# EVALUATION OF THE OUTCOME OF SCLEROTHERAPY, COMPLICATIONS AND PREDICTORS OF TREATMENT SUCCESS FOR VENOUS MALFORMATIONS IN HOSPITAL KUALA LUMPUR.

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# TABLE OF CONTENTS

# List of Tables

# List of Figures

# List of Appendices

# List of Abbreviations

| | |
|---|---|
| VM | Venous Malformation |
| LM | Lymphatic Malformation |
| CT | Computed Tomography |
| MRI | Magnetic Resonance Imaging |
| LMWH | Low-Molecular-Weight Heparin |
| STS | Sodium Tetradecyl Sulfate |
| CIRSE | Cardiovascular and Interventional Radiological Society of Europe |

# ABSTRAK

**Objektif**: Penilaian hasil skleroterapi untuk malformasi vena (VM) kulit dan peramal kejayaan rawatan.

**Pengenalan:** skleroterapi sering dianggap sebagai rawatan untuk pesakit malformasi vena.

**Kaedah**: Seramai 149 pesakit yang mengalami malformasi vena telah dirawat di Hospital Kuala Lumpur dalam tempoh 10 tahun dari 2010 hingga 2020. 88 pesakit bersetuju untuk menyertai kajian ini, soal selidik diberi kepada semua peserta untuk menjawab tentang hasil rawatan dan kepuasan terhadap rawatan skleroterapi. Data demografi dan maklumat pesakit mengenai rawatan vm juga didapati daripada fail pesakit dan data pengimejan. Regresi logistik digunakan untuk menentukan peramal yang ketara kepada kepuasan pesakit.

**Keputusan**: Malformasi vena paling kerap didapati di kawasan kepala dan leher (76.1%). Kebanyakan pesakit mempunyai simptom bengkak (97.7%, n=86). Skleroterapi paling berkesan dalam mengurangkan bengkak dan aduan estetik, tetapi kurang berkesan dalam mengurangkan kesakitan. Secara keseluruhan, 65 (73.9%) pesakit berpuas hati dengan rawatan skleroterapi. Daripada jumlah 207 sesi, hanya seorang pesakit mengalami komplikasi yang lebih rumit (Tahap 3 CIRSE), komplikasi yang paling biasa adalah bengkak selepas prosedur (78.4%). Tiada peramal kejayaan rawatan dikenal pasti dalam kajian ini.

**Kesimpulan**: Rawatan skleroterapi menggunakan STS sebagai sclerosant adalah rawatan yang berkesan untuk malformasi vena dan lebih selamat. Namun begitu, ia mempunyai kadar berulang yang tinggi.

# ABSTRACT:

**Title:** Evaluation of the Outcome of Sclerotherapy, Complications and Predictors of Treatment Success for Venous malformations in Hospital Kuala Lumpur

**Introduction:** Percutaneous sclerotherapy is often considered as the first-line intervention for patient with cutaneous venous malformations.

**Objective**: To determine the outcome of percutaneous sclerotherapy for cutaneous venous malformation (VM) and predictors of positive response to treatment.

**Method**: A total of 149 patients with venous malformation were treated in Hospital Kuala Lumpur during the 10 years span of 2010 to 2020. 88 patients were successfully recruited for the study, all of them were given the same questionnaire to answer regarding treatment outcome and patient satisfaction. Patient files and imaging data were retrieved to obtain demographic data and information regarding the VM treatment. Logistic regression was used to determine significant predictors to patient satisfaction.

**Result**: Most common site of VMs is the head and neck region (76.1%). Majority of the patients presented with swelling (97.7%, n=86) as symptoms. Sclerotherapy is most efficient in managing swelling and aesthetic complaints, but not pain. In all, 65 (73.9%) patients satisfied with the sclerotherapy. Out of 207 total sessions, only one patient had major complication (Grade 3 CIRSE), most common complications are post-procedure swelling (78.4%). No positive predictors were identified.

**Conclusion**: Percutaneous sclerotherapy using Sodium Tetradecyl Sulfate (STS) as the sclerosant is an effective treatment for venous malformation with minimum major complications. Nevertheless, it resulted in a high recurrence rate.

# CHAPTER 1: INTRODUCTION

Vascular anomalies are congenital disorder of the blood vessels endothelium with up to 10% of neonates were affected(1). They are subdivided into two major categories: vascular tumors and vascular malformation. The cellular characteristics of the two groups set them apart from one another. Classical characteristics for vascular tumours are their endothelial hyperplasia, a multilaminated basement membrane, and rapid growth. On the other hand, vascular malformations have normal endothelium turnover, they are resulted from error during vascular developmental and morphogenesis(1–3).

Venous malformations (VMs) are the most common type of vascular malformation with an estimated incidence of 1-2/10000 and an estimated prevalence of 1%. Their location can be superficial, affecting the dermis and subcutaneous tissue, or deeper, involving muscle or bone. They can occur throughout the whole body, including visceral locations(4–7). Their growth usually corresponds to the patient's growth. Individuals may experience sudden rapid increment of the size during pregnancy and puberty due changes in hormonal level.

Majority of the VMs are sporadic. There are also familial cases of VMs which are believed to be inherited in an autosomal dominant fashion(4). A recent study demonstrated somatic mutation of several genes and receptors, which are responsible for the development of VMs, most notably the TIE2 receptor, TEK and PIK3CA gene mutations(8–10). They lead to dysregulation of angiogenic growth factors, and formation of enlarged, thin-walled vessels with a large lumen lined with thin layers of smooth muscle and pericytes(10).

The clinical course of VMs is unpredictable. VMs are present at birth, but occasionally they are not detected until much later in life. Most commonly, VMs

presented as soft mass with bluish to purple hue, that are compressible and with the ability to refill in a short period of time. On palpation, sometimes hard masses can be felt, they are known as phlebolith, and there is no thrill or bruit.

Although the majority of VMs can be diagnosed based on clinical history and physical examination, diagnostic imaging can help distinguish them from other types of lesions and confirm the diagnosis. Duplex ultrasonography is typically the first-choice imaging investigation because it is non-invasive and readily available in the vast majority of hospital settings. Duplex ultrasonography can determine the flow rate, also able to identify phleboliths in VMs as they are present in 16% of the cases(9). In contrast to Lymphatic Malformations (LMs), which show as non-compressible cystic spaces, VMs typically manifest as hypoechoic or anechoic compressible vascular spaces. Doppler-mode is utilized to distinguish VMs from AVMs, as VMs exhibit slow-flow in comparison to AVMs' high-flow.

MRI is the image modalities of choice for the study of vascular malformations. It has a 98.9% sensitivity and 90% specificity(11). It confirms the extent of the lesion and distinguishes between different type of soft tissues and vascular structure involved. It also delineates the feeding and draining vessels. All these details are necessary for the treatment planning of VMs. The downside of MRI is that infants and children must be sedated for the scan to proceed smoothly. Infrequently are more invasive diagnostic tests, including as conventional angiography and venography, required to establish the diagnosis of VMs, they can be deferred until intervention is required.

Some people with VMs exhibit no symptoms, while others may have different symptoms such as pain, swelling, functional impairment, bleeding, and deformity. Patients with vascular malformation are reported to have suffering psychologically with

lower self-esteem, feeling stigmatized, and increased tendency towards antisocial behavior. In fact, study has demonstrated that some parents of children with congenital abnormalities also endured difficult times as they attempted to adjust and accept their children's abnormality(9).

Treatment of VMs can be mainly divided into medical or interventional strategies. The indications for treatment include severe threats to the function of one or several organs or systems and serious compromise of the patient’s quality of life. Medical treatment consists of compression garments, anti-inflammatory drugs, and low-molecular-weight heparin (LMWH). Interventional treatment of VMs can be based on sclerotherapy, surgical resection, or a combination of both.

Percutaneous sclerotherapy is frequently considered the first line of treatment to use when conservative management has failed. By injecting sclerosant intra-vascularly, disrupting the phospholipid bilayer of the endothelial cells will lead to activation of the coagulation cascade, causing thrombosis and fibrosis of the anomalous vessels. The goal of the therapy should be to control symptoms and improve functional and cosmetic outcomes. Patients must understand the expected course of the therapy and have realistic expectations. They should be counselled about the complications even though it is a minimally invasive procedure. There is no absolute safe procedure, and percutaneous sclerotherapy is linked with a range of complications, from temporary swelling, pain, or skin pigmentation to permanent neurological deficits and skin necrosis(9,12–14).

# CHAPTER 2: LITERATURE REVIEW

## 2.1 SCLEROTHERAPY

Percutaneous sclerotherapy has proven to be a very effective treatment for VM. Van der Linden et al conducted a national study with the longest follow-up after sclerotherapy of vascular malformations with a good size cohort. They followed up 66 patients for a mean follow-up time of 39 months (median, 30 months; range, 6–147 months). A single questionnaire was sent to the patients to determine the overall satisfaction towards sclerotherapy and asked about specific symptoms before and after treatment and about the occurrence of any complications. The data showed that complete or partial clinical improvement at 3 months is expected in 58% of the patients irrespective of the size or classification of vascular malformation. An interesting finding from their results was that long-term (5-year) complete relief of symptom was only reported in eight (12%) of 66 patients, and all of these patients had a complete initial response(12).

In a study conducted by Sumera Ali et al, 116 patients with a median follow-up time of 2.5 months, observed an overall improvement in 88 (76%). They further explored the clinical improvement for patients with at least 3 months, 6 months, and 1 year of follow-up. Although the number of patients dropped over time, they showed a similar trend in the improvement scale the short-term outcomes (months) remain relatively stable over time (1–5 years)(15).

Thus, both studies have shown that complete response at short-term follow-up may be predictive of decreased or no recurrence in the long term. Both studies use Ethanol as sclerosant.

Jin et al studied-on sclerotherapy using absolute ethanol and bleomycin A5 for VMs in 201 cases. Their experience using this combined form of sclerotherapy has brought great success with 97.5% of patients reported an improvement in symptoms. The patients who participated in the study were divided into 2 main groups based on the lesion margin in initial imaging studies (MRI). The first group consist of 120 VMs patients who had a well-defined or circumscribed margin with a clear plane from surrounding tissue (limited VMs). The second group consist of 81 VMs patient with ill-defined margin, without a clear plane (infiltrating VMs). The study showed that only 35% of the patient from the first group needed more than 3 sessions of sclerotherapy,

and 70.4% of patients from the second groups underwent more than three sessions. Among the patients whose treatment was completed, 90 (75%) of the limited VMs disappeared or became nearly normal. Even though none of the infiltrating VMs showed complete cure from disease, the treatment still proved beneficial in 46 of the 81 patients (56.8%), who had markedly improved symptoms(16). Although some studies suggested that limited VM lesions responded better to sclerotherapy and should be used as first-line treatment(16–18), but others believe small localized, well-defined lesion respond well to surgical excision, although it may not be completely excised in most cases(19).

In 2014, Nakamura et al conducted a similar study with only patients with extremities VM included. A total of 40 patients included in the study with a mean follow-up period of 2.3 years (range, 7 months-7.5 years). Nakamura's results showed that out of 40 patients included in the studies, there was an 80% satisfaction rate from VM therapy in the extremities. The majority of the patient (90%) had disabling pain before the treatment and 83% of them reported a "good response" towards the therapy. Out of 40 patients who participated in questionnaires, there are only 2 major complications occurred (5%). Pain, swelling, and functional limitations were improved in about 80% of patients, whereas cosmetic improvement was seen in 50% of patients. As for predictors of response to sclerotherapy, the author identified adjacent bone change as a significant predictor of patient dissatisfaction, with bone and joint involvement associated with higher risk of symptom recurrence and they are associated with more discomfort(14).

## 2.2 SCLEROSANTS

There are many sclerosants that are available, and their utilization is often institution specific and depends on the radiologist preference. According to reviews by Qiu (20) and Ali (15), the common sclerosant used was Ethanol, Polidocanol, Ethanolamine Oleate, Sodium Morrhuate and Sodium Tetradecyl Sulfate (STS). All the above mentioned sclerosant produced good outcome except for Sodium Tetradecyl Sulfate which showed lowest cure rate and higher recurrence rate, and this recurrence is believed due to its gentler properties compared to other sclerosant(17).

Sometimes they can be use in combinations depending on the lesion morphology and clinical judgement. For example, combination of ethanol and antitumor agent, Bleomycin A5. They treated the draining vein first with a small dose of ethanol followed by bleomycin injection into the lesion. It produced good outcome with 95% of the patients showing marked improvement(16).

Although using Ethanol as sclerosant for sclerotherapy has shown promising results in treating venous malformation, it has also lowest recurrence rate, and is also associated with higher rate of complications(13,21,22). Skin damage (10%) is the most common complication, including skin blistering, skin ulcer, skin necrosis, cutaneous fistula, and pigmentation. Other common minor complications after sclerotherapy treatment involved nerve damage, muscle fibrosis, and transient hemoglobinuria. However, most cases of nerve damage were reversible(15,20).

It is an undeniable fact that sclerotherapy produces good outcome in most of the VM patient with many foreign studies has shown high success rate in alleviating symptoms(12,14–17,23,24). However, some do not show improvement and even cause deterioration of the symptoms. Because of the long course of treatment and difficulty for the medical practitioner to accurately identify the changes that happen in the lesion, it has been a challenge for us to evaluate how much improvement achieved after a session of sclerotherapy in everyone.

In terms of predictor of treatment success, some studies suggested that smaller lesion size, and no osseous infiltration tend to respond better to therapy and lower recurrence rate. Some author reported that the higher the number of sessions, the better the response, while other suggested the opposite(14,18,25).

## 2.3 RATIONAL OF STUDY

As previously stated, percutaneous sclerotherapy is now the treatment of choice for VMs. Numerous international studies have demonstrated its effectiveness in managing

VMs and improving patients' quality of life. In Malaysia, however, not all VM patients are able to experience these benefits, as percutaneous sclerotherapy is only offered at a handful of big government hospitals and universities. Frequently, patients must travel great distances to seek treatment, and those who cannot afford to do so, may end up defaulting the treatment.

Therefore, I would like to conduct a study to find out the outcome and complications of sclerotherapy on cutaneous VMs patients in the biggest hospital in Malaysia, Hospital Kuala Lumpur. This can help us gain a better understanding of the outcome of treatments from patients' perspective, discover the predictors of positive response to sclerotherapy treatment, and compare the results to those of other studies. This will help to improve patient selection and to plan for the treatment regime in the future. It can be a supportive finding to enhance the growth of sclerotherapy service in Malaysia.

# CHAPTER 3: OBJECTIVE OF STUDY

## 3.1 General Objective

To Evaluate the outcome of sclerotherapy for venous malformations, complications, and predictors of treatment success.

## 3.2 Specific Objectives

1. To determine the effectiveness of percutaneous sclerotherapy from the patient's perspective including the changes of symptoms after treatment, and general satisfaction towards therapy.
2. To determine the factors that contribute to the success of sclerotherapy. These factors including age, gender, size and location of lesion, pre-treatment symptoms and number of treatments.
3. To determine the differences in volume of sclerosant and time needed for improvement according to VMs sizes.

# CHAPTER 4: METHODOLOGY

## 4.1 Study Design

This is a retrospective questionnaire based clinical study conduct in a tertiary care center. Patient with cutaneous venous malformation who underwent intra-lesional sclerotherapy between the years 2010 and 2020 can be recruited into this study. A questionnaire-based survey will be conducted among all the participants to evaluate the outcome of the sclerotherapy treatment and to determine the factors contributing to the success of it.

## 4.2 Study Location

Study conducts at Plastic Surgery Ward (Ward 15) or Plastic and Reconstructive Surgery Clinic, Hospital Kuala Lumpur.

## 4.3 Study Population and Sample

All patients diagnosed with venous malformation, who underwent percutaneous sclerotherapy treatment in Hospital Kuala Lumpur from 1st January 2010 – 31st December 2020.

## 4.4 Patient Recruitment

List of potential study candidates were obtained from Plastic Surgery clinic and Interventional Radiology department records. During their clinic visits, those who

fulfill the inclusion criteria were approached and asked for their permission to participate in this study. Once subject agreed to participate, an electronic device (handphone or tablet) containing the online questionnaire and consent forms will be passed to the participant. They were given enough time to fill up the forms and answer the questionnaire.

Potential study candidates without clinic follow-up or defaulted follow-up were contacted by telephone and asked for permission to recruit into the study. Once agree, subjects will be given an appointment date to see in clinic. For those who cannot come for clinic visit, or recruitment done during the COVID-19 lock-down period, the link for online questionnaire form and consent forms were forwarded to the patients via digital communication means (email or instant messaging applications) for completion.

All data is automatically collected from the questionnaire is then stored in the secure webpage host server.

## 4.5 Inclusion Criteria

All patients diagnosed with cutaneous venous malformation who has done percutaneous sclerotherapy treatment in Hospital Kuala Lumpur during the period of 1st January 2010 – 31st December 2020.

## 4.6 Exclusion Criteria

- Patients with incomplete medical records
- Patients still planned for sclerotherapy treatment
- Patients who underwent additional treatments in another center.
- Not consented (either by self or parents/caretaker)
- Not fluent in Malay or English

## 4.7 Sample Size Calculation

Universal sampling will be done.

All patients with cutaneous venous malformation who received percutaneous sclerotherapy treatment from 1st January 2010 to 31st December 2020 and fulfill the inclusion criteria will be considered for the study, the estimation is around **100** patients.

Same patients had received multiple session of sclerotherapy during that time frame, but each of them will be recruited as one subject. Therefore, there will be no repetitive subject recruitment.

## 4.8 Research Tools

This is a questionnaire-based study, the questionnaire is based on the same grading principles used by Boris Khaitovich and some others(12,18). Permission to use the questionnaire were granted from the original author. This questionnaire for the patient will be translate into Malay language with backward forward translation by a linguistic and bilingual person. Once translated, a face validation will be conducted to 10 respondents who agree to participate and consented. This is to detect any ambiguity of words, misinterpretation of questionnaires and sensitive question. If there is any correction, it will be rectified and re-distributed to another 10 consented patients until the final questionnaire is reconstructed.

Demographic data and additional data will also be collected from patient's medical records and filled into the data collection form.

## 4.9 Data collection

A questionnaire will be used to collect the data from participants. The questionnaire contains total of 9 questions, which can be completed within 10 minutes. Subjects will be asked for specific symptoms (pain, swelling, and functional and cosmetic complaints). It is also possible to fill in additional symptoms. The improvement of each symptom will be assessed using four categories grading scale: "significantly improved", "slightly improved", "did not change" and "worsened". They will be asked whether there was any initial clinical success after treatment, whether symptoms had recurred, and if so, for how long after treatment. Finally, they will be asked to indicate whether they were significantly satisfied, slightly satisfied, unsatisfied or significantly dissatisfied from their treatment. For the purposes of this study, patients who gives one

of the two former responses will be categorized as the ‘‘satisfied group’’ and those who gives one of the two latter responses will be categorized as the ‘‘dissatisfied group’’. Lastly, patients will be asked to describe any other complications that occurred after therapy and whether there was any permanent damage. All unclear responses will be clarified with the participants.

Finally, patient will be asked to describe any other complications that occurred after therapy and whether there was any permanent damage. Treatment complications were described upon their occurrence and were classify according to the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) guideline(26) in figure 1.

| GRADE | DESCRIPTION |
|---|---|
| **1** | Complication during the procedure which could be solved within the same session; no additional therapy, no post-procedure sequelae, no deviation from the normal post-therapeutic course. |
| **2** | Prolonged observation including overnight stay (as a deviation from the normal post-therapeutic course <48 h); no additional post-procedure therapy, no post-procedure sequelae. |
| **3** | Additional post-procedure therapy or prolonged hospital stay (>48 h) required; no post procedure sequelae |
| **4** | Complication causing a permanent mild sequelae (resuming work and independent living) |
| **5** | Complication causing a permanent mild sequelae (requiring ongoing assistance in daily life) |
| **6** | Death |

Figure 1: CIRSE classification system

The diagnosis of all participating patients was based on clinical findings along with imaging studies such as ultrasound and MRI. VM’s location was categorized as either head and neck, lower extremities, upper extremities, trunk, or buttocks/perineum. All demographic data, clinical findings and pretreatment imaging results were retrieved from patients’ medical records and radiologic archives.

## 4.10 Study Flow chart

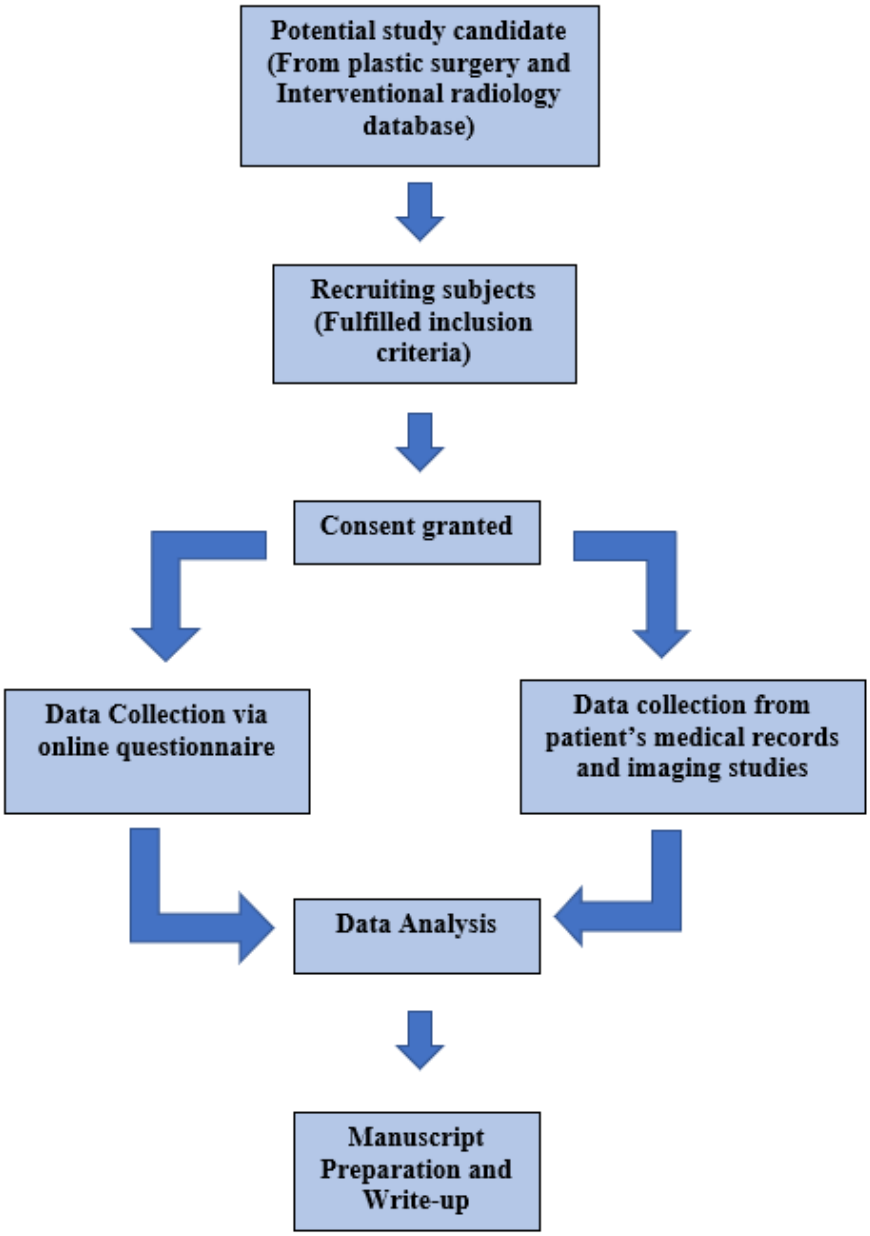


**Figure 2: Study Flow chart**

## 4.11 Statistical Analysis

Statistical analysis was done using SPSS version 27.0 for windows. A value of $P<0.05$ was considered as statistically significant. Descriptive statistics for categorical