. Non involuting

Infantile haemangiomas are one of the commonest vascular tumours of infancy – more commonly found in preterm infants with a female pre-ponderance (3:1) with an incidence of 23 % in low birth weight neonates. Head and neck region is the most common region to be affected (>60%) (14) with more than 80% being solitary.

The molecular marker for infantile haemangioma is glucose transporter 1 (GLUT-1), which is characteristically absent from congenital haemangiomas (13).

Radiological findings on ultrasound include echogenic soft tissue component with an arterial or fast component noted within the mass. CT is generally not indicated in diagnosis or management, with an additional risk of radiation exposure.

MRI is useful in delineating the anatomical structures such as the airway, vital neurovascular proximity and has the become the standard of care before planning pharmacological treatment or a minimally invasive surgical procedure (13).

Haemangiomas are the commonest vascular tumours which regress in childhood. Other tumours which have been described have borderline or malignant behaviour, where there's a risk of the Kasabach-Merritt phenomenon – in which there's a risk of a consumptive coagulopathy and subsequent disseminated intravascular coagulopathy with life threatening consequences. Hence early assessment of vascular tumours are essential (7).

VASCULAR MALFORMATIONS

Vascular malformations are generally occur from birth, although most of them may not be symptomatic at birth. A variety of factors during early childhood and development lead to overt clinical manifestations of these malformations. A good history combined with a clinical examination supplemented with appropriate imaging is necessary for diagnosis. They may occur sporadically or as part of certain syndromes in combination with other

vascular malformations. Described below are specific features of each malformation:

SPECIFIC FEATURES OF EACH SUBTYPE

CAPILLARY MALFORMATIONS

Capillary malformations, are most commonly referred to loosely as a ‘port wine stain’. They usually occur as sporadic findings, however some of them maybe associated with sinister syndromes like Sturge weber syndromes which is associated with classical findings such as facial angioma, seizures, glaucoma, mental retardation and arterio-venous malformation in the brain. Thus an isolated capillary malformation must not be taken lightly and should be investigated to rule out systemic abnormalities associated with fatal syndromes (9).

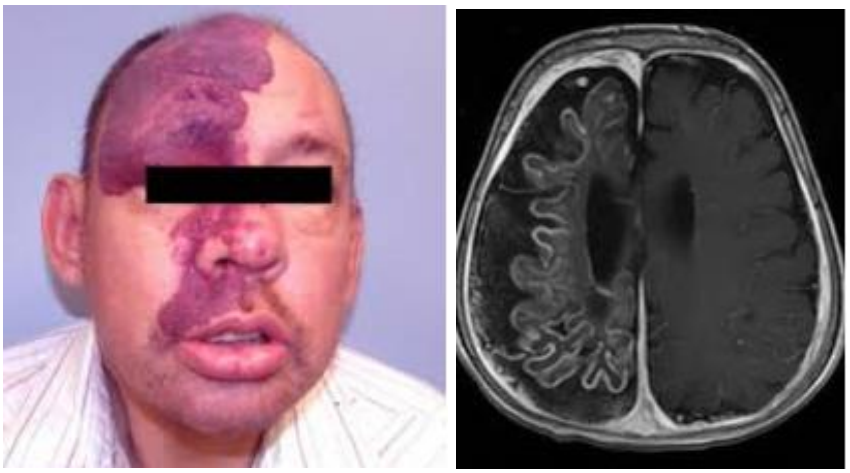


Figure 2

Above is a gentleman with Sturge Weber syndrome. Clinical photograph showing facial cutaneous malformation (port wine stain). T1W axial MRI image showing right sided cerebral hemiatrophy (6)

Most of these patients present with a flat macule, which is pink in colour, blanches on application of pressure. If the location of such a lesion occurs on the face, it warrants a MRI study of the brain, to look for arterio-venous malformations of the underlying brain, associated with a gyral pattern of calcification, classically described as tram-track calcification on a plain CT study of the brain in these patients.

The standard of care is pulsed dyed laser, which acts by a mechanism of photo-thermolysis, where haemoglobin selectively absorbs laser light, thereby converting it to heat, causing blood to coagulate. Significant relapses can occur, alternative therapies include pulse light and photo-dynamic therapy (15). Sclerotherapy is generally not used in capillary malformations.

VENOUS MALFORMATIONS

Venous malformations are most common type of slow flow vascular malformations. Hamburg et al classified it as truncular, and extra-truncular with the distribution following a near pattern of symmetry in the form of head and neck constituting 40%, truncal being 20% and extremities being 40%.

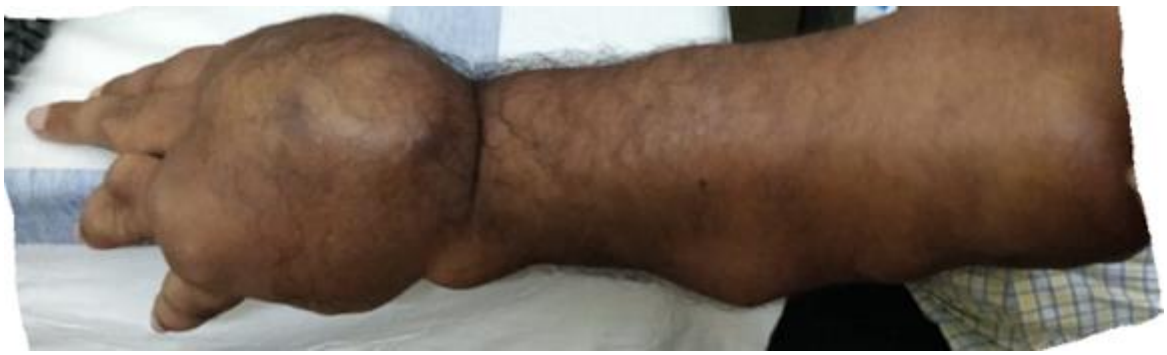


Figure 3: Soft tissue swelling and cosmetic disfigurement due an extensive trans-spatial venous malformation in this patient with serial number 13 in the current study.

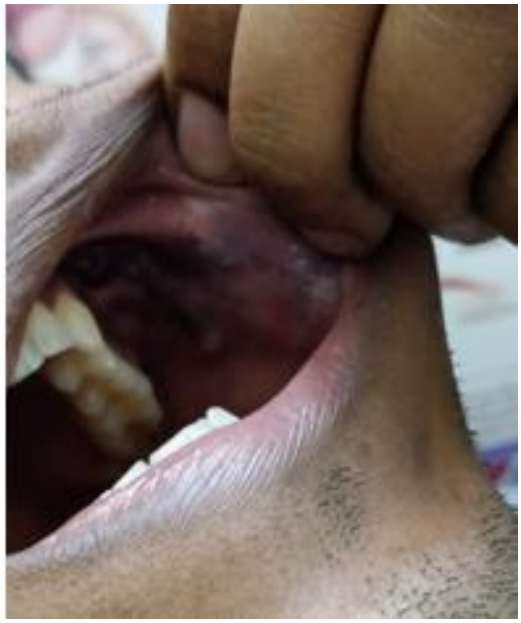
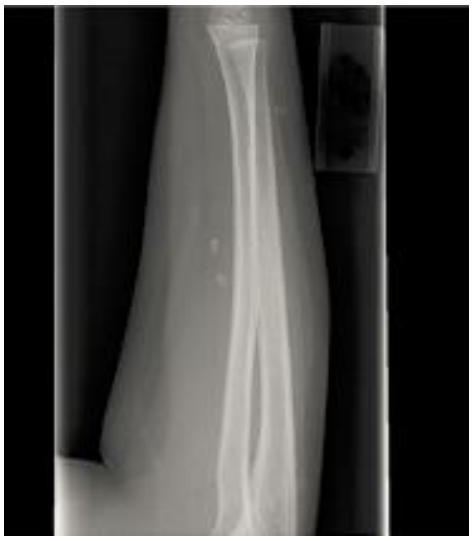


Figure 4*:* Bluish discoloration of the oral mucosa in a patient with bleeding following eating. Venous malformation of the entire oral mucosa is seen.



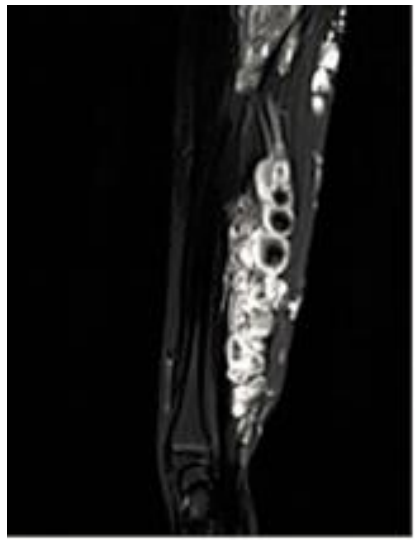
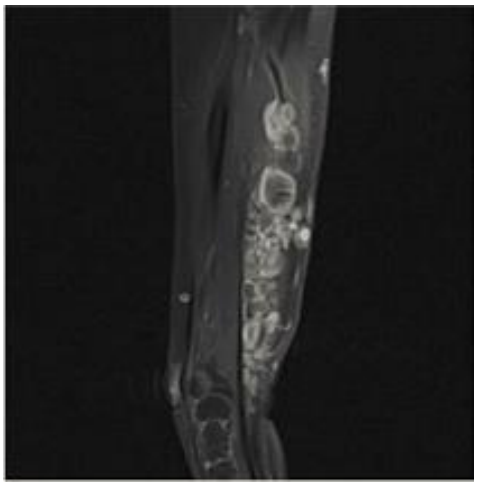


Figure 5: Serial number 17 patient in this study – plain radiograph of the left forearm showing soft tissue density with a few calcifications within them. Fat suppressed coronal STIR images show hyperintense spaces with multiple phleboliths, appearing as STIR hypointense discrete foci.



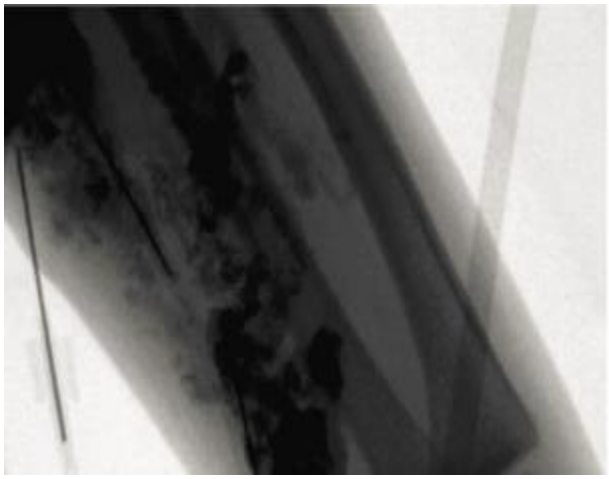


Figure 5: Serial 23 patient in this study – 13-year-old child with right thigh swelling – fat supressed coronal STIR images showing multiple hyperintense spaces in the posterior intramuscular component, with multiple phleboliths. Corresponding fluoroscopy image during sclerotherapy showing diffuse nature of this VM.

CLASSIFICATION OF VENOUS MALFORMATIONS (13,16)

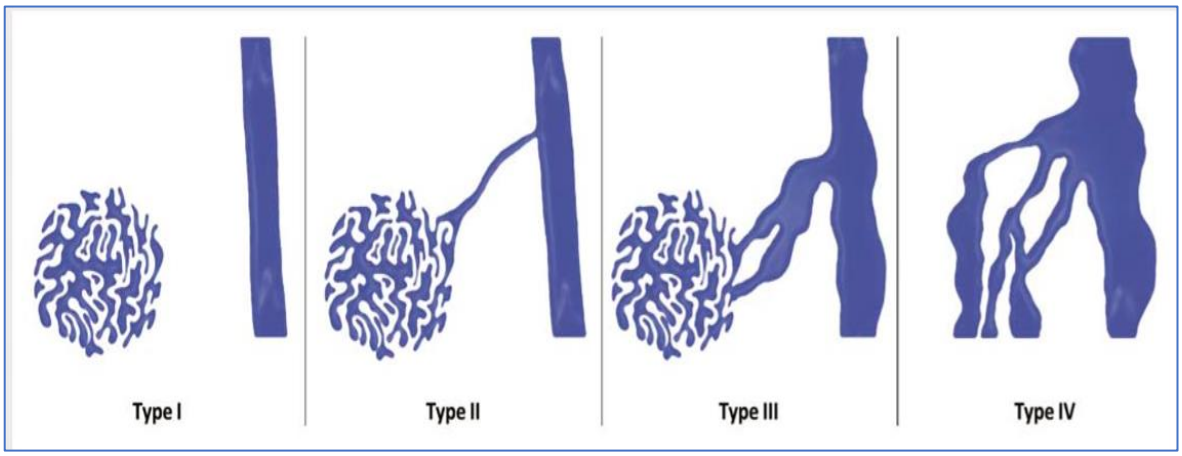


Figure 6:The updated ISSVA classification (2017) for venous malformations (13) is based on the type of cystic spaces with the venous drainage evident on DSA.

The classification of venous malformations is essentially based on the phlebography appearance of these lesions once contrast is injected: -

Type I denotes an isolated venous malformation with no visible venous drainage.

Type II denotes normal sized venous drainage nearby.

Type III denotes enlarged venous drainage.

Type IV essentially consists of enlarged dysplastic venous channels which are ectatic.

This classification is important in management of these lesions, as the amount of sclerosant, use of a proximal tourniquet for proximal venous occlusion is dependent on the type of the venous malformation.

Clinically they present as bluish lesions that increase in size with any increase in pressure such as Valsalva, or cough impulse. They also cause bluish discoloration. They can be classified as focal or diffuse, with diffuse involving multiple soft tissue planes. These diffuse venous malformations often require multiple sessions of treatment, and often recur (17).

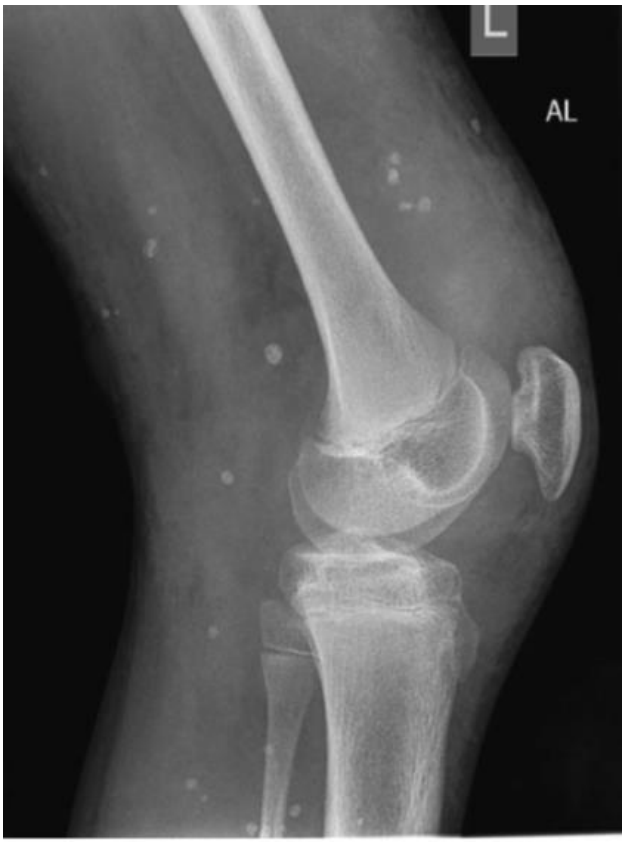
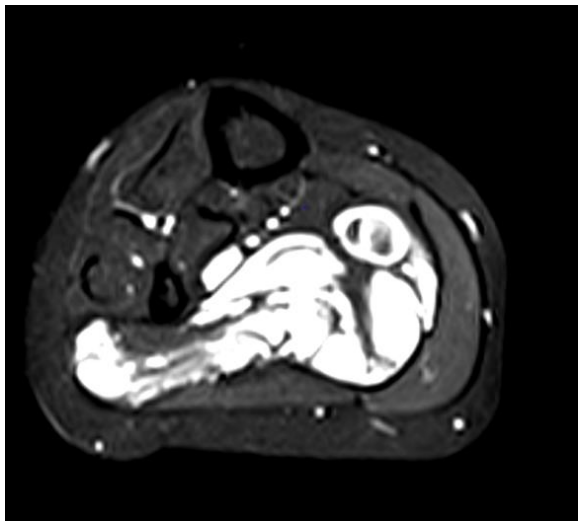


Figure 7: 9-year-old child with diffuse VM of the left lower limb - plain radiograph of the left knee showing multiple soft tissue calcifications in patient with known VM – phleboliths because of prior thrombophlebitis



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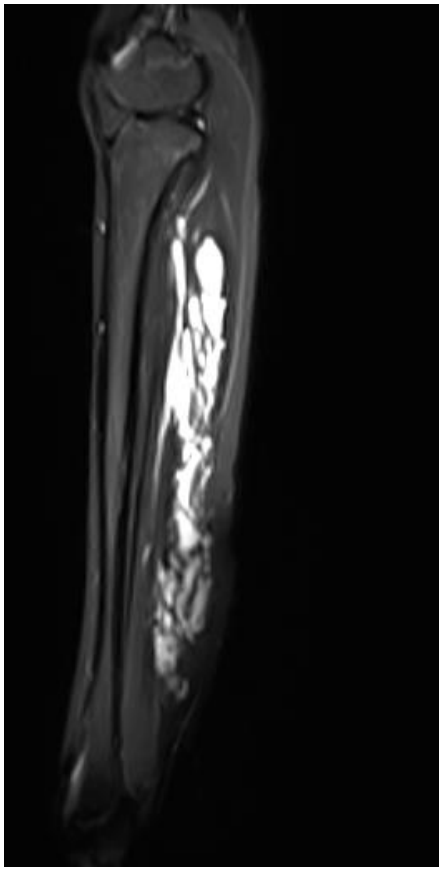


Figure 8*:* Serial 8 patient in the current study is a 15-year-old child, VM of the left lower limb -with intramuscular STIR hyperintense cystic spaces in the left calf with a few hypointense foci suggestive of phleboliths

The symptoms they cause could be due to regional mass effect causing cosmetic effect or an obstruction of the airway in the head and neck region, or a high risk of thrombo-embolism due to dysplastic veins in the lower limbs. Close proximity to a large synovial joint (e.g.: knee) can cause hemosiderotic arthropathy which predisposes to early degenerative changes within the joint leading to restriction of range of movement along with pain (13).

Conventional radiography of these lesions reveals multiple calcified phleboliths which represent calcified thrombi because of delayed venous clearance due to previous thrombophlebitis.

MRI is the primary imaging modality for assessing venous malformations. T2-weighted short tau inversion recovery (STIR) imaging provides the best sequence for assessing the extent of the VM and the vascular flow rate and will demonstrate a soft tissue with phleboliths. Additionally, lesions with large vascular channels appear cyst-like, hyperintense and septated, whereas lesions with smaller vascular channels are more solid with intermediate signal intensity. On T1 weighted imaging, the lobulated area has variable signal intensity with regional fat hypertrophy. Following contrast injection, T1 weighted imaging demonstrates homogeneous or heterogeneous

enhancement within the lesion MRI is also useful in determining adjacent tissue involvement, as vascular malformations can be well circumscribed or infiltrate into adjacent soft tissue or the lymphatic system.

Conservative management of these venous malformations include graded compression stockings (13,16) used to reduce pain and deformity along with slowing the progression of the disease, However these are not definitive treatment modalities.

The definitive treatment of venous malformations include sclerotherapy with agents like sodium tetradecyl sulphate (STS), polidocanol and absolute alcohol, each of which have their own advantages and disadvantages (18).

In extensive venous malformations, in which there is no symptomatic improvement despite sclerotherapy or other conservative methods-m-TOR inhibitors (mammalian target of rapamycin) such as Sirolimus have shown promising results, although long term effects are not known & the data is based on small case series with no large scale randomised controlled trials (19).

LYMPHATIC MALFORMATIONS

Lymphatic malformations (LMs) account for approximately 2.8/100,000 hospital admissions and present before the age of 2 years in 90% of cases.

They are low-flow vascular malformations consisting of malformed lymphatic channels within the lymphatic system and are cystic in nature. LMs can be divided by size into macrocystic (>0.1 cm) and microcystic (<0.1 cm) groups. Typically, microcystic LMs are more common and present later than macrocystic LMs, which are usually present at birth (20).
The appearance of LMs depends on their location. Superficial LMs are typically skin-coloured masses and ballotable on palpation, whereas they appear as red or yellow blisters when involving mucous membranes. LMs have a predilection for the head and neck with 70–80% of cases in this location, and an additional 20% occurring in the axilla and a minority of cases occurring in the superior mediastinum, mesentery, retroperitoneum, pelvis and lower limbs (21). They typically grow slowly, although rarely LMs can rapidly expand in size after intralesional haemorrhage or superinfection. In these cases, LMs can become life threatening if they cause adjacent mass effect and compression of vital structures (20).

Podoplanin D2-40 is a molecular marker that is positive in lymphatic endothelium, and may be used to differentiate between other vascular malformation, when there are overlapping clinical features (16).

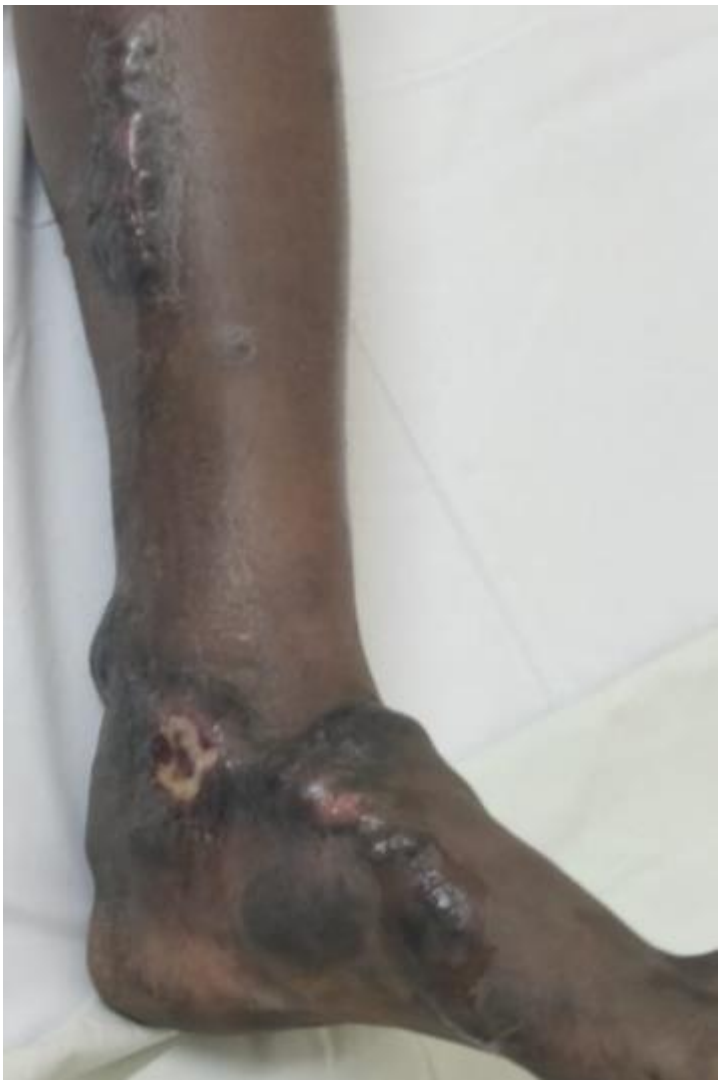


Figure 9: Microcystic lymphatic malformation with recurrence following surgery with non-healing ulcer, lymphatic ooze and discoloration in a 13-year-old boy, who had been referred to the interventional radiology clinic. He was offered m-TOR inhibitor- sirolimus in view of the diffuse microcystic LM.

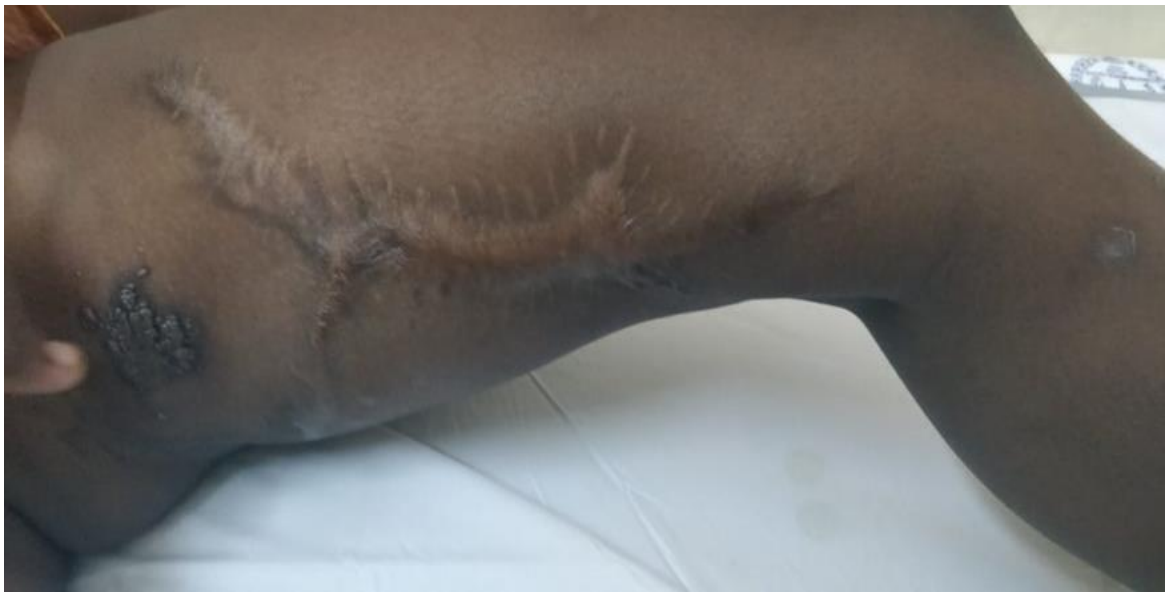
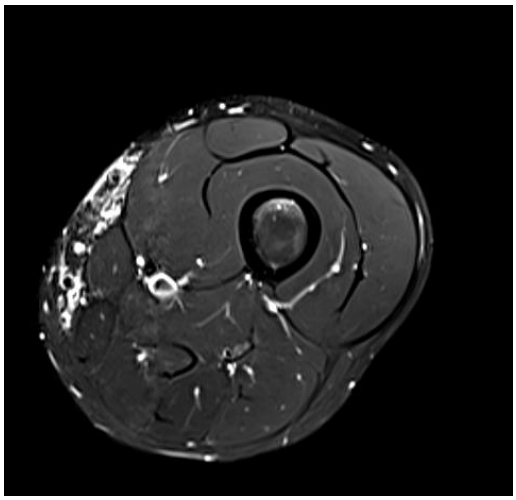


Figure 10: Vesicular appearance of microcystic lymphatic malformations- note scar of prior surgery in a 13-year-old boy referred to the interventional radiology clinic. Sirolimus was offered**.**



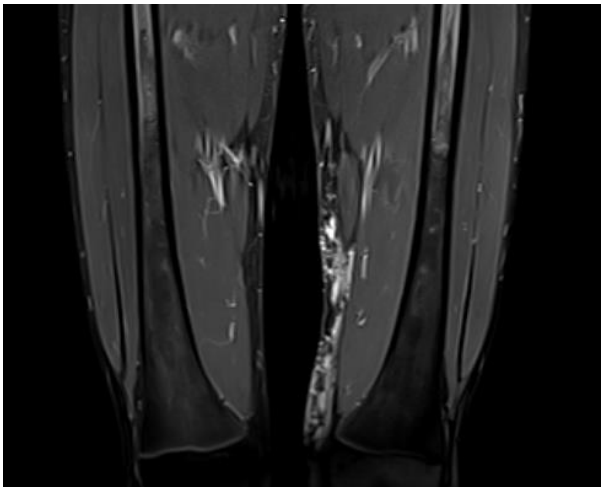
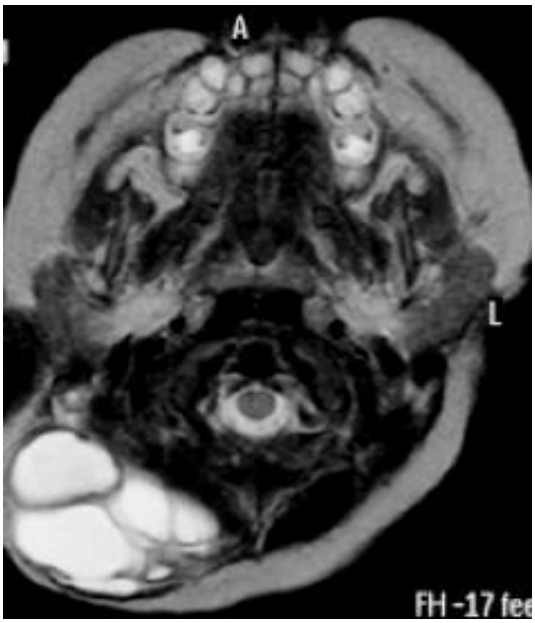


Figure 11 : The young child in the Fig 11 clinical picture – corresponding STIR axial and coronal MRI images shows a microcystic LM with STIR hyperintensities in the skin and subcutaneous tissues of the medial thigh.



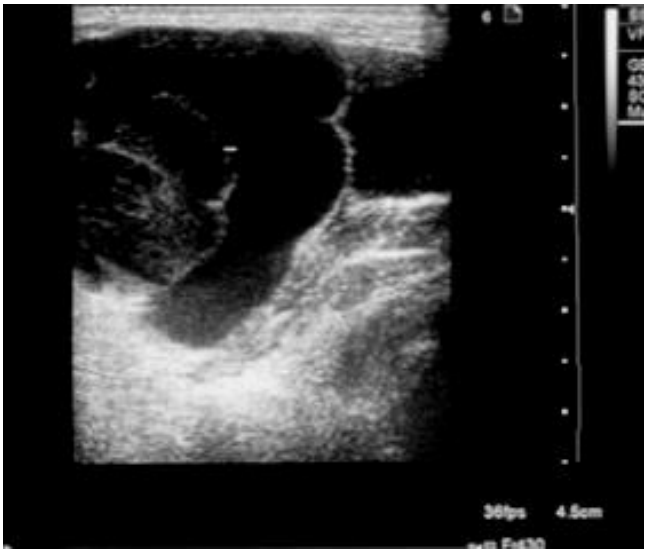


Figure 12:Serial number 16 of 3-year-old child in thus study with a large swelling in the right side of the neck - corresponding T2w images show a macrocystic LM with fluid-fluid level and multiple septae. Ultrasound images show a cystic lesion with dependent low-level echoes.

The evaluation of LMs is highly reliant on imaging to discern the size and characteristics of the lesion, as these directly dictate treatment strategies and outcome. As with other vascular anomalies, MRI is the best imaging modality for diagnosing and defining LMs because of its superior soft-tissue resolution. Microcystic and macrocystic LMs have distinct appearances on MRI owing to the size difference in their cystic component. On T2 weighted MRI and T2 weighted STIR imaging, LMs are typically well defined, lobulated and hyperintense T1 weighted imaging of macrocystic LMs typically shows a septated cystic mass that ranges from hypointense to isointense and that is often heterogeneous owing to proteinaceous fluid or fluid–fluid levels. Post-contrast T1 weighted images are also important tools for differentiating macrocystic LMs from VMs, as LMs typically do not enhance after contrast injection unlike VMs. By contrast, the small cystic compartments of microcystic LMs appear as diffuse hypointensity on T1 weighted imaging and diffuse hyperintensity on T2 weighted imaging.

Sometimes, other imaging modalities may be needed to further define the lesion or differentiate an LM from other vascular anomalies. Ultrasound is a particularly useful method for discriminating LMs from VMs. Macrocystic LMs typically manifest as anechoic spaces divided by septa, whereas

microcystic LMs appear hyperechoic owing to their small cavity size. Ultrasound is also useful for evaluating prior haemorrhage and demonstrating fluid–fluid levels. In addition, Doppler examination of LMs demonstrates no flow through the lesion, which helps distinguish them from VMs, where flow is seen in 85% of cases. Conventional radiology can also be useful in the work-up of large LMs near bone, as they can cause bony hypertrophy and bone warping. Although usually not necessary for the diagnosis of LMs, CT imaging demonstrates a fluid-filled low-attenuation mass with little contrast enhancement. In cases of intralesional haemorrhage, fluid–fluid levels may be visible on CT. Treatment indications for LMs are like those of other vascular malformations, with lesions located in life-threatening areas such as retropharyngeal LMs requiring prompt treatment.

Any LM that has experienced a haemorrhagic or infectious event should also be treated and requires antibiotics and steroids in addition to definitive treatment of the LM. Relative indications for treatment include patient discomfort, impaired mobility, aesthetic dissatisfaction or any other cause that significantly impairs quality of life.

FAST FLOW MALFORMATIONS

The vascular malformations included here are arteriovenous malformations and arteriovenous fistulae. Although these can commonly occur sporadically, they can occur in combination with other vascular malformations or in association with other malformations. These can give rise to various syndromes. The Klippel-Trenaunay syndrome is the commonest.

ARTERIO-VENOUS MALFORMATIONS:

These are abnormal connections or shunts between arteries and veins without any network of capillaries between them. The cluster of abnormal connections or shunts in these malformations is called a nidus (16). In an arterio-venous fistula, there's shunting of blood through a single arterialised vein.

AVMs can occur anywhere in the body and thus have varied clinical manifestations depending upon the local effects it causes. AVMs generally present as pulsatile masses, with increased local warmth, generally associated with a palpable thrill if it is superficially located. Schobinger classification

accurately describes the various stages of an AVM and is thus helpful in directing clinical management.

SCHOBINGER CLASSIFICATION OF AVMs

Stage	Description	Findings
I	Quiescence	Cutaneous blush & warmth
II	Expansion	Bruit or thrill with increasing size, pulsation, no pain
III	Local destruction	Pain, bleeding, infection, skin necrosis or ulceration
IV	Decompensation	High output cardiac output failure

AVMs in the final stage can cause high output cardiac failure due to rapid arterio-venous shunting which increases the cardiac pre-load. AVMs generally are symptomatic during puberty when there's a hormonal influence

on angiogenesis and during pregnancy when there's a rapid increase in blood volume. Trauma and incomplete endovascular treatment with embolic agents can cause an increase in pro-angiogenic factors and thus worsening of the clinical symptoms.

Two syndromes which are commonly associated with AVMs are hereditary haemorrhagic telangiectasia (HHT), which are associated with multiple telangiectasias of skin and mucosa.

SCLEROTHERAPY FOR SLOW FLOW VASCULAR MALFORMATIONS

Foam sclerotherapy has become the standard of care for slow flow vascular malformations (venous, lymphatic, venolymphatic). Several sclerosants have been used for slow flow vascular malformations, but the most widely used in our centre is sodium tetradecyl sulphate 3% by volume and bleomycin if there is a lymphatic component involved.

WORKUP FOR PATIENTS PRIOR TO SCLEROTHERAPY

A thorough history and clinical examination is performed with specific regard to their predominant symptom. Then an ultrasound or doppler is done to confirm the presence of cystic compressible vascular spaces with absence of arterial flow within the lesions. MRI is done in all patients to accurately delineate the soft tissue extent of the malformation with specific regards to the neurovascular proximity, airway in head and neck lesions and intra-osseous or intra-articular extensions as all of them have a bearing on the outcome.

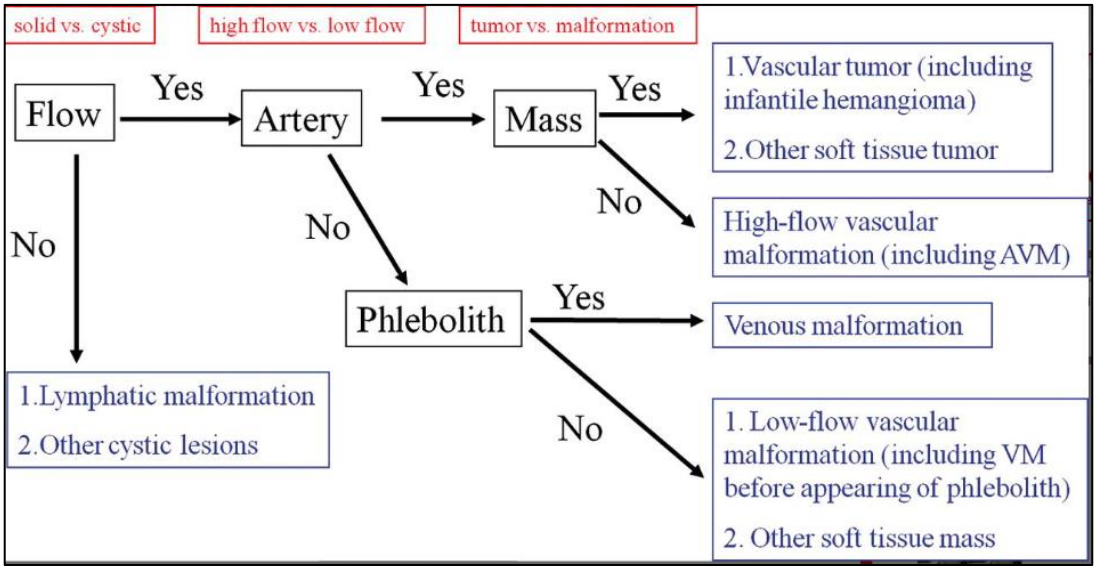


Figure 13 A practical algorithm used by interventional radiology for identifying the diagnosis and the type of treatment using ultrasound and doppler examination (6)

Basic blood investigations are done such as haemoglobin, blood borne viral status, bleeding parameters such as prothrombin time, partial thromboplastin time, and platelet count.

A recent recommendation is D-dimer levels particularly patients with large lesions, as there is usually associated localised intravascular coagulation (22), which can progress to disseminated intravascular coagulation in large lesions. Thus, a close monitoring of patients should be done in the ward. Any prolonged bleeding episodes must be dealt with caution.

D dimer can also be a used a lab predictor of future recurrence of these lesions or a reliable predictor of outcome. Leung et al (22) have shown that an increase in D dimer post procedure generally favours a better outcome

PROCEDURE – SCLEROTHERAPY

Sclerotherapy has become the standard of care for management of slow flow vascular malformations. The basic principle of sclerotherapy is that it induces an inflammatory response, which results in pro-fibrotic growth factor release, which ultimately leads to intimal fibrosis, thus leading to decrease in the size of the cystic spaces which reduces the patient's symptoms.

Generally multiple sessions of sclerotherapy are needed for a complete response, with a minimum interval of 6 weeks between sessions to induce intimal fibrosis. In our centre, with most patients have a median time interval varying between 3 months to a year. Most patients require a minimum of 3-4 sessions of sclerotherapy, although it depends on the type, location and largely on the size of the lesion prior to therapy. Larger lesions may require multiple sessions, although extensive lesions may benefit from sirolimus (m-TOR inhibitors).

The primary endpoint of the treatment of these malformations for sclerotherapy is reduction in the degree of the symptoms, especially in the extremities, where these vascular malformations tend to cause debilitating pain restricting their activities of daily living. The endpoint of therapy for

malformations in the head and neck region include improvement in the cosmesis or improvement of their quality of life.

The decision for repeat sclerotherapy is also determined prior to the procedure, by assessing the presence of cystic, compressible spaces with absence of arterial component which would be designated as spaces amenable for sclerotherapy.

The procedures are carried out under general anaesthesia as these sessions are painful due to the immediate action of the sclerosant on the endothelial cells. All procedures were carried out in a digital subtraction angiography suite (Artis Ziehm© biplane Seimens®) under strict aseptic precautions.

Figure 15: Artis Ziehm© biplane Seimens® apparatus used for sclerotherapy.

Based on the location, after anesthetising the patient a tourniquet may be used especially in extremity venous malformations, to make the cystic spaces more prominent before access with a 21G needle. The cystic spaces are marked out on the skin with superficial transducer probe (7.5-10 MHz)

machine.

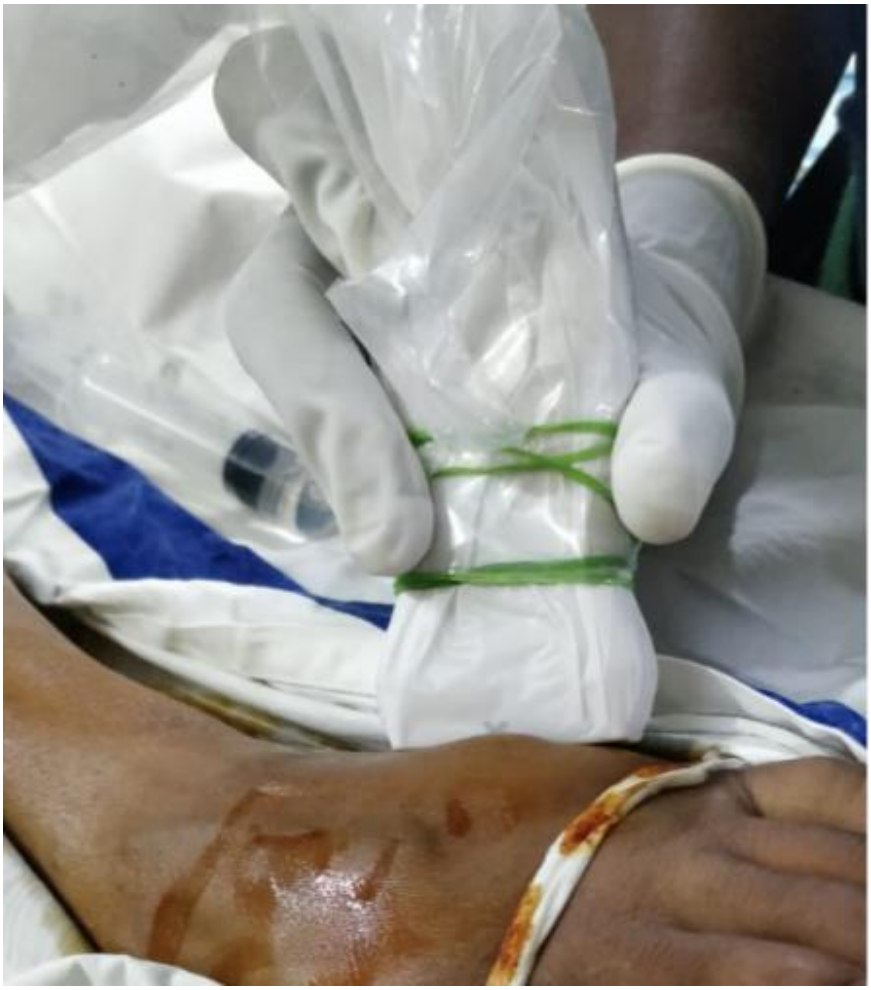


Figure 16: Under aseptic precautions ultrasound being used for accurate localisation of the slow flow vascular malformation

The venous malformations are accessed under strict aseptic precautions with either a scalp needle (22 G) or a lumbar puncture needle (21 G) based on

how superficial or deep the lesion for access. Generally multiple needles are placed in the cystic spaces to equally distribute the sclerosant foam volume into the slow flow vascular malformation.

Figure 17: 22G LP needle for access to deeper lesions

Figure 18: 24G scalp needle used for superficial access

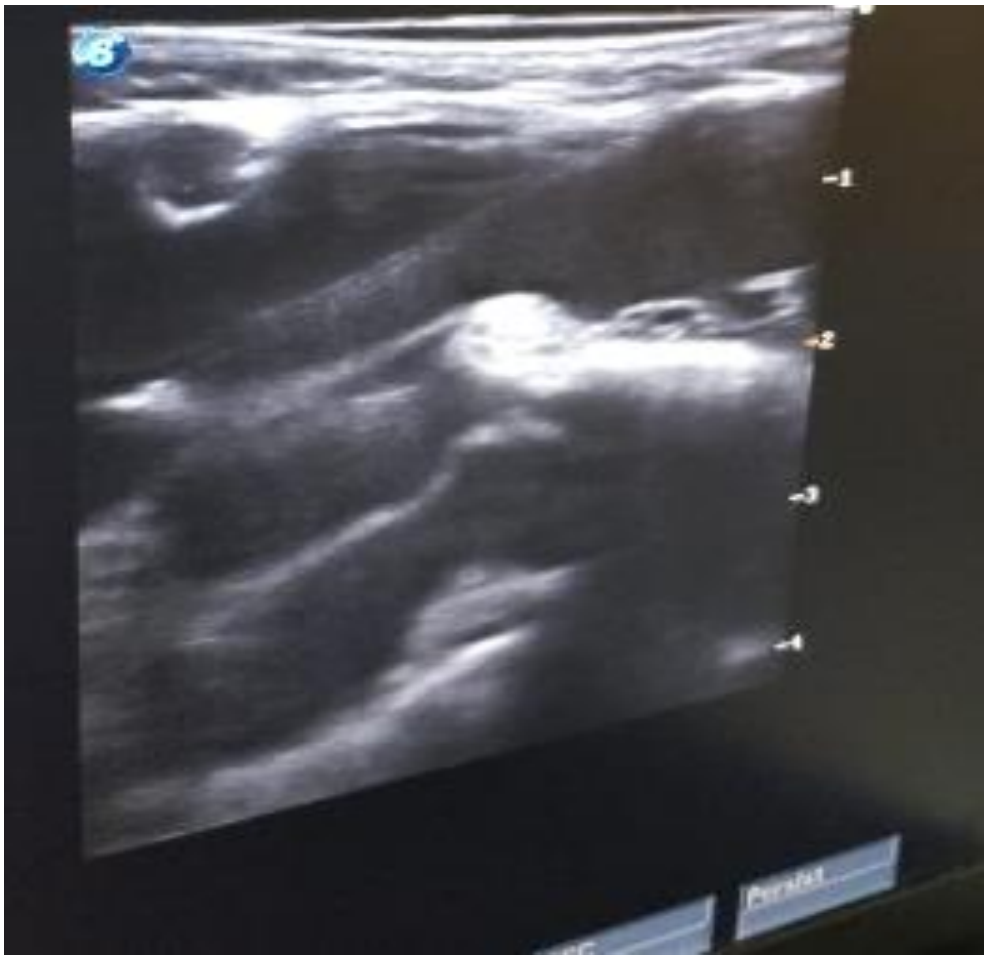


Figure 19: Cystic spaces accessed with 22G LP needle under USG guidance

Access into the cystic spaces of the venous malformation under direct visualisation of ultrasound

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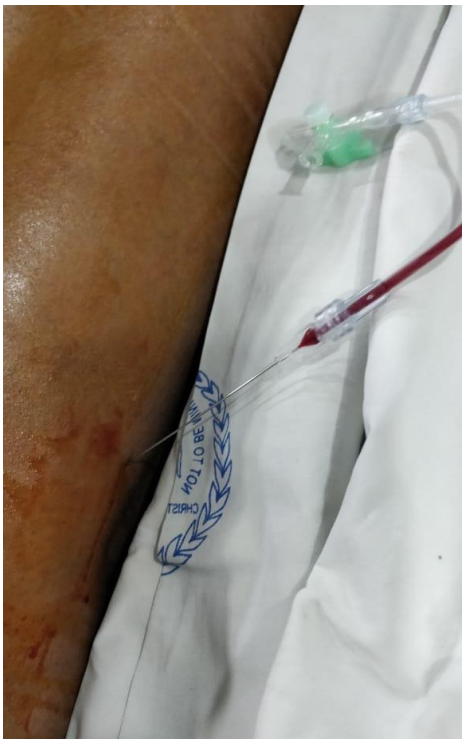


Figure 20 : Figure showing free flow of blood confirming the location of the needle within the slow flow vascular malformation.

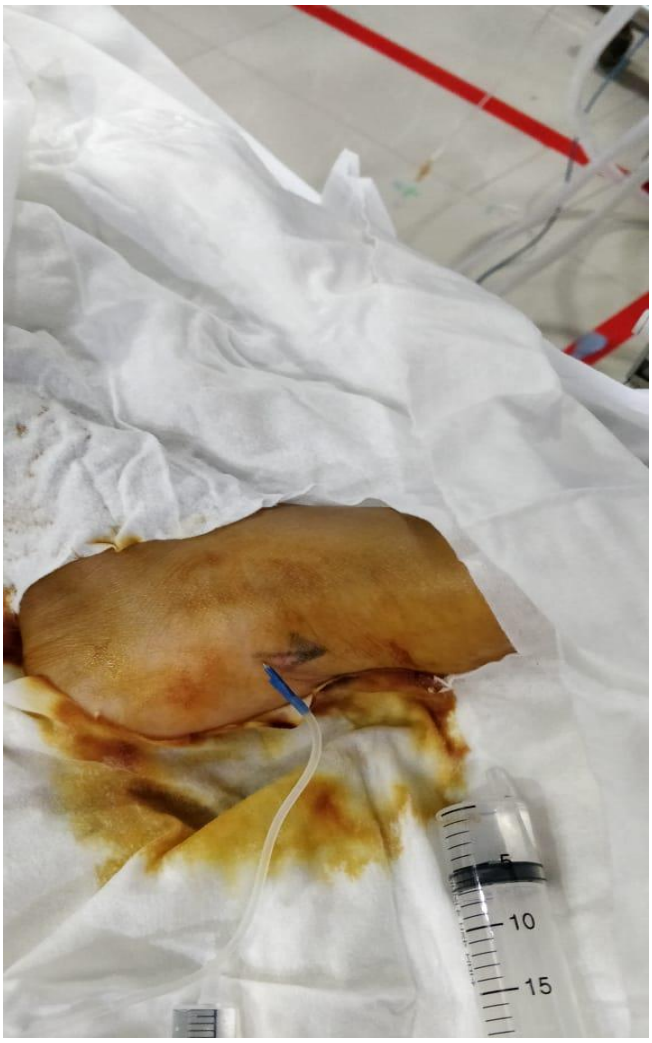


Figure 21: Saline infusion into the tubing to prevent the clotting of blood, after free backflow was identified.

Minimal saline infused into the extension of the needle to prevent blood from clotting in the tract prior to injection.

After accurately placing the needle in the cystic spaces of the slow flow vascular malformation using ultrasound guidance, a small amount of contrast is injected with a ‘Roadmap’ mode chosen on the DSA machine. Contrast is injected till there is faint opacification of a draining systemic vein. This serves as a surrogate marker for the dose of the sclerosant foam to be injected.

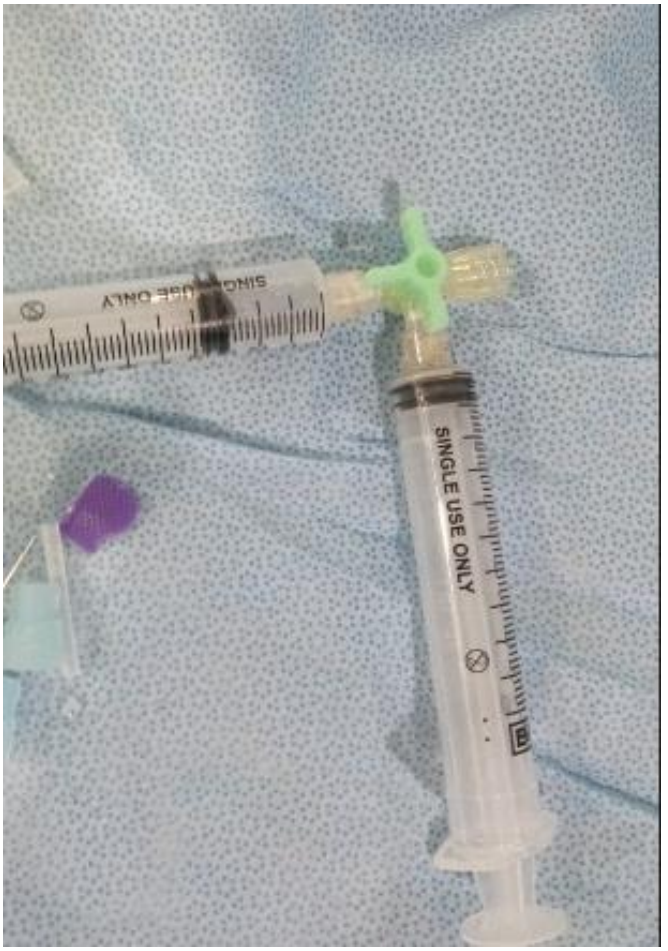


Figure 22: 3 way & stop cock used to prepare foam

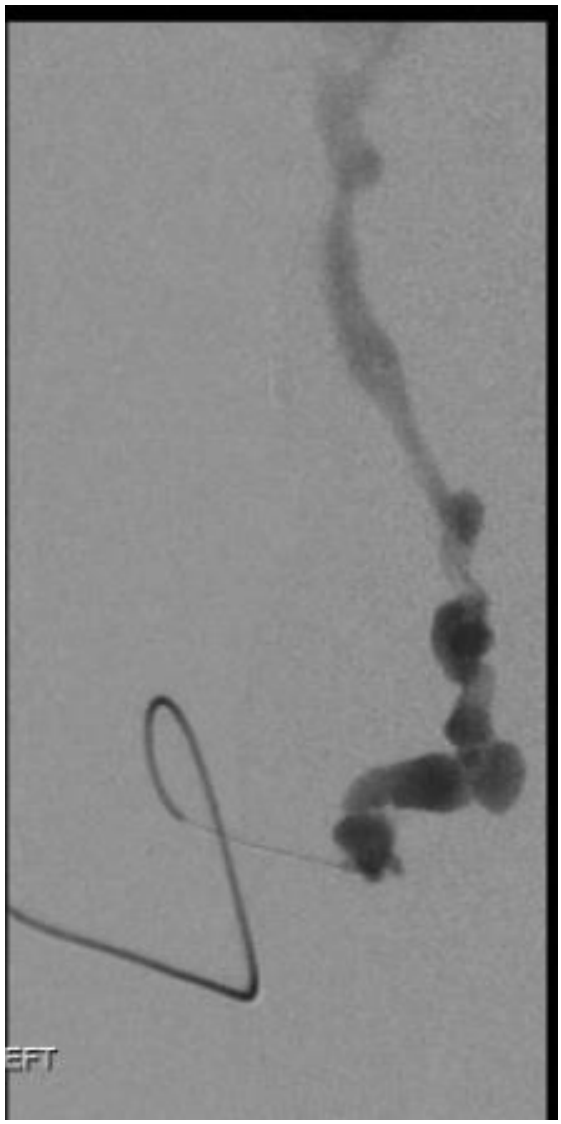


Figure 23: Venogram or phlebogram (using the 'Roadmap' setting in DSA) through the venous malformation to look for type of venous drainage and to calculate approximate dose of sclerosant. Above is type IV venous malformation with dysplastic large venous channels with a large normal draining vein cranially.

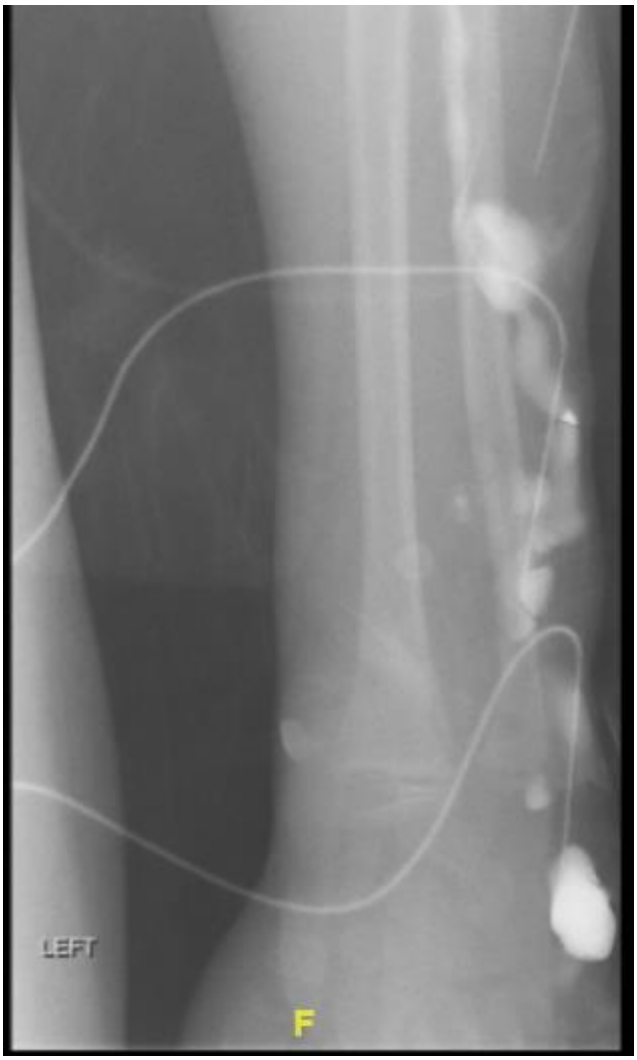


Figure 24: Inverted flouro-save image of venous malformation with multiple needles within it with contrast being injected to determine the type of venous malformation and the approximate dose to be injected into each needle . Also note multiple phleboliths which are calcified thrombi in the venous malformation in the left foot which are diagnostic of a venous malformation on plain radiographs.

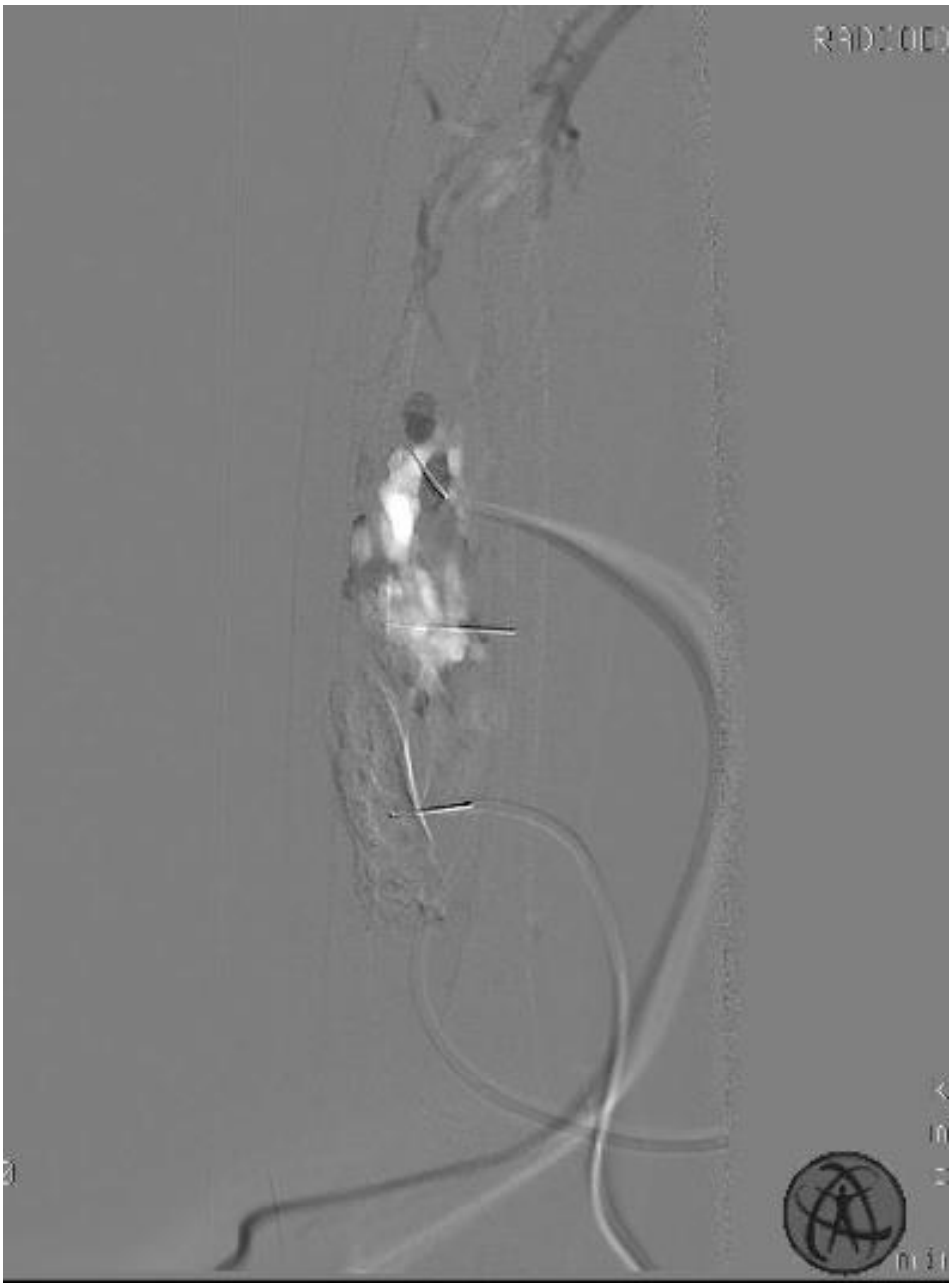


Figure 25: DSA image of a venous malformation being injected through multiple needles. Note the presence of air in the foam appearing as hyperdense on the negative DSA image.

If it is a large venous or veno-lymphatic malformation, blood or lymph is aspirated to decrease the overall volume of the malformation, so that the relative concentration of the sclerosant injected is much higher, to act on the endothelial cells in the wall of the slow flow vascular malformation.

Foam sclerotherapy is a concept where there is an equal amount of air aspirated through the syringe and mixed with the liquid sclerosant to form a foam using a three-way and another syringe. This serves two purposes. It reduces the total amount of the actual sclerosant being injected, and has a larger surface area of distribution, thus increasing the efficacy of the sclerotherapy.

Post-injection, the needles are usually left in place for a period of 5 to10 minutes, following which they are removed. Slow flow vascular malformations which are superficial and are in the head and neck region tend to increase in size post-sclerotherapy which resolve usually by 3 days. The amount of immediate post procedure pain also increases as there is immediate acute inflammatory response within, leading to pain, swelling, which can be managed with simple NSAIDs in the ward.

SCLEROSANTS USED FOR SCLEROTHERAPY

Multiple agents have been used in the past as sclerosants for slow flow vascular malformations. By far the most common sclerosant agent used is sodium tetradecyl sulphate (used as 3% weight per volume). The other sclerosants used are:

BLEOMYCIN

Bleomycin was initially developed as an anti-tumour antibiotic which acts at the cellular level to inhibit DNA synthesis. However, in recent studies it was shown to induce non-specific inflammatory reaction on the endothelial cells. It was first used on macrolymphatic malformations which was earlier called cystic hygroma. In a comparative study comparing alcohol and Bleomycin stated that alcohol is more effective in deeper lesions and Bleomycin is useful in superficial lesions.

Bleomycin in our department and institution is used primarily when there's a lymphatic component in the slow flow vascular malformation. It is primarily available as powder which is then reconstituted using normal saline to the desired dilution.

Figure 26: Bleomycin used in our current practice

SODIUM TETRADECYL SULPHATE:

Sodium tetradecyl sulphate is a commonly used sclerosant in clinical practice for other indications such as varicose veins. It is an anionic detergent agent (23) that acts by destroying or meddling with the lipid bilayer of the cell membrane. It also acts by denaturing intracellular proteins such as clotting factors and thereby inducing thrombosis of these vascular spaces, thus inducing fibrosis and decrease in size of the lesion (23). It is one of the most widely used sclerosing agents used worldwide for sclerotherapy for venous malformations. It has one of the best safety profiles with very rare risk of rhabdomyolysis and subsequent haemoglobinuria, which can cause renal failure. Hence all patients post procedure are advised adequate hydration, with strict monitoring of fluid intake and urine output.

Sodium tetradecyl sulphate is commonly available as a 3% w/v solution which is diluted with an equal amount of air to create foam sclerosant, which is then used for therapy.

The upper limit for usage is 1 ml/kg of liquid sclerosant in total for the entire patient. Thus, in children and infants with slow flow malformation in the

head and neck region, with proximity to the airway, dose is calculated prior to the procedure based on their weight, as excess dose can cause increased risk which can cause complications with increased hospital stay.

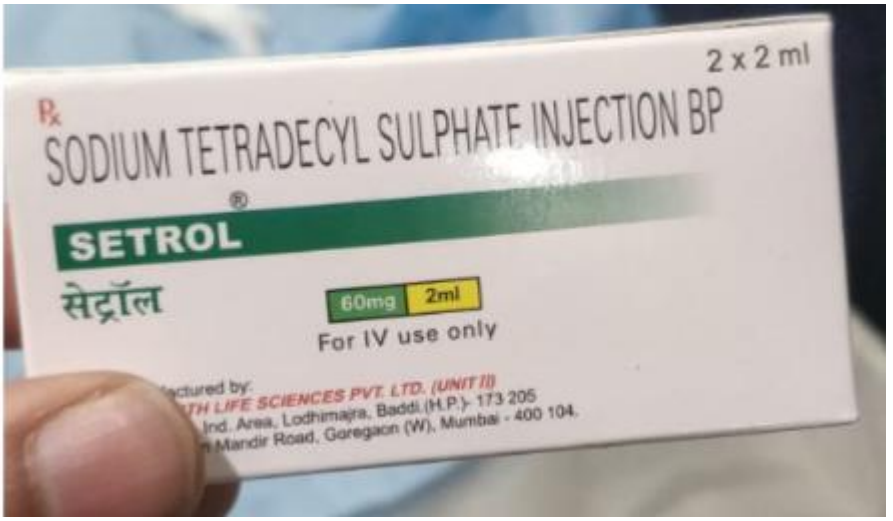


Figure 28: STS foam used in our practice

ETHANOLAMINE OLEATE

Ethanolamine oleate is a cytotoxic agent which is a mixture or emulsion of fatty acids which primarily acts on the endothelial cells, thus inducing thrombosis of the vascular spaces. This is not used in India currently due to its non-availability. It has a decent safety record with the reported complications being skin necrosis and ulceration which are observed in less than 5 percent of patients.

OK 432 (PICIBANIL)

Picibanil is bacterial origin antibiotic which primarily acts as an immune-stimulant, which causes local increase in the cytokines, thereby causing a local inflammatory response and endothelial cell damage and local thrombosis (23). It consists of a lyophilised mixture of low virulence group A streptococcus pyogenes mixed with benzyl penicillin (23).

This has been widely used in the head and neck region with a safe profile of use which includes transient facial nerve paresis (23) and skin reaction. This is not currently available in India.

ABSOLUTE ETHANOL

Absolute alcohol was used earlier in the management of slow flow vascular malformations. It acts primarily by denaturing cellular proteins, damage to the endothelial cell, thus inducing thrombosis within the lumen. Its use for slow flow vascular malformations has been abandoned due to the high risk of local complications which include skin ulceration, non-healing ulcers which result in bad cosmetic outcomes. This has a high risk of damage to the local

neurovascular structures up to 60% (23). Thus, its use is limited to direct percutaneous injections of the nidus in AVMs.

DOXYCYLINE

This widely available tetracycline antibiotic has been used widely in the treatment of lymphatic malformations. Exact mechanism of action remains unknown, although the possible mechanisms include inhibition of matrix metallo-proteinases (MMP's) and inhibition of VEGF which causes angiogenesis and lymphangiogenesis.

These have been primarily used in the management of macrocystic lymphatic malformations with no complications being reported after its use in literature (10).

POLIDOCANOL

Polidocanol is non-ionic agent which acts at the cell membrane level of the endothelial cells thereby causing endothelial damage and thrombosis. Its safety profile is like other sclerosants, and its usage is limited by the lack of availability.

PINGYANGMYCIN

Structurally like bleomycin (also called bleomycin A5), was discovered in china, hence the name. It is cost effective and the reported complications are transient fever and skin reaction. However, its use in India is limited by the lack of availability

COMPLICATIONS OF SCLEROTHERAPY

The most common complications following sclerotherapy are local skin reaction and pain which increase post-sclerotherapy. Careful counselling of patients is necessary, and they must be educated that the initial increase in pain and swelling is transient and is not a cause for alarm. The most severe of skin reactions include skin ulceration and necrosis and subsequent infection of necrotic tissues which can result in increased duration of hospital stays.

The mechanism of haemoglobinuria in patients who have had sclerotherapy is the presence of free extracellular haemoglobin which depletes haptoglobin and nitric oxide which are normally free radical scavengers in the blood.

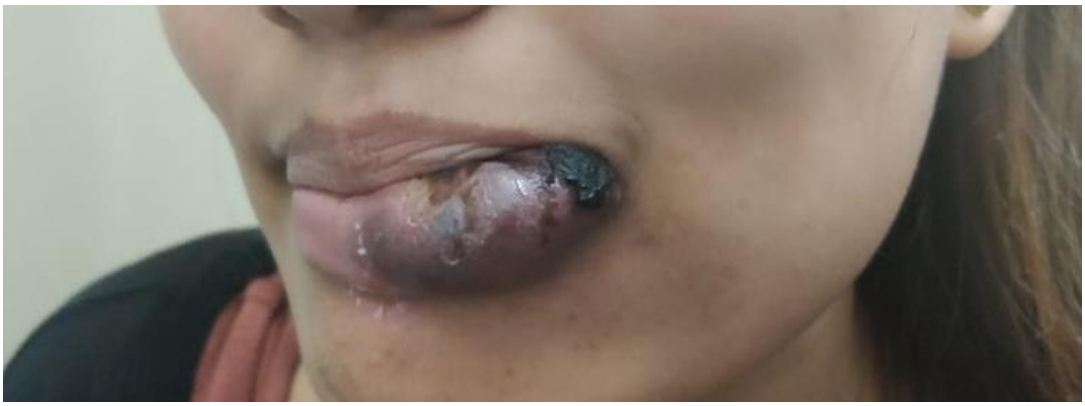


Figure 29: Lip ulceration and bleeding in a lady 3rd day post sclerotherapy. This was managed conservatively with daily sterile dressings following which it resolved almost completely.

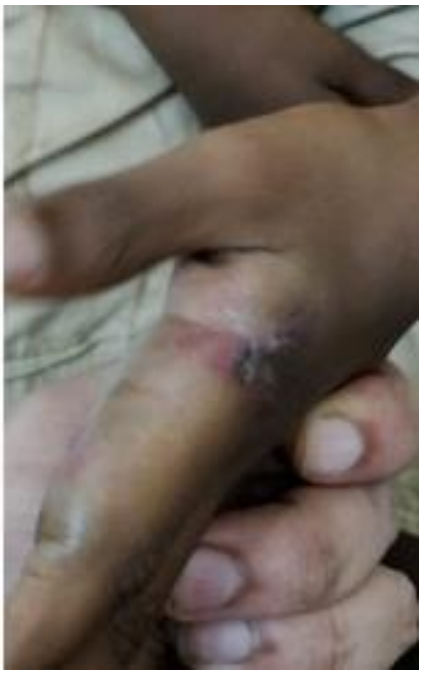


Figure 30: Mild discoloration and ulceration in a 10-year-old child following sclerotherapy for a venous malformation

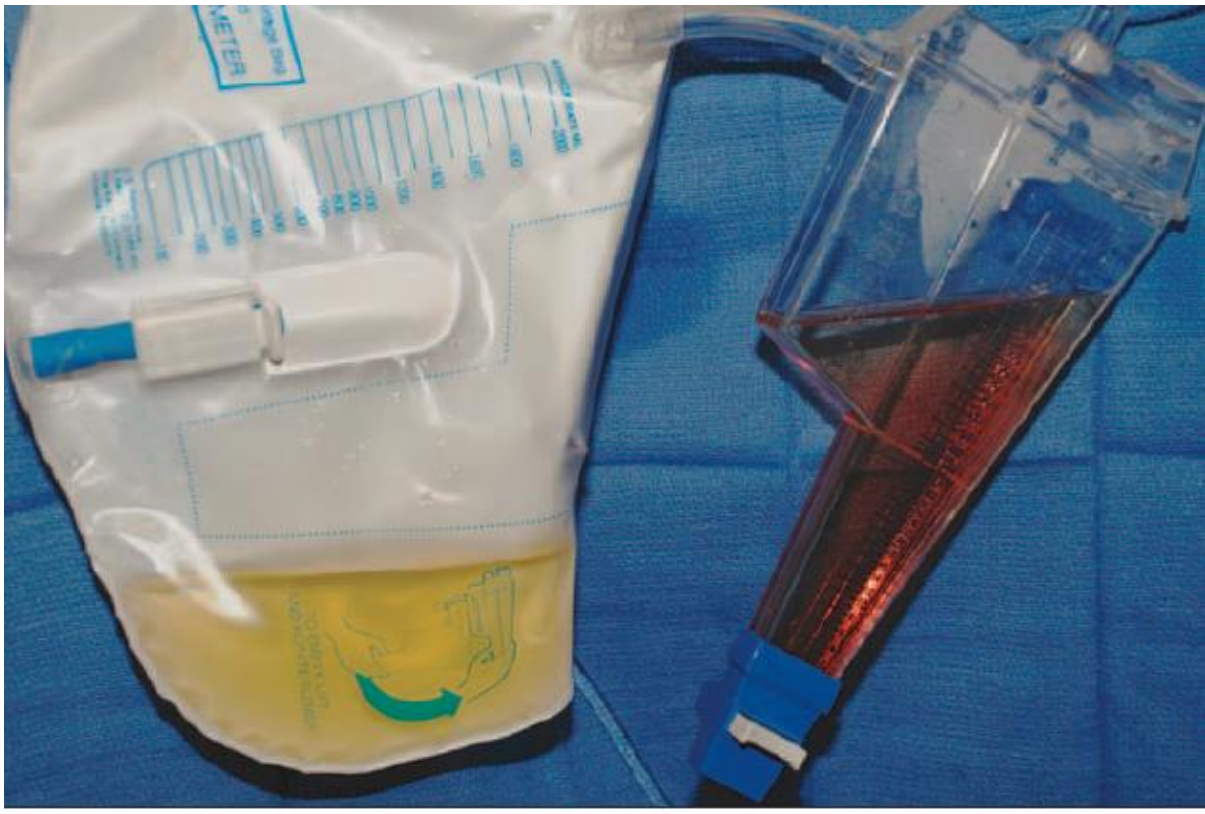


Figure 31: Picture from the study done by Alomari et al *(5)* shows brownish early discoloration of urine following sclerotherapy. Note that the earlier urine was normal in colour.

Thus, urine colour and output must be carefully monitored in patients post sclerotherapy especially in large lesions into which higher volume of sclerosant has been injected. Oliguria defined as urine output < 1 mL/kg/hr, which is managed with a bolus of normal saline of 10-20 ml / Kg with use of loop diuretics such as furosemide (0.25 mg/kg).

For gross haemoglobinuria, the IV fluid was modified to 5% dextrose in water with 75 mEq/L sodium bicarbonate at the maintenance rate to alkalinize the urine. Additional fluid was administered as lactated Ringer solution or normal saline.

MATERIALS AND METHODS

Type of study: A prospective cohort study

Population of study:

The study population included patients which included children and adults who were diagnosed as having a slow flow vascular malformation (venous, venolymphatic or lymphatic) from the various departments within the Christian Medical College Vellore (CMC) hospital and were being referred to the interventional radiology department for sclerotherapy.

Each patient was seen by a multidisciplinary team which consisted of interventional radiology, surgeons (vascular surgery, plastic surgery, paediatric surgery), anaesthetists.

The patients were given an explanation regarding the nature of the vascular malformation that they have. The various treatment modalities were explained, and sclerotherapy was offered to them as a treatment option after explaining possible risks and benefits.

The patients in this study were included after they gave informed consent. As a significant group of patients in this study were children, the children above the age of 7 were given an explanation in simple vernacular language and an assent was taken. For infants and children younger than 7 years of age, informed consent for participating in this study was obtained from the parents.

INCLUSION CRITERIA:

Patients who have presented to CMC hospital for the first time and have been diagnosed with a slow flow vascular malformation, and who have not undergone any prior surgical treatment or sclerotherapy were included in the study. They also should give their consent to be treated by sclerotherapy procedure and be available for follow up questions and clinical evaluation.

EXCLUSION CRITERIA:

Patients who had received prior treatment either sclerotherapy or surgery in any hospital or treatment centre were excluded from this study. Patients who did not consent to be part of this study were also excluded.

SAMPLE SIZE CALCULATION:

The sample size of the study was calculated using a statistician's guidance. A pilot study was initially performed with 20 patients to plan for the sample size of the study since there was no data from India on the quality of life after sclerotherapy.

A sample size of 50 was found to be required, to detect a change of 1cm of lesion size from pre-sclerotherapy size after 6 months following sclerotherapy with a standard deviation (SD) of 2.5 cm and 80% power with a 5% level of significance using paired t test.

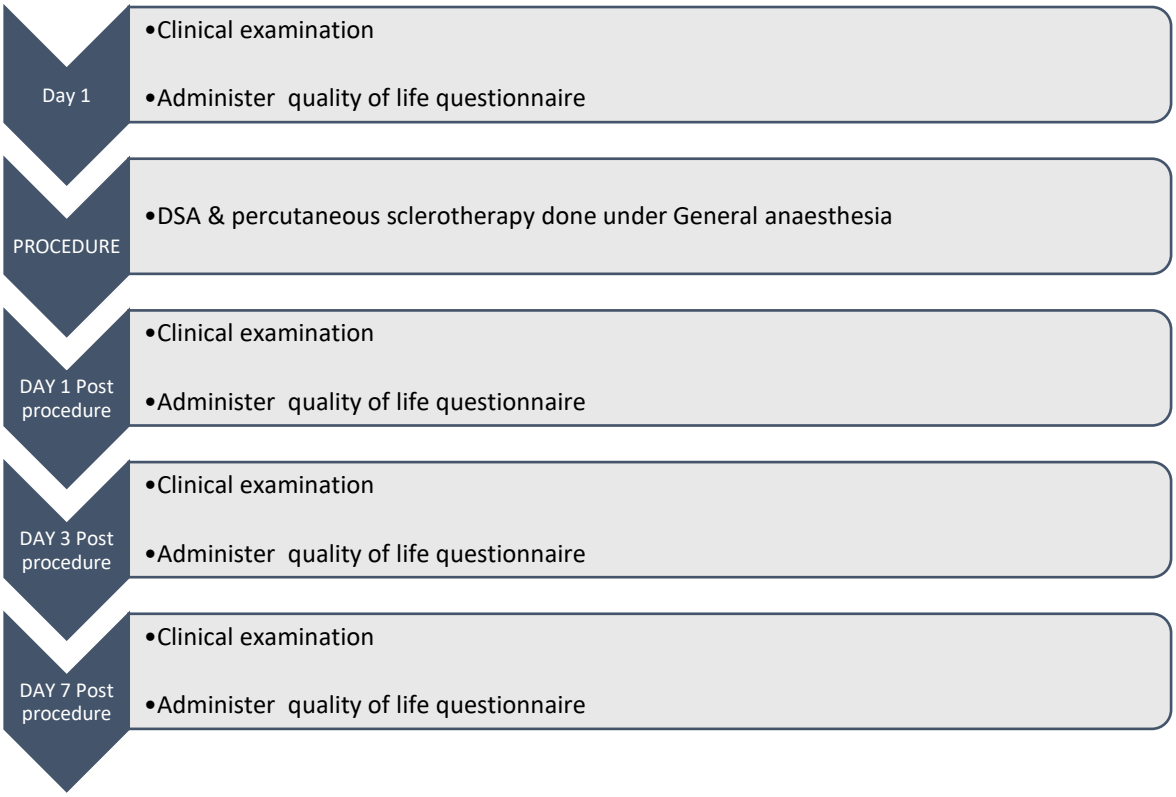
TOOLS USED:

A standardised questionnaire called the SF-36 was used, which is a widely used tool for assessing quality of life. This was modified after the pilot study in 20 patients, to modify the questionnaire to suit the Indian population.

This questionnaire consisted of assessment in 4 domains- which included pain, regional symptoms (related to the location of venolymphatic malformation) including activities of daily living (ADL), psychological which included morale issues related to the malformation and the cosmetic issues especially the malformations in the head and neck region. This modified SF-36 questionnaire is attached in the appendix of this manuscript.

To objectively assess for any decrease in size of the vascular malformation, a few regional MRI sequences were done in patients who had returned for follow up.

Detailed diagrammatic Algorithm of the study



On being referred by various departments for assessment in intervention radiology for considering treatment, the patient was seen in the interventional radiology consultation room where history taking, and clinical examination would be done along with ultrasonography and colour Doppler studies to determine the presence of vascular spaces, and pattern of blood flow within.

The questionnaire was administered to them at multiple stages of the treatment plan: pre-procedure, and on day 1, 3 and 7 after the procedure. Follow up was advised for all patients between 6 weeks and 6 months after the procedure, during which the same questionnaire would be administered to ascertain the long-term outcome of quality of life.

For patients who came for follow up and agreed to undergo MR imaging, a few MRI sections were performed to objectively assess the reduction in size in the vascular malformation.

DATA PROCESSING & STATISTICAL ANALYSIS:

The data was collected in terms of variables such as general demographics, type of malformation (venous, venolymphatic, pure lymphatic), location, maximal dimension, quality of life scores and post sclerotherapy quality of life scores. All these variables were entered in a spreadsheet program such as MS-Excel 2018®. The software used for data entry was Epidata ®. Data analysis was done using SPSS (IBM corporation® version 23). Bibliography was managed used Zotero(Centre at George Mason University®).

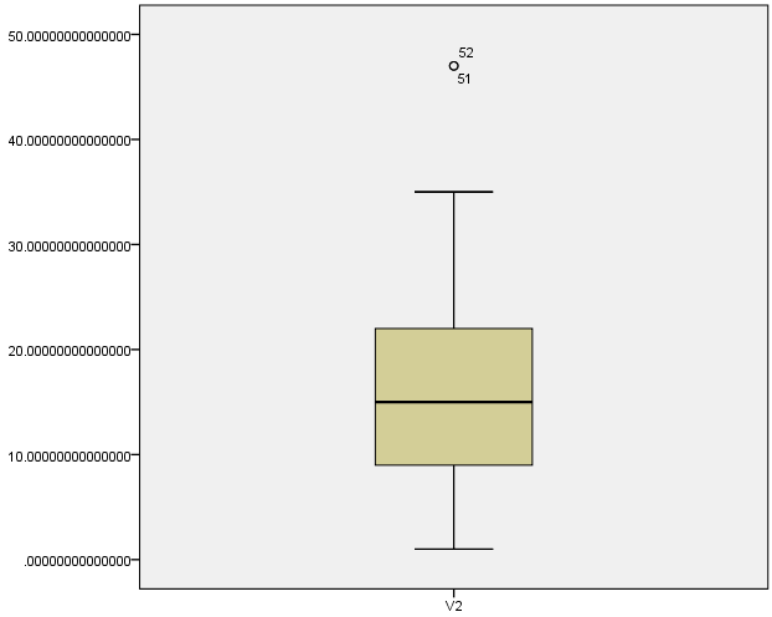
RESULTS

DESCRIPTIVE RESULTS

Distribution of age:

The range of ages of the patients in this study was 2-47 years with a mean of 15.8 years with a standard deviation of 10 years.

Figure 1: This is a box plot showing the age distribution. The interquartile range (25^{th} – 75^{th} centile) ranged between 10 – 22 years with a median age of 14 years. There were 2 outliers, both at age of 47 years.



Gender:

Almost equal distribution of females and males with slightly higher female preponderance noted (57 %) in this study.

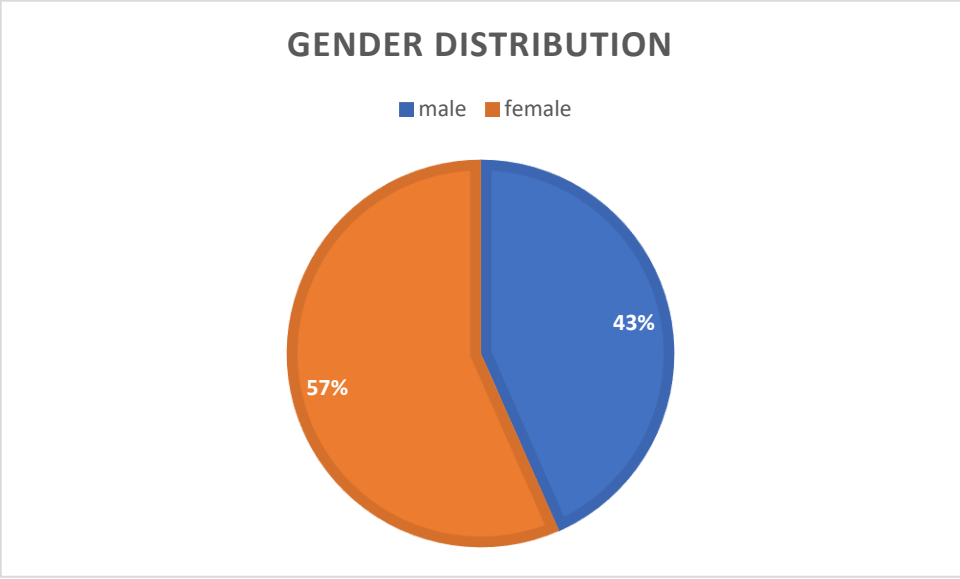


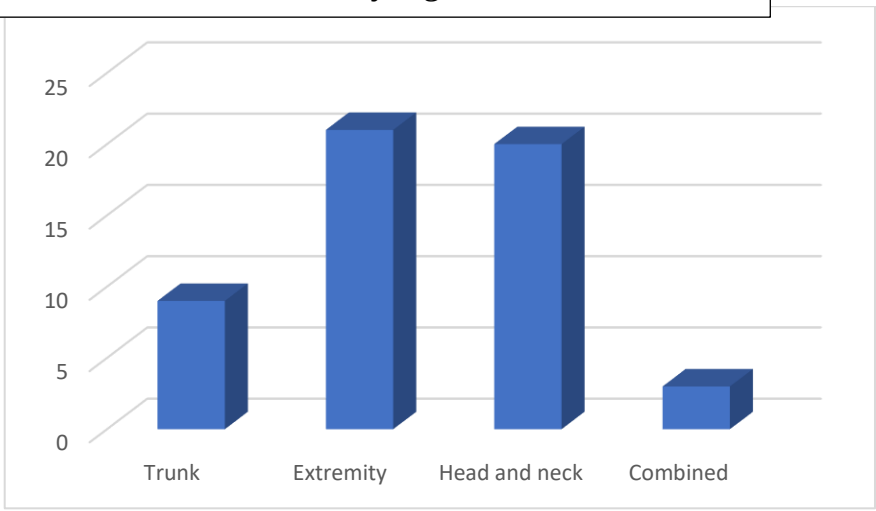
Figure 2: Pie chart showing near equal distribution of males and females in this study with a slightly higher female predominance

LOCATION:

The location of the slow flow vascular malformation was broadly divided into

1. Extremity
2. Head and neck region
3. Trunk – which included chest and abdomen

Figure 3: Bar diagram showing the distribution of slow flow malformations by region



There were near equal distribution of extremity and head and neck slow flow vascular malformations in this study. The most common location of extremity slow flow vascular malformation was the lower limb. Among the head and neck slow flow malformations in this study, many lesions involved the tongue, lip and oral mucosa with an equal distribution in the neck especially the lymphatic malformations which presented as large macro-lymphatic malformations in the neck with multiple deep spaces of the neck being involved.

PLANE OF THE SLOW FLOW VASCULAR MALFORMATIONS:

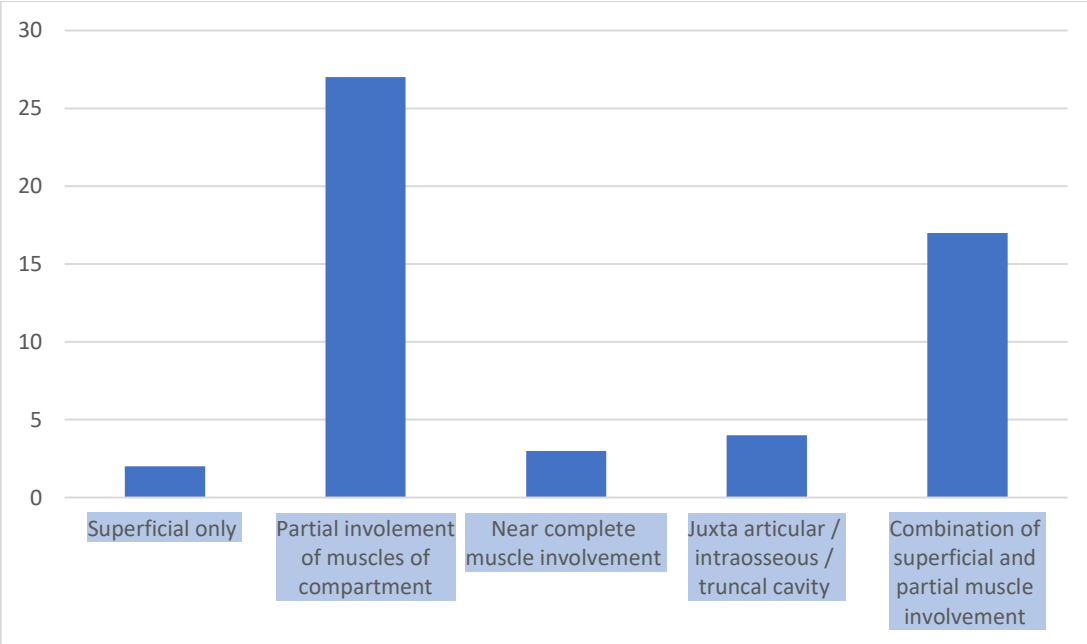
All patients prior to the sclerotherapy had an MRI scan of that region, which was used for prior planning, for assessing the depth of the lesion from the skin, specific regions such as head and neck malformations for involvement of the airway for specific anaesthetic risks as all the sclerotherapy for these procedures were carried out under general anaesthesia.

The planes of involvement were broadly classified as:

1. Superficial – involvement of the skin and subcutaneous tissue only.
2. Deep – partial inclusion of the muscles of the entire compartment.
3. Near complete involvement of the muscles of the compartment.
4. Juxta-articular / intra-osseous / thoracic cavity / peritoneal involvement.

This classification was used to help evaluate these slow flow malformations, to be used for further subgroup analysis.

Figure 4: Bar diagram showing the plane of the malformation based on pre-therapy MRI

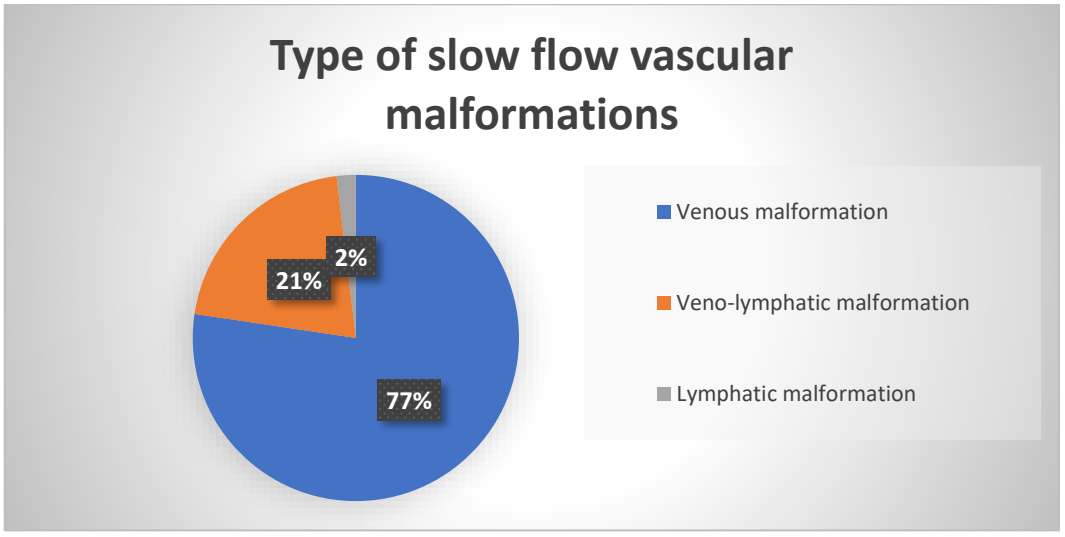


Majority of the venous malformations, especially the extremity-located VM had a partial involvement of the muscles of their respective compartments.

TYPE OF SLOW FLOW VASCULAR MALFORMATION:

The lesions on MRI were further subclassified based on specific imaging features if they were venous, lymphatic or venolymphatic malformation. This subdivision was important as it determined the addition of intralesional Bleomycin along with sodium tetradecyl sulphate which was the primary sclerosant of choice.

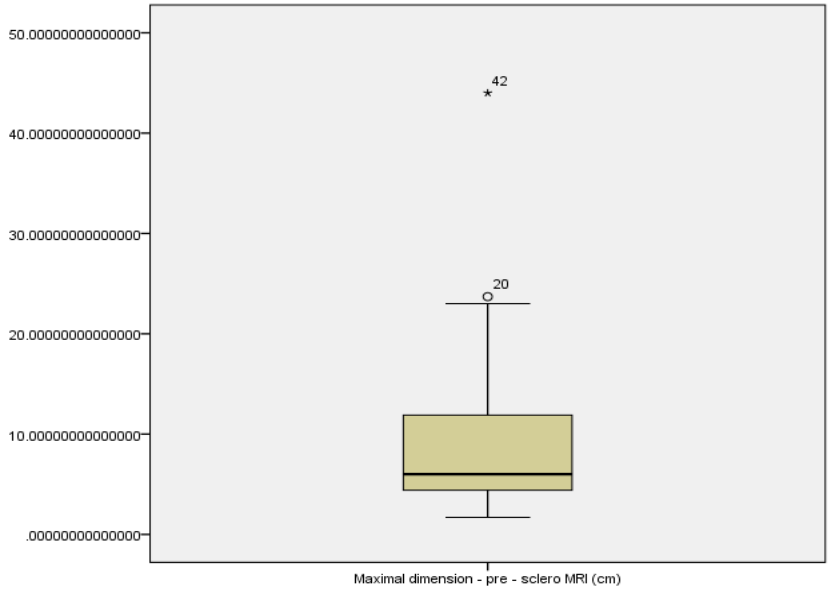
Figure 5: Pie diagram showing the type of slow flow vascular malformations



MAXIMAL DIMENSION ON PRE-TREATMENT MRI:

As part of the initial work up prior to sclerotherapy, regional MRI scan was done to plan treatment. Specifically, fat supressed sequences were used to delineate these vascular malformations as they would be hyperintense compared to the background fat, soft tissue and bone. A maximal dimension was taken in any of the standard orthogonal planes, in whichever plane was the largest. This was further used for analysis. The range of size of the lesion varied from 1.7 – 44 cm with an interquartile range (25^{th} -75^{th} centile) of 3-11cms, with a median size of 6 cm.

Figure 6: Box plot showing the maximum dimension of the slow flow vascular malformation in the pre-treatment MRI. Range of size of the lesion varied from 1.7 – 44 cm with an interquartile range (25^{th} -75^{th} centile) of 3- 11cms, with a median size of 6 cm



ANALYTICAL RESULTS:

1. STATISTICAL RELATIONSHIP BETWEEN AGE & QUALITY OF LIFE:

ANOVA (analysis of variance) **and logistic regression** were used to analyse the statistical difference between age at presentation and quality of life scores at day 7. This showed **a statistically significant difference** (p=0.019), with a Pearson coefficient of 0.320, suggesting moderate correlation**)** between the age of presentation and quality of life scores, suggesting that patients with earlier age of presentation had a better quality of life.

2. STATISTICAL RELATIONSHIP BETWEEN GENDER AND QUALITY OF LIFE

Independent sample T test was used to assess if there was any statistical significance between the gender and the outcome following sclerotherapy. There was **no statistical significant difference** between the 2 genders (**p=0.856**)

3. STATISTICAL DIFFERENCE IN MEANS OF QUALITY OF LIFE AT DIFFERENT POINTS:

The mean quality of life (QOL) scores were calculated at 3 points of the follow up, at day 1, 3 and 7th day post sclerotherapy was calculated. The **Wilks's lambda score** was used which showed a **statistically significant difference** ($p<0.001$) between the means of the quality of life pre-sclerotherapy and day 3 and day 7 of sclerotherapy**.**

Table 1: This is a table showing the mean and the standard deviation of the quality of life scores among the study subjects

	Mean	Std. Deviation	N
Score Day 1 pre- sclero	15.34	3.605	53
Score Day 1 post sclero	17.72	3.313	53
Score day 3 sclero	11.21	2.514	53
Day 7 score	10.32	2.352	53

TESTS USED	Value	F	p value
Wilks lambda	0.0094	160.894	<0.0001
Pillai's trace	0.906	160.894	<0.0001

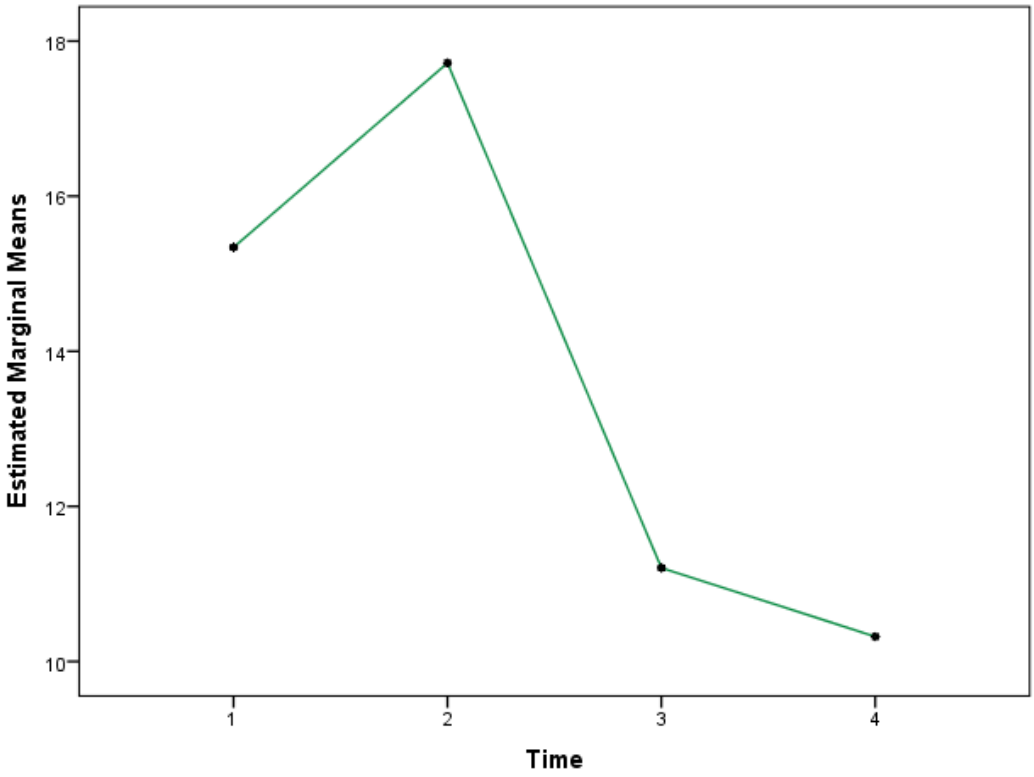
Table 2: Wilks's lambda test was used the statistical test used for comparing the means pre and post sclerotherapy which showed a statistically significant difference

Relationship with time:

The mean quality of life scores showed an increase on day1 post sclerotherapy, which subsequently remained higher than pre-sclerotherapy scores on day 3, and showed a decrease in scores on day 7, less than the baseline score. This is elucidated in the graph given below. The X-axis contains the different time points at which quality of life was assessed. On the x-axis, the point '1' refers to the day 1 pre-sclerotherapy, '2' refers to day 1 post sclerotherapy, '3' refers to day 3 post sclerotherapy, and '4' refers to day 7 post sclerotherapy.

The Y-axis contains the average of all the quality of life scores.

TABLE 3 : Graph showing the quality of life scores versus time. This shows a temporary worsening at day 1 post sclerotherapy which comes back to lesser than baseline pre-sclerotherapy scores



4. RELATIONSHIP BETWEEN QUALITY OF LIFE & LOCATION OF MALFORMATION:

ANOVA (analysis of variance) test was used to specifically assess if there was any association between the final quality of life (as assessed on day 7)

and the specific location (either head & neck, extremity or trunk) which did not reveal a statistically significant relationship (p=0.359).

A subgroup analysis was done to look for any relationship between the different planes (for example skin and subcutaneous plane involvement only, partial involvement of muscles, complete involvement of muscles, intra-thoracic/abdominal or joint involvement) that were involved on pre-sclerotherapy MRI and final quality of life ANOVA was used and it showed that there was no **statistically significant difference** between the groups **(p= 0.639).**

5. RELATIONSHIP BETWEEN TYPE OF SLOW FLOW MALFORMATION AND QUALITY OF LIFE:

Non-parametric tests like the independent samples **Kruskal -Willis test** was used to assess the relationship between the different types of slow flow vascular malformations (VM, VLM, LM) & the quality of life. There was **no statistical difference (p=0.242)** between the different types of slow flow vascular malformations & quality of life.

6. RELATIONSHIP BETWEEN NUMBER OF NEEDLES USED & QUALITY OF LIFE:

Logistic regression was used to analyse if there was any statistical difference between the number of needles used for sclerotherapy and quality of life at day 7 post-procedure. It revealed **no significant correlation** (Pearson regression coefficient of 0.010- poor correlation, p value of 0.942) between the number of needles and day 7 quality of life.

7. RELATIONSHIP BETWEEN PRE-TREATMENT SIZE & QUALITY OF LIFE:

The ANOVA test was used to assess if there was a relationship between pre-sclerotherapy size of the lesion and the quality of life on day 7. It **revealed no significant correlation** (p value = 0.622) between the pre-treatment size and day 7 quality of life.

8. RELATIONSHIP BETWEEN VOLUME OF SCLEROSANT FOAM INJECTED AND QUALITY OF LIFE:

Logistic regression and ANOVA were used to look for any statistical correlation between the volume of foam sclerosant injected and quality of life on day 7. It showed **a statistically significant correlation** (p value of 0.031, Pearson coefficient of 0.297, showing a moderate strength of association) between the volume of sclerosant injected and quality of life on day 7. The ANOVA results are given below:

TABLE 4: Table showing the ANOVA test to correlate between the volume of foam sclerosant injected and quality of life score

VOLUME INJECTED	Sum of Squares	Mean Square	P value
Regression	25.346	25.346	.031[b]
Residual	262.201	5.141	
Total	287.547		

SUMMARY OF ANALYTICAL STATISTICS:

Table 5: Summary of all the clinico-radiological variables with quality of life

Number	Relationship between variables	p value
1	Age & quality of life	**0.019**
2	Gender & quality of life	0.856
3	Difference in means pre and post sclerotherapy QOL (day 7)	**<0.0001**
4	Location of the malformation & quality of life	0.359
5	Plane of malformation & quality of life	0.639
6	Type of malformation & quality of life	0.242
7	No of needles used for sclerosant injection & QOL	0.942
8	Pre-treatment size & quality of life	0.622
9	Volume of sclerosant foam & quality of life	**0.031**

DISCUSSION

DISCUSSION OF QUALITY OF LIFE AFTER TREATMENT:

This study demonstrated that there was a statistical difference between the mean quality of life scores pre-sclerotherapy and post sclerotherapy **(p <0.001).** This was comparable to prior studies which were done earlier by Riita Rautio and their group in Finland (17) & Long Li et al (24) who had used similar clinical outcomes and criteria.

FACTORS DETERMINING OUTCOME:

The analysis looked at multiple clinical and radiological factors which could determine the quality of life.

An earlier age at which sclerotherapy is done was associated with a better quality of life (P=0.019). The Pearson coefficient of 0.320 is suggestive of moderate strength of correlation. This was comparable to the study done by Riita Rautio and their group in Finland (17) which showed a similar conclusion.

Significant correlation (**p=0.031**) was also noted between the volume of foam sclerosant used and the quality of life outcomes.

The sclerosant (sodium tetradecyl sulphate) was made into a foam by mixing with an equal amount of air. The maximum volume of sclerosant which can be used in clinical practice is based on the weight of the patient and is 1ml/kg.

Larger size of the lesions sometimes warrants a higher volume of sclerosant to be used. However, especially in the lesions of the head and neck, higher volume is associated with increased risk of complications in view of increased vascularity and proximity to the vital structures such as the airway which would require stay in the intensive care unit and thereby increase overall morbidity.

In this study, two patients had complications of the lip and tongue, in which there was necrosis and blackish discoloration. This required hospital admission and some debridement by the surgeons and wound care. Both wounds healed completely without any further complication. Thus, although this study demonstrated a better quality of life with higher volume of sclerosant injected, the final decision should be made on table by the

interventional radiologist performing the procedure after comparing the risks and benefits.

There was no statistically significant difference between the location and the quality of life **(p=0.359)**. This is different compared to earlier studies (17) that showed that head and neck lesions had a poorer outcome in terms of quality of life.

In this study there was no statistically significant difference **(p=0.659)** between the anatomical plane of the slow flow malformation and the quality of life. This is different compared to earlier studies by Riitta et al (17)which showed that extremity malformations with a near complete involvement of the muscles of the compartment showed a poorer outcome in comparison to the ones with superficial or partial muscular compartment involvement.

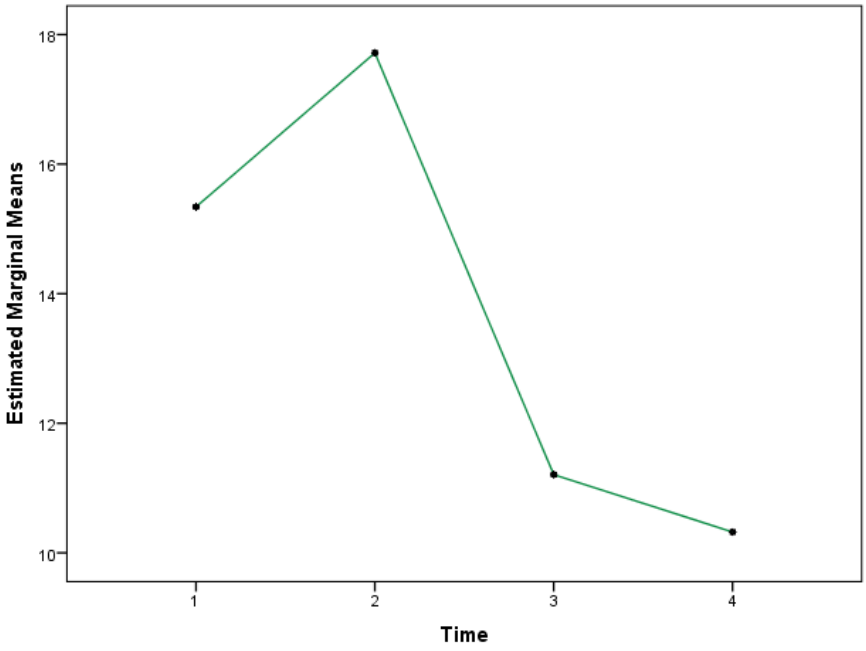
There was no statistical association between the type of slow flow malformation and outcome **(p=0.242)**. Although there have been no studies in this regard, venous malformations due to the involvement of the muscular compartment can cause significant pain & reduce the quality of life.

There was no statistical association between the quality of life and the pre-treatment size of the lesion **(p=0.622).** Although in earlier studies by Riitta et

al (17) there was an association between the size and quality of life- larger size corresponding to poorer outcome

There was no statistical association between gender, the number of needles used for sclerosant injection.

TEMPORAL PROFILE POST-SCLEROTHERAPY:



This graph elucidates the patient's quality of life post-sclerosant injection. It shows that there is a worsening of quality of life scores immediately following sclerotherapy, following which, there is a decrease at day 3 and decreases further on day 7. This can be explained by fact that there is

inflammation of the endothelium and the surrounding tissues due to the sclerosant injection. This leads to worsening of pain and worsening of regional symptoms. This phenomenon should be explained to the patient and their family prior to sclerotherapy as apparent worsening of appearance or symptoms post-procedure can cause further apprehension.

This worsening immediately can be managed with non-steroidal anti-inflammatory agents and good hydration as there is an improvement within 48 hours usually.

COMPLICATIONS:

Most patients in this study had minor pain and worsening of the swelling after the sclerosant injection which was managed conservatively with NSAIDs and local symptomatic measures.

However, there were 2 patients who had developed skin necrosis. Both these patients had venous malformations involving the head and neck. The first patient was a 16-year-old male with venous malformation involving the lip and lower face. He developed blackish discoloration of the lesion the next day following sclerotherapy. He was re-admitted into the hospital, required debridement of the necrotic tissues with a flap cover by plastic surgery

department. The rest of his follow up period was uneventful, and he is currently on follow up.

The second patient was a 14-year-old girl with venous malformation of the tongue and lip, who developed black discoloration of the tongue and lower lip, who was re-admitted to the hospital, and required debridement. Her post-operative period was also uneventful, and she is on follow up.

The third was a patient was 11-year-old boy with a presumed venolymphatic malformation of the left side of the face, neck involving the parapharyngeal and parotid spaces who underwent one session of foam sclerotherapy. The child was well post procedure & on follow up 6 months later was operated by the paediatric surgeons. The biopsy revealed a predominant venolymphatic malformation with a focus of low grade muco-epidermoid carcinoma. On reviewing the imaging there were no solid enhancing components within the multicystic lesion.

SUMMARY AND CONCLUSIONS

This study demonstrates that sclerotherapy for slow flow vascular malformations is a safe and reliable way to alleviate the symptoms of the patients. Accurate delineation of the lesion before treatment facilitates the planning the appropriate therapy. To achieve optimal results a multidisciplinary approach with interventional radiology, dermatologists, surgeons, and anaesthetists is often necessary. Sodium tetradecyl sulphate and Bleomycin are effective sclerosants for therapy.

This study demonstrated a few clinical and radiological factors of favourable outcome. Earlier age of first sclerotherapy was associated with a significantly better outcome in terms of quality of life. Although a significant association was demonstrated between the volume of foam sclerosant injected and better quality of life, there should be a careful use of sclerosant, especially in the head of neck region (lip and tongue) where there is a higher risk of tissue necrosis. Complete cure may never be possible in larger lesions, but sclerotherapy is an effective remedy for alleviating the patient's symptoms. Patients should be counselled regarding the natural course of events, where there is a significant worsening of the symptoms immediately after sclerotherapy due to the local inflammatory response.

APPENDIX

APPENDIX 1 - BIBLIOGRAPHY

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APPENDIX 2 – INSTITUTIONAL REVIEW BOARD APPROVAL

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho MS Ortho DNB Ortho.
Chairperson, Research Committee & Principal

Dr. Biju George, MBBS., MD., DM
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

August 16, 2016.

Dr. Joshua Anand S,
PG Registrar,
Department of Radiodiagnosis.
Christian Medical College,
Vellore – 632 002.

Sub: **Research Funding: New Proposal**
Clinico-radiological predictors of outcome and quality of life in patients undergoing percutaneous sclerotherapy for venolymphatic malformations.
Dr. Joshua Anand S Employment Number: 29546, PG registrar, radiology, Dr. George Koshy Chiramel, Employment Number: 28364 , Radiology, Dr. Shyamkumar NK, Radiology, Dr. Vinu Moses, Professor, Radiology Dr. Munawwar Ahmed, , Radiology . Dr Edwin Stephen , ,Vascular surgery , Dr Sunil Agarwal ,Vascular surgery, f. Dr Dheepak Selvaraj, Vascular surgery, Dr Reju Thomas , , Pediatric surgery, Dr Susan , Pediatric surgery, Dr Ashish Gupta Plastic surgery

Ref: IRB Min. No. 10213 dated 08.08.2016

Dear Dr. Joshua Anand S,

The Institutional Review Board **(Blue**, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Clinico-radiological predictors of outcome and quality of life in patients undergoing percutaneous sclerotherapy for venolymphatic malformations." on August 08th 2016. I am quoting below the minutes of the meeting.

The Committee raises the following queries:

1. Present knowledge and bibliography very sketchy – needs better write up
2. Who makes the decision on whether sclerotherapy needs to be done
3. Put in details on which patients will benefit from sclerotherapy and how you decide on which patients need sclerotherapy
4. Some patients need more than 1 session – then when will you administer the questionnaire
5. No complications mentioned in the proforma
6. Is the 6 months follow up compulsory
7. Will you get relevant information over the phone in 3 months time
8. How will you do MRI in these patients who do not come for follow up 1 of 2

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
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Dr. Biju George, MBBS., MD., DM
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

9. Questionnaire – all words together – make sure they are spaced out
10. Will the same questionnaire be used for all the follow ups
11. Will any other investigations be done during the follow up – need to mention it
12. No specification of the number of sessions
13. No details in the Tamil form
14. For children, you need to have a parent information sheet and consent form, assent form for the child and an information sheet for the child
15. Tamil information sheet needs to be given
16. No CVs given
17. Specify complications in the information sheet.

Drs. Joshua Anand and George Koshy were present during the presentation of the proposal and satisfactorily responded to the queries raised by the Members. After discussion, it was resolved to **ACCEPT the proposal after receiving the suggested modifications and answers to the queries.**

Note:
1. Kindly HIGHLIGHT the modifications in the revised proposal.
2. Keep a covering letter and point out the answer to the queries.
3. Reply to the queries should be submitted within 3 months duration from the time of the thesis/ protocol presentation, if not the thesis/protocol have to be resubmitted to the IRB.
4. The checklist has to be sent along with the answers to queries.

Email the details to research@cmcvellore.ac.in and send a hard copy through internal dispatch to Dr. Biju George, Addl. Vice-Principal (Research), Principal's Office, CMC.

Yours sincerely,

Chairperson (Research Committee) & Principal
Christian Medical College
Vellore - 632 002, Tamil Nadu, India

Dr. Alfred Job Daniel
Principal & Chairperson (Research Committee)
Institutional Review Board

Cc: Dr. George Koshy Chiramel, Department of Radiodiagnosis, CMC Vellore.

IRB Min. No. 10213 dated 08.08.2016

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

APPENDIX 3 – Child information sheet – English

CHILD INFORMATION SHEET

TITLE: Outcomes of sclerotherapy for venous malformations

PRINCIPAL INVESTIGATOR: Dr Joshua

Doctors at CMC are doing a research study and would like to ask you for your help.

Some children have a little bit of pain,swelling and discoloration, just like you do.

To reduce the problems, we give a small injection into them, which is called sclerotherapy which will slowly reduce the problem.This injection will not causeyou anypain, since you would be completely asleep.

You don't have to do anything in particular for this study. A doctor would ask you a few questions as to how you felt before and after the treatment .It would not cause any pain as there are noextra injections or treatment.

This would help other children like you, who have similar problems and would help the doctors give them better treatment.

You don't need to compulsorily take part. Nobody would be cross or upset if you say no, and you would still get the regular treatment (sclerotherapy) that you need.

Your name and the things about you would be kept a secret .Only a few people, who are helping you with the treatment, would know.

Take time to decide if you want to take part.Please ask us, if there is anything you have not understood or feel worried about.

Thank you,

Joshua

APPENDIX 3 – PATIENT INFORMATION SHEET, CONSENT & ASSENT

FORMS – Child information sheet Telugu

చిన్నపిల్లల సమాచార పత్రావళి

శీర్షిక – సిరల వైకల్యాల యొక్క పరిశోధన అంశాలను సవివరముగ తెలిసికొనే ప్రయత్నము

పరిశోధక వైద్యుడు: జాషువ

సి. యమ్. సి. సంస్థ లోని వైద్యులు ఈ అంశము పైన పరిశోధనను చేయుచున్నారు. కనుక మిమ్మల్ని కొన్ని ప్రశ్నలు వేయుదురు. దయచేసి సహకరించావలేననిప్రార్థన.

ఈ సిరల వైకల్యాలాతో ఉన్న చిన్న పిల్లలకు కొంత నొప్పి, వాపు మరియు రంగు మార్పు జరుగుట సాధారణము.

ఇటువంటి సమస్యలతో ఉన్నవారిని ఒక చిన్న సూది మందు ద్వారా వారి సమస్యను తగ్గించవచ్చును. ఈ సూది మందు ద్వార ఎటువంటి బాధ ఉండదు గాని చిన్న పిల్లవాడు నిద్రనిద్రలో ఉంటాడు.

ఈ సూది ఇచ్చిన తర్వాత చిన్న పిల్లవాడిని కొన్ని ప్రశ్నలు అడుగుటద్వార కొంత సమాచారమును మేము పొందుతాము గాని అతనికి ఎటువంటి నొప్పి ఉండదు.

దీనిలో మీరు తప్పక పాలుపొందవలేనన్న బలవంతము లేదు. అయిననను మీకు క్రమంగా ఇచ్చే ట్రీట్మెంట్ మీకు ఇస్తాము.

మాపరిశోధనా ఉద్దేశ్యములో ఇటువ్నటి వైకల్యాలను గల చిన్న పిల్లలను కనుగొని వారిని మా పరిశోధనలో అధ్యయనం చేయుట ద్వార ఆ వైకల్యాలను బాగుచేయవచ్చు నని మా ఉద్దేశ్యము. ఇటువంటి జబ్బులతోఉన్న వారికి మీరు సహకరించిన వారవుతారు.

మీ పేరును మేము బహిర్ధతము చేయము. మీరు సమయము తీసుకొని ఆలోచించి మాకు ఈ పరిశోధనలో సహకరించాలని కోరిక ఉంటె మాతో సంప్రదించగలరు.

ధన్యవాదములు

వైద్యుడు: జాషువ

ఫోన్ నెంబరు: 9700040138

APPENDIX 3 – Child information sheet – Tamil

குழந்தை பற்றிய தகவல் பக்கம்

தலைப்பு:

நரம்பில் உள்ள ஒழுங்கற்ற உருவ மாற்றத்தில் ஸ்கிலிரோதெரபியின் பயன்கள் (ஒழுங்கற்ற உருவத்தை சரி செய்யும் முறைக்கு பெயர்தான் ஸ்கிலிரோதெரபி)

முதன்மை ஆராய்ச்சியாளர்:

டாக்டர் ஜோகவா ஆனந்த்

சி.எம்.சி. மருத்துவமனையில் பணிபுரியும் மருத்துவர்களாகிய நாங்கள் ஒரு ஆராய்ச்சியை மேற்கொண்டுள்ளோம். அதற்காக உங்களிடம் உதவி கோர விரும்புகிறோம்.

சில குழந்தைகளுக்கு வலி மற்றும் வீக்கம், நிறம் மாறுதல் போன்ற பிரச்சனைகள் வரும், உங்களைப்போல

இதை தவிர்க்க, நாங்கள் ஒரு மருந்தினை, சிறிய ஊசியின் உதவியுடன் உங்களுக்கு செலுத்துவோம். அதற்கு பெயர்தான் ஸ்கிலிரோதெரபி **(Sclerotheraphy)** அது உங்களுடைய பிரச்சனையை மேலோட்டமாக சரி செய்யும்.

இந்த மருந்தானது உங்களுக்கு எந்தவொரு, வலியையும் ஏற்படுத்தாது, அதாவது நீங்கள் நல்ல உறக்கத்தில் இருப்பீர்களேயானால்.

நீங்கள் குறிப்பிட்டு எந்தவொரு வேலையையும் செய்யத் தேவையில்லை இந்த ஆராய்ச்சியில், மருத்துவர்கள் உங்களிடம் சில கேள்விகள் மட்டும் கேட்பார்கள். அதாவது ஆராய்ச்சிக்கு முன் மற்றும் ஆராய்ச்சிக்குப் பின் உங்களின் நிலை பற்றிய தகவல்.

இந்த முறையில் கூடுதலாக எந்தவொரு மருந்துகளும் செலுத்தப்படவில்லையென்றால், உங்களுக்கு எந்தவொரு வலியும் இருக்காது.

இந்த ஆராய்ச்சியானது மற்ற குழந்தைகளுக்கு உதவியாய் இருக்கும். குறிப்பாக, உங்களை போன்ற பிரச்சனை உள்ள குழந்தைகளுக்கும் மற்றும் மருத்துவர்களுக்கு சிறந்த சிகிச்சை அளிக்கவும் உதவியாய் இருக்கும்.

(இந்த ஆராய்ச்சியில் கலந்து கொள்ள வேண்டும் என்பது கட்டாயமல்ல, உங்கள் விருப்பத்தில் குறிக்கிடமாட்டார்கள். நீங்கள் வேண்டாம் என்றபோதிலும் உங்களுக்கு தேவையான சிகிச்சையை, அதாவது நீங்கள் பெற்றுக்கொண்டிருக்கும் சிகிச்சை உங்களுக்கு தொடாச்சியாக தரப்படும்)

உங்களுடைய பெயர், உங்களைப் பற்றிய தகவல்கள் அனைத்தும் இரகசியமாக வைக்கப்பட்டிருக்கும். ஒரு சிலரே, அதாவது உங்களுக்கு உதவி புரிபவர்கள் மட்டுமே அறிவர்.

இதில் பங்கேற்பதற்கான முடிவை மேற்கொள்ள நீங்கள் உங்களின் நேரத்தை எடுத்துக்கொள்ளுங்கள்.

அதேபோல் தயவு செய்து எங்களிடம் கேள்வி கேட்க தயங்காதீர்கள், உங்களுக்கு இதைபற்றி புரியவில்லை என்றால்.

நன்றி,

ஜோசுவா ஆனந்த்

கைபேசி: 97000 40138

e-mail:joshananda349@gmail.com

APPENDIX -3 CHILD INFORMATION SHEET – HINDI

रोगी सूचना पत्र

अध्ययन शीर्षक: नस की कुरूपता के लिए किए गये जाँच स्क्लीरोथेरापि के परिणाम

मुख्य जाँचकर्ता: डा. सीलम जोशुआ

सी.एम.सी के डाक्टरें एक अध्ययन में आपको भाग लेने के लिए विनती कर रहें हैं.
कभी कभी आपके जैसे बच्चों के हाथ पाँव में सूजन, दर्द और मलिंकिरण होती हैं.
इस तकलीफ़ को कम करने के लिए हम उको एक छोटी सी इंजेक्शन के द्वारा एक दावा देते हैं जिसके द्वारा सूजन कम हो जाती है. इंजेक्शन देने के वक्त आपको सुला दिया जाएगा और अपपको किसी प्रकार का दर्द नहीं पहुँचाया जाएगा.

इस अध्ययन में भाग लेने के लिए आपको कुछ ख़ास चीज़ करने की ज़रूरत नहीं पड़ेगी.

इस अध्ययन में भाग लेने के लिए आपको कुछ ख़ास चीज़ करने की ज़रूरत नहीं पड़ेगी. डाक्टर साहब इंजेक्शन के पहले और बाद के अनुभव के बारे में सवाल पूछेंगे. इसके द्वारा अपपको किसी तारह का दर्द नहीं पहुँचाया जाएगा.

आपके इस अध्ययन में भाग लेने से आपके जैसे पीदित बच्चों की मदद की जा सकती हैं और उनके लिए और बेहतर इलाज दी जा सकती हैं.

इस अध्ययन में आपका भाग लेना अनिवार्य नहीं है. इस में भाग न लेने पर आपसे कोई नाराज़ नहीं होंगे और आपके इलाज में कोई कमी नहीं पड़ेगी.

आपकी पहचान और आपके बारे में सभी जानकारी गुप्त रखा जाएगा. सिर्फ़ आपके इलाज करने वाले डाक्टर को जानकारी डी जाएगी.

इस अध्ययन के बारे में अधिक जानकारी के लिए और संदेहों को स्पष्ट करने के लिए हमें संपर्क करें.

APPENDIX 3 – Child assent form- ENGLISH

CHILD'S ASSENT FORM FOR PARTICIPATION

Project Title: Outcomes of Sclerotherapy in venous malformation
Investigator: Dr Joshua

We are doing a research study about abnormal blood vessels called venous malformations. A research study is a way to learn more about people, who have a similar problem like yours.

If you decide that you want to be part of this study, you will be asked a few questions about how the swelling is.

This study does not involve anything that would cause pain or harm to you.

Your answers would be really helpful to children who have similar problems, and it would help us to treat them.

After the study, we will publish a report which will not include your details.

You do not have to be in this study if you do not want to. You can stop at any time. Your parents know about the study too.

If you decide you want to be in this study, please sign your name below

I, _____, want to be in this research study.

_____ _____
(Sign your name here) (Date)

APPENDIX 3 – Child assent form – Telugu

ప్రాజెక్టు శీర్షిక: సిరల సైకల్యం - స్క్లెరోసిస్ - - పరిశోధన మరియు అధ్యయనం -
ఫలితాలపైన విషయాలు పై నివేదిక
పరిశోధకుడు : డాక్టర్ జాహ్నవి

అసాధారణ రక్త నాళాలపై వాటి సైకల్యాలపై అనగా మేము అధ్యయనం చేస్తున్నాము . ఇటువంటి సమస్యలు
వ్యక్తులను కనుగొని వారిపై చేసిన అధ్యయ నం ఎలాగ వీటిని గురించి సవిచరంగా
తెలిసికొనుటయే మూలాధ్యం. మా పరిశోధన లో ఇటువంటి

వ్యక్తులను కనుగొని వారి ద్వారా విషయాలు తెలిసికొని, పరిశోధించి అధ్యయనం చేయుటలో మీరు ఒక భాగము.

మీరు మాతోసహకరించి మా పరిశోధనలో ఒక భాగం కావాలని కోరితే మిమ్మల్ని కొన్ని ప్రశ్నలు అడుగుతాము. మాతో సహకరించి వివరించండి.

మీ వాపు ఎలా వున్నది అని తెలుసుకోవ డానికి ఈమా ప్రశ్నలు ఎంతో ఉపయోగ పడతాయి. డాలా సహాయం చేసిన వారవుతారు .

ఇదే సమస్యతో వున్న చిన్నపిల్లల ను మీరు సులభంగా ఆయము చేసిన వారవుతారు.

మా ఈ పరిశోధన మరియు అధ్యయనం తరువాత మేము ఒక నివేదిక ను ప్రదరిస్తాము . దానిలో ఎక్కడ మీపేరును మరియు మీ వివరాలను

మేము చేర్చము.

మేము అడిగే ప్రశ్నలు మీకు ఇబ్బందికరంగా అనిపించితే మీరు మధ్య లోనే నినిష్క్రమించ వచ్చును. మీ ఎన్నికలకుమీ విషయాలను

తెలియ జేయ వచ్చును .

ఈమా ప్రయాస పరిశోధనలో మీరు భాగమై మీకును ఇతరులకు ను సహాయం చేయాలనుకొంటే మీ పేరును క్రింద లైను పై వ్రాయండి

APPENDIX 3 – Child assent form – Tamil

பங்கேற்பதற்கான குழந்தையின் ஒப்புதல் படிவம்

திட்ட தலைப்பு:

நரம்பின் ஒழுங்கற்ற வடிவமைப்பில் ஸ்கிளிரோ தெரபியின் பயன்கள்

ஆராய்ச்சியாளர்:

டாக்டர் ஜோகவா ஆனந்த்

நாங்கள் இரத்த குழாய்களில் நரம்பின் ஒழுங்கற்ற வடிவமைப்பை பற்றிய ஆராய்ச்சியை மேற்கொண்டுள்ளோம். இந்த ஆராய்ச்சியானது மற்ற மக்களிடம் உள்ள உங்களை போன்ற பிரச்சனைகளை பற்றி நிறைய தெரிந்துகொள்ள உதவுகிறது.

உங்களுக்கு இந்த ஆராய்ச்சியில் ஒரு பகுதியாக இருக்க விருப்பம் இருக்குமாயின், நீங்கள் உங்களின் வீக்கத்தினை பற்றிய சில கேள்விகளுக்கு உட்படுத்தப்படுவீர்கள்.

இந்த ஆராய்ச்சியானது எந்த விதத்திலும் உங்களுக்கு வலியையோ அல்லது எந்த கஷ்டத்தையோ தராது.

இது போன்ற பிரச்சனை உள்ள மற்ற குழந்தைகளுக்கு உங்களின் பதில்கள் மிகவும் பயனுள்ளதாகவும் மற்றும் உங்களுக்கு சிகிச்சை அளிக்கவும் உதவியாய் இருக்கும்.

இந்த ஆராய்ச்சி முடிந்த பிறகு, ஆராய்ச்சியின் அறிக்கை மற்றும் தகவல்கள் அனைவருக்கும் அறிவிக்கப்படும். ஆனால் அதில் உங்களுடைய எந்தவொரு தகவல்களும் இருக்காது (எ.கா.) பெயர், முகவரி, தொலைபேசி எண்

உங்களுக்கு இதில் பங்கேற்க விருப்பமாயின், தயவு செய்து கீழே உள்ள பதிவேட்டில் கையொப்பம் இடவும்.

நான்_____ இந்த ஆராய்ச்சியில் பங்கேற்க விரும்புகிறேன்.

APPENDIX 3 – Child assent form –Hindi

लिखित सूचित सहमती

सी. एम. सी में हम नस की कुरूपता के बारे में एक अध्ययन करना चाहते हैं. इस अध्ययन के द्वारा हम उन लोगों के अनुसंधान करना चाहते है जिनको आपकी जैसी तकलीफ़ हो.

अगर तुम इस अध्ययन में भाग लेना चाहते है तो आपके तकलीफ़ के बारे मे कुछ सवाल पूच लिए जाएँगे.

इस अध्ययन में भाग लेने से आपको अधिक दर्द नहीं पहुँचाया जाएगा.
आपसे पूछे गये सवाल के जवाब उन बच्चों की इलाज में मदद करेगी जिनको अपपकी जैसी तकलीफ़ हैं.

अध्ययन के बाद आपकी तकलीफ़ और उसकी इलाज के बारे में एक रिपोर्ट लिखी जाएगी.

इस अध्ययन में तुम्हारा भाग लेना अनिवार्य नहीं है.

आपके माता-पिताजी भी इस अध्ययन के बारे में जानते है.

अगर आप इस अध्ययन में भाग लेना चाहते हो तो अपनी हस्ताक्षर को नीचे लिखें.

मैं _____ इस अध्ययन में भाग लेना चाहता/ चाहती हूँ.

हस्ताक्षर दिनांक

APPENDIX – INFORMATION SHEET ADULT – TAMIL

நோயாளி தகவல் தாள்

படிப்புக் தலைப்பு: வாஸ்குலர் குறைபாட்டுக்கு முடிவுகள்
ஸ்கெலரோதெரபி விளைவுகளை

லொகாலிட்டி: CMCH, வேலூர்

முக்கிய புலன்விசாரணை: டாக்டர் யோசுவா

தொடர்பு தொலைபேசி எண்: 9700040138

நீங்கள் ஸ்கெலரோதெரபி ஒரு ஆய்வு பங்கேற்க வாஸ்குலர் anomaliesநீங்கள் எடுத்து இருந்தாலும், இல்லாவிட்டாலும் பகுதியாக உங்கள் தேர்வு அழைக்கப்படுவார்கள். நீங்கள் பங்கேற்க விரும்பவில்லை என்றால், நீங்கள் ஒரு காரணம் கொடுக்க வேண்டிய அவசியம் இல்லை, அதை நீங்கள் பெற பாதுகாப்பு பாதிக்காது. நீங்கள் இப்போது பங்கேற்க ஆனால் உங்கள் மனதை மாற்றிக் கொள்ள வேண்டும் என்றால், நீங்கள் எந்த நேரத்திலும் ஆய்வு வெளியே இழுக்க முடியும்.

இந்த பங்கேற்பாளர் தகவல் தாள் நீங்கள் கலந்து கொள்ள விரும்பினால் நீங்கள் முடிவு உதவும். நாங்கள் ஆய்வு செய்கிறார்கள் ஏன் அது அவுட் அமைக்கிறது, உங்கள் பங்கு ஈடுபட வேண்டும் என்பது என்ன, என்ன நன்மைகள் மற்றும் அபாயங்கள் உங்களுக்கு இருக்கலாம், மற்றும் ஆய்வு முடிவடையும்போது என்ன நடக்கும் என்று. நாம் இந்தத் தகவலை வழியாக சென்று ஏதேனும் கேள்விகள் உங்களிடம் பதில் அளிக்க வேண்டும். நீங்கள் இந்த ஆய்வில் பங்கேற்க இல்லையா என்பதை இன்று

முடிவு இல்லை. நீங்கள் தீர்மானிக்க முன் நீங்கள் போன்ற குடும்பம், whānau, நண்பர்கள், அல்லது சுகாதார வழங்குநர்கள் மற்ற மக்கள், ஆய்வு பற்றி பேச வேண்டும். இதை செய்ய தயங்க.

இந்த ஆய்வில் கலந்து கொள்ள ஒப்பு கொண்டால், நீங்கள் இந்த ஆவணத்தின் கடைசி பக்கத்தில் ஒப்புதல் படிவத்தில் கையெழுத்திட கேட்கப்படும். நீங்கள் வைத்து பங்கேற்பாளர் தகவல் தாள் மற்றும் ஒப்புதல் படிவம் இருவரும் ஒரு பிரதியை வழங்கப்படும்

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இந்த ஆய்வின் நோக்கம்:

இந்த ஆய்வின் நோக்கம் venolymphaticகப்பல் ஒழுங்கற்ற இரத்த குழாய்கள் நோய்கள், வழக்கத்துக்கு மாறாக பெரிய மற்றும் பெரும்பாலும் தோலின் கீழே அல்லது சில நேரங்களில் தசை அல்லது எலும்பு உள்ள ஒரு சிறிய ஆழ்ந்த விரிவாக்கும் இவை .These உள்ளன என்று ஒரு குறிப்பிட்ட நோய் நிலைமை நோயாளிகளுக்கு மதிப்பிட வேண்டும் .These வலி, நடமாட்டத்தையும், சில ஒப்பனை disfigurement போன்ற, அவை அமைந்துள்ள அடிப்படையில் பல்வேறு பிரச்சினைகளுக்கு ஏற்படுத்தும்

தற்போதைய சிகிச்சை நிலையான அதன் மூலம் அளவு மற்றும் பிற அறிகுறிகள் குறைக்க பயன்படுகிறது சில அடைப்பு அல்லது இரத்த உறைவு, ஏற்படுத்தும் என, இந்த இரத்த குழாய்கள் ஒரு இரசாயன ஒரு குறிப்பிட்ட வகையான ஊசி உள்ளது.

ஆய்வு உங்கள் அறிகுறிகள் குறைக்கும் (இரசாயன ஊசி) ஸ்கெலரோதெரபி விளைவுகளை பார்க்க முயற்சிக்கிறது

என் பங்கு என்ன செய்ய வேண்டும்:

-இந்த ஆய்வு சில கேள்விகள் அதாவது அடிப்படையில் ஒரு முற்றிலும் கேள்வி நீங்கள் சிகிச்சை மற்றும் பிறகு முன் உணர்கிறேன் என்று எப்படி என்று கேட்டார் என்று உள்ளது.

-இல்லை கூடுதல் உளசி / சிகிச்சை தேவைப்படும்

-probably மிகவும் பிற்தைய தேதியில் ஒரு தொலைபேசி அழைப்பு அது எப்படி செய்கிறீர்கள் சரிபார்க்க

நீங்கள் சிகிச்சை பெற்று எப்படி நன்றாக மீண்டும் செய்யலாம் முந்தைய செய்யப்பட்டது usg / எம்ஆர்ஐ.. போன்ற -ஒரு சில சோதனைகள் பார்க்க

சாத்தியமான பலன்களை / ஆபத்துக்கள் என்ன

உன் மிகவும் தகவல் வேண்டும் என்று போன்ற -possible நன்மைகளை ஒரு ஒத்த நோய் நிலைமை மக்கள் அடங்கும்

-ஒரு மிகவும் நெருக்கமாக உங்கள் நோய் நிலைமை பிரதிபலிப்புகளும் வரை சிகிச்சை மற்றும் மேலும் சிகிச்சை தேவை வேகமாக முடியும் ஆராய வேண்டும் பின்பற்ற

இந்த ஆய்வு தொடர்புடைய இடர்கள் வெளிவரவில்லை உள்ளன

யார் இந்த செலுத்துகிறது

அதாவது பங்கு இந்த எந்த கூடுதல் கட்டணம் செலுத்த வேண்டும் இல்லை

அதாவது வரை பின்பற்ற தேர்வு / தொலைபேசி பேட்டியில் நோயாளி முற்றிலும் இலவசமாக இருக்கும்

என்ன ஏதாவது தவறு நடந்தால்

-இருக்கின்றன இந்த ஆய்வில் கலந்து கொண்டு நோயாளிக்கு எந்த கூடுதல் ஆபத்து உள்ளது

-இந்த ஆய்வு நோயாளி உள்ளடக்கியது மாட்டேன் எந்த ஆபத்தான நடைமுறையின் ஒரு பகுதியாக இருக்க வேண்டும்

நோயாளியின் தற்போதைய சுகாதார எந்த விளைவுகள் இல்லை இது போன்ற USG / MRI ந்தேதி அதாவது ஈராக் ஒரு சில சோதனைகள்

நான் என் மனதில் மாற்ற என்ன நடக்கும்:

-நீங்கள் விட்டு / நேரம் எந்த இடத்தில் ஆய்வு ஒரு பகுதியாக இருக்க வேண்டும் தேர்வு எல்லா உரிமையும் உள்ளது.

நீங்கள் பெறுவீர்கள் சிகிச்சை -இதுதான் வகை இந்த ஆய்வில் கலந்து விட்டேன் உண்மையில் எந்த சம்பந்தமும் இல்லை.

எதுவாக நீங்கள் இந்த ஆய்வில் அல்லது பங்கேற்க தயாராக இருக்கிறோம் இல்லையா என்பதை. திட்டமிட்டபடி உங்கள் நோய் நிலைமை சபைகளின் சிகிச்சை போகும்.

APPENDIX 4 – QUESTIONNAIRE USED (Modified SF-36)

Questionnaire for patients with venous malformations (slow flow vascular malformations)

The following questions relate to a certain number of symptoms, sensations or discomforts that can make everyday life difficult. For each symptom listed we ask you to answer the corresponding question in the following manner:

Please indicate whether you have experienced what is described in the sentence, and if so, to what intensity.

1. If you have felt pain, what was the intensity of this pain?

No pain	Light pain	Moderate	Strong	Intense
1	2	3	4	5

2. To what extent did you feel bothered/limited in your work or other daily activities because of your problem?

Not limited	A little limited	Moderately limited	Very limited	Extremely limited
1	2	3	4	5

3. Have you slept badly because of your problems, and how often?

Never	Seldom	Fairly often	Very often	Every
1	2	3	4	5

To what extent did your problems bother/limit you while doing the movements or activities listed below?

		Not bothered/ limited at all	A little bothered/ limited	Moderately bothered	Very bothered /limited	Impossible to do
4.	Standing for a long time	1	2	3	4	5
5.	Climbing stairs	1	2	3	4	5
6.	Crouching, kneeling	1	2	3	4	5
7.	Walking briskly	1	2	3	4	5
8.	Travel by car, bus, plane	1	2	3	4	5
9.	Housework such as working in the kitchen, carrying a child, cleaning floors, doing ironing	1	2	3	4	5
10.	Going to weddings, parties	1	2	3	4	5
11.	Sporting activities	1	2	3	4	5

Problems can also influence one's morale. To what extent do the following sentences correspond to the way you have felt?

		Not at all	A little	Moderately	A lot	Absolute
12	I feel myself nervous	1	2	3	4	5
13	I become tired quickly	1	2	3	4	5
14	I feel I am a burden to people	1	2	3	4	5
15	I must always be careful with my extremity	1	2	3	4	5
16	I am embarrassed to show my extremity	1	2	3	4	5
17	I get irritated easily	1	2	3	4	5
18	I feel handicapped	1	2	3	4	5
19	I do not feel like going out	1	2	3	4	5
20	I feel myself depressive	1	2	3	4	5
20.	ADL (Toilet care, household)	1	2	3	4	5
21.	Regional symptoms -	1	2	3	4	5

(Head and neck- turning neck

Upper limb – lifting objects

Lower limb – Walking, running)

APPENDIX 5 – DATA ENTRY SHEET – EXCEL SPREADSHEET

hospital number	age	sex	location	Specific locations	Maximal dimension - pre - sclero MRI	type	score Day 1 pre- sc	Score Day 1 post	score day 3 scle	day 7 score	No of needles us	Sclerosant used	Total volume injected (ml)	Major complications	Minor complications	Further sessions	Details of further sessions
055850H	2	m	1- left thigh	2	3.8	VM	11	18	10	9	3	2	4	n	n	1	
845926G	4	m	2- neck and masticator	1 & 2	5.8	VLM	13	15	10	10	2	2	4.4	n	n	1	
873372G	7	f	3 & 1 - right gluteal and abdominal	3 & 4	7.7	VM	15	17	11	10	2	2	10.2	n	n	1	
616944G	9	m	3 - axilla	2	16	VLM	19	21	15	12	1	2	10.5	n	n	1	
024338H	10	f	1 - left foot	1 & 2	4.5	VM	18	22	10	10	2	2	8.6	n	n	1	
070248H	35	f	2 -Right neck	2	5.9	VLM	15	23	11	10	3	2	13	n	n	1	
908989G	14	f	2 - left parotid	1 & 2	4.5	VLM	11	13	11	10	3	2	8.5	n	n	2:1 more 10 + 6	
022089H	1	f	3 - chest wall	1 & 2	6.7	VLM	12	17	12	10	2	1	6	n	n	1	
117188H	1	m	2- Left submandibular	1 & 2	11.1	VLM	8	13	6	6	4	1	18	n	n	2:1 more 16 ml	
893296G	3	f	1 - thumb	2	2.7	VM	15	17	11	11	2	1	2	n	n	1	
193653H	3	m	2-Right cheek	1 & 3	10.8	VM	13	23	9	9	5	1	15	n	n	1	
842795G	6	f	1 - thigh	2	1.7	VM	17	14	14	12	5	1	6.5	n	n	2:3 more sessions	
885075G	6	f	2 - left cheek & orbit	2	5.5	VM	11	14	11	11	2	1	5	n	n	1	
833499G	7	m	2- parotid	1 & 2	2.7	VLM	15	14	11	9	3	1	6	n	n	1	
812327G	8	f	2- chin and submandibular	1 & 2	3.4	VLM	15	13	10	10	3	1	4	n	n	2:1 more 12 ml	
129242H	8	m	3 -Right chest wall	4	9.2	VM	12	20	8	8	3	1	7.5	n	n	1	
074778H	9	f	1 -Right leg	2	12.5	VM	16	19	10	10	2	1	4	n	n	2:1 more 6 ml	
774710g	10	m	3 - abdomen	2	5.8	VM	15	11	9	9	5	1	11	n	n	2:1 more 5.5 ml	
695731G	10	f	1 - thigh	2	16	VM	18	19	11	10	2	1	3	n	n	1	
631735g	11	f	1 - forearm	1 & 2	23.7	VM	19	18	13	12	4	1	5.5	N	N	2:1 more session	
084213H	11	f	3- retroperitoneum	2	6.7	VLM	16	19	10	10	3	1	3	n	n	1	
092987G	11	m	1 -left lower limb	2	22.2	VM	13	17	9	9	4	1	18	n	n	1	
690101G	12	m	3 & 1 -Trunk + Upper limb	1 & 3	23	VLM	18	20	11	11	4	1	21	n	n	2:1 more 38 ml kt syndrome	
919939G	12	m	1- medial thigh	2	4.5	VM	12	15	12	10	2	1	4	n	n	1	
083190H	13	m	2- parotid and neck	1 & 2	4.5	VM	17	21	12	11	2	1	1.5	n	n	1	
273038C	15	m	1- thigh	1	16.6	LM	22	20	15	14	2	1	4	n	n	1	
904090G	15	F	1 - left lower limb	1 & 2	4.4	VM	15	18	12	12	2	1	2	n	n	1	
924121G	15	m	2 - left submandibular	2	5.5	VM	13	16	12	11	5	1	9	n	n	1	
107358H	15	m	3 -Right chest	2	6	VM	9	14	7	6	2	1	8	n	n	1	
079043G	16	F	1 - Upper limb forearm	2	7.5	VM	19	20	16	14	2	1	2	n	n	2:1 more 2 ml	
894750G	16	f	1 - right calf	3	21.2	VM	14	17	11	10	4	1	12	n	n	2:2 more sessions	
135617H	16	f	1 -left leg	2	3.5	VM	20	22	10	10	2	1	3	n	n	1	
834685g	17	f	1 - thigh	2	6.3	VM	17	12	11	8	2	1	4	n	n	2:2 more sessions	
890719G	17	f	2 - tongue and submandibular	2	4.4	VM	14	16	12	11	4	1	9	n	n	2:1 more 4 ml	
903574G	18	f	2- left cheek and lip	1 & 2	2.7	VM	17	18	12	12	2	1	3.5	n	n	2:1 more 3.5 ml	
011902H	18	m	3 -intra-abdominal	4	13.8	VM	18	21	13	13	2	1	5	n	n	2:1 more 2 ml	
099954H	18	f	1 - Left thigh	2	8.8	VM	12	18	9	8	2	1	2	n	n	2:1 more 3 ml	
127588H	18	f	1 -Left lower limb	4	3.3	VM	15	21	9	8	3	1	8	n	n	1	
048099H	19	m	1- Right thigh	2	3.6	VM	22	23	11	9	3	1	7	n	n	1	
852589G	22	f	1 - forearm	3 & 4	11.9	VM	17	19	11	11	7	1	7	n	n	1:1 more 8 ml	
610489G	22	f	3 - abdomen	1	3.9	VM	16	18	14	12	2	1	2.5	n	n	1	
948671G	22	m	3 & 1 - left ul and chest wall	3 & 4	44	VM	12	15	10	9	3	1	21	n	n	1	
485134G	23	m	2 - submandibular	1 & 2	12	VM	20	21	17	15	4	1	8	N	N	1	
500129C	23	m	2 - Right frontal region	3	16.2	VM	14	17	9	9	3	1	10	n	n	1	
116432H	26	f	3 - Left chest wall	2	4.4	VM	11	19	7	7	3	1	5	n	n	1	
630913g	27	m	2 - lip	1	2.9	VM	16	12	12	9	2	1	4	debridement	discoloration	1	
929892G	27	m	1 - foot	2	4	VM	18	20	15	14	3	1	4	n	n	1	
947213G	28	f	2 - right neck	2	7.4	VM	11	15	9	7	2	1	5	n	n	1	
020300H	29	f	2 -Right supraclavicular	2	7.2	VM	12	18	11	10	3	1	7	n	n	2:1 more 8 ml	
540285G	35	m	2 - face(masseter)	2	2.3	VM	20	20	11	11	1	1	2	n	n	1	
837519g	47	f	2 - cheek	2	5.1	VM	16	14	12	10	2	1	7.5	debridement	discoloration	1	
820426G	47	f	1 - thigh	2	7.7	VM	27	26	20	20	3	1	4	n	n	1	
943047G	4	f	3 - left axilla and chest	3	12.9	VLM	12	16	9	8	3	2	19.2	n	n	2:1 more 10 + 3 units	

1- extremity	1- superficial (skin and subcutaneous)	VM - venous malformation	1 - STS only
2- head and neck	2- deep -partial involvement of muscles of the compartment	VLM - venolymphatic malformation	2 - STS & bleomycin
3 - trunk	3 - Near complete involvement of muscles of the compartment	LM- Lymphatic malformation	
	4- Juxta-articular / intra-osseous / intraabdominal / thoracic involvement		

5 units of bleomycin - 1ml

Urkund Analysis Result

Analysed Document:	Joshua for thesis submission.docx (D42264562)
Submitted:	10/8/2018 11:12:00 AM
Submitted By:	joshanand349@gmail.com
Significance:	1 %

Sources included in the report:

Haemangioma.docx (D38532200)
http://www.authorstream.com/Presentation/drarafat878-1118600-vascular-anomalies-essay/
http://www.novanews.org/information/vascular-malformations

Instances where selected sources appear:

4