

A single-center, single-arm, prospective, open-label trial to evaluate the efficacy and safety of percutaneous sclerotherapy with polidocanol for painful venous malformations (SCIRO-2001): study protocol

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ABSTRACT

This single-center, single-arm, prospective open-label trial is being conducted to evaluate the short-term efficacy and safety of percutaneous sclerotherapy with polidocanol foam for painful venous malformations. This study will include patients who were clinically diagnosed with venous malformation by using ultrasound and/or magnetic resonance imaging, and whose pain persisted even after treatment with medications. Written informed consent for sclerotherapy will be obtained from all patients. The institutional review board approved this prospective study protocol. The primary endpoint is pain relief at three months after sclerotherapy. Local pain related to venous malformation will be evaluated using a numeric rating scale. Patient recruitment commenced in December of 2020. Enrolment of 13 patients is planned over a 3-year recruitment period. Herein, we describe the details of the clinical trial protocol.

Keywords: venous malformation, sclerotherapy, intervention

Abbreviations:

NRS: numeric rating scale

VAS: visual analog scale

VM: venous malformation

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INTRODUCTION

Vascular malformations are congenital vascular anomalies characterized by dysplastic vascular channels with normal cell proliferation. Different subtypes of vascular malformations have

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been classified by the International Society for the Study of Vascular Anomalies (ISSVA)¹: capillary malformations, lymphatic malformations, venous malformations (VMs), arteriovenous malformations, combined vascular malformations, or vascular malformations associated with other anomalies. VMs are the most common type of vascular malformation²; the number of patients with VMs among all vascular malformations is estimated to be about 20,000 in Japan.³

Most VMs may not be visible even years after birth; most superficial lesions are asymptomatic, and the use of supportive treatment (eg, simple observation, compression garments, or drugs such as corticosteroid ointment) is recommended for such asymptomatic superficial lesions. However, some lesions grow in size, leading to palpable local swelling, local pain, or bleeding. The severity of the symptoms varies greatly depending on lesion size, blood flow through the vascular components, and lesion location (superficial or deep). These factors should be considered when determining the treatment strategies.

The effectiveness of interventional therapies such as surgical resection,⁴ percutaneous cryoablation,^{5,6} and sclerotherapy⁷⁻¹⁰ for symptomatic VMs has been previously studied. Surgical resection is the most curative, but it is also the most invasive option. In particular, for lesions that invade deeply into the muscle, the indications for surgical resection are limited due to the potential for functional or cosmetic problems. Percutaneous sclerotherapy has been recently suggested as an alternative to surgery. Various sclerosing agents, including polidocanol,^{8,9} ethanol,⁹ and sodium tetradecyl sulfate (STS),¹⁰ have been used in these studies. The use of ethanol, the most powerful sclerosing agent, has been reported to result in a higher frequency of serious complications.⁹ Percutaneous sclerotherapy using polidocanol for painful VM reduces pain in 90% of patients and rarely causes serious complications.⁷ However, in Japan, the use of polidocanol for sclerotherapy of VMs has not been covered by national health insurance; as a result, sclerotherapy using polidocanol is not widely performed and is used only in specific medical institutions with expertise in the treatment of VMs. Thus, sclerotherapy using polidocanol has not yet been standardized in terms of appropriate candidates and the appropriate use of the agent (eg, dosage and administration method). In addition, previous studies were mostly based on retrospective case series. Therefore, prospective studies on sclerotherapy using polidocanol are required to confirm its safety and effectiveness. We plan to conduct an exploratory prospective clinical trial to evaluate the short-term efficacy and safety of percutaneous sclerotherapy with polidocanol for painful VMs. Herein, we describe the details of this prospective open-label trial protocol.

METHODS

Study objectives

The main purpose of this study is to evaluate the therapeutic efficacy and safety of percutaneous sclerotherapy by using polidocanol foam for painful VMs.

Study design

This is a single-center, single-arm, prospective open-label trial. The investigators will be required to obtain written informed consent from the patient before any screening or inclusion procedure. This study is being conducted in compliance with the principles of the Declaration of Helsinki, and the protocol has been approved by the institutional review board of the participating hospital (approval number of IRB: CRB6180001). This study was registered with the Japan Registry of Clinical Trial (jRCT) in Japan (trial registration number: jRCTs061200036).

Eligibility criteria

All patients who meet the main inclusion and exclusion criteria will be screened. The main inclusion and exclusion criteria are listed in Table 1.

Table 1 Patient eligibility**< Inclusion criteria >**

- 1) Painful venous malformations.
- 2) Age \geq 12 years.
- 3) Diagnosis of venous malformations by image examination before participation in this study.
- 4) A puncture cavity is visible on CT or US.
- 5) The preoperative and postoperative effects of the target lesion can be determined by MRI.
- 6) Performance status (PS) is 0 to 2.
- 7) Written consent has been obtained from the patient or the patient's legal representative if the patient is under 20 years of age.

< Exclusion criteria >

- 1) An important organ or vessel is present in the percutaneous puncture route.
- 2) The patient has a systemic active infectious disease.
- 3) The patient is pregnant or may be pregnant by the time of the interview.
- 4) The patient has facial and head lesions.
- 5) The serum creatinine (Cr) level at screening exceeds 2.0 mg/dL.
- 6) The platelet count at screening is less than 50,000/ μ L.
- 7) The PT-INR at screening is 1.5 or more.
- 8) The patient has received pretreatment (surgery, irradiation, percutaneous sclerotherapy, etc) for the target lesion with the last three months.
- 9) The patient has a history of deep vein thrombosis.
- 10) The patient shows comorbid arterial blood circulation disorders (including arteriosclerosis or diabetic microangiopathy)
- 11) The patient's general condition is unstable.
- 12) The patient has comorbid serious heart disease.
- 13) The patient has comorbid active bronchial asthma.
- 14) The patient has a history of hypersensitivity to contrast media or polidocanol components.
- 15) Active inflammation or ulcer is present in and around the treatment site.
- 16) The patient has a history of stroke due to paradoxical embolism-mediated patent foramen ovale.
- 17) Any other condition determined by the doctor to be inappropriate for this study due to conflicts of interest.

Interventional procedure

Percutaneous sclerotherapy for painful VMs in the trunk or extremities will be performed using 3% polidocanol (Polidocasklerol 3% Inj. 2 mL; Zeria Pharmaceutical Co, Ltd, Tokyo, Japan) by board-certified interventional radiologists with experience in the treatment of vascular malformations. Immediately before administration, polidocanol will be mixed with carbon dioxide at a ratio of 1:4 by using the Tessari method¹¹ and administered as a foam sclerosing agent.

A 21–23-gauge needle is punctured into the VM under ultrasound or CT guidance. After confirming that the needle tip was located in the lesion by observing the backflow of blood,

the polidocanol foam is administered under X-ray fluoroscopy. The amount of polidocanol foam administered by one injection is determined according to the lesion size and should be no more than 5 mL. If necessary, foam injection is repeated via multiple puncture sites. The total dose of polidocanol administered in one procedure should be no more than 2 mg/kg.

Outcome measurement/follow-up

The primary endpoint is short-term pain relief, which will be determined as the difference in the numeric rating scale (NRS) scores before and 3 months after the therapy.

The secondary endpoints are as follows:

- 1) Target lesion volume reduction rate in MRI at 3 months post-treatment in comparison with the volume pre-treatment.
- 2) Incidence of serious diseases up to 1, 3, and 6 months after the treatment.
- 3) Incidence of procedure-related diseases up to 1 month after the treatment.
- 4) Percentage of patients showing pain reduction after the treatment.
- 5) Difference in NRS between before and 6 months after the treatment.
- 6) Difference in visual analog scale (VAS) between before and 3 or 6 months after the treatment.
- 7) Percentage of patients whose pain frequency increased or decreased after the treatment.
- 8) Percentage of patients whose medication dose increased or decreased after the treatment.
- 9) Difference in the quality of life (QOL) score (SF-36v2) before and 3 or 6 months after the treatment, respectively.

The NRS and VAS will be obtained by the principal investigator, subcontractors, or other medical personnel who are not involved in the study treatment.

Statistical considerations

For the main analysis of the continuous endpoints, the mean value of the difference between measurements obtained pre- and post-treatment will be calculated, and the two-sided confidence interval will be estimated assuming a normal distribution. In addition, the Wilcoxon signed-rank test will be conducted as an analysis that does not rely on the distribution of the mean of the differences. Considering a continuous endpoint, the null and alternative hypotheses are as follows:

H₀: Mean difference = 0.

H_a: Mean difference ≠ 0.

The other clinical data obtained in this study will be summarized using descriptive statistics.

The sample size is calculated using the following procedure: After reviewing the clinical data of patients treated at our hospital from April 2009 to March 2019, 50 patients who met the following criteria were selected to represent historical data: (1) painful VMs in the extremities and trunk, (2) age 12 years or older, (3) percutaneous sclerotherapy with polidocanol, and (4) NRS score was obtained before and after 3 months of treatment. The pre-treatment NRS score for the historical data was 6.6 ± 1.8 (mean \pm standard deviation), and the NRS score at 3 months post-treatment was 2.7 ± 3.0 . Then, the NRS difference before and after treatment was expected to be 3.9 ± 2.9 , but we conservatively assumed a mean of 3 and a standard deviation of 3 to account for the sham effect. Under these conditions, the number of study participants required to ensure that the confidence interval did not include zero, assuming a normal distribution for the NRS difference, was 13. The 95% confidence interval of the mean NRS difference, in this case, will be 1.19-4.81.

Interim analysis and monitoring

Interim analysis is not planned during the study period. In-house monitoring will be performed

to ensure patient eligibility and protocol compliance and evaluate data submission and adverse events related to percutaneous sclerotherapy.

DISCUSSION

This single-arm, prospective, open-label exploratory clinical trial has been designed to confirm the relatively short-term efficacy of polidocanol sclerotherapy on the basis of historical data. We hope that this trial will provide novel data for the establishment of a treatment strategy for patients with painful VM.

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AUTHOR CONTRIBUTIONS

The authors MU and JS took part in the trial design and trial setup. MU, JS, and TM participated in sample size calculations. All authors contributed to protocol writing, approved the final manuscript, and accept personal responsibility for the accuracy and integrity of the presentation of this protocol.

CONFLICT OF INTEREST

The authors have no commercial, financial, or other conflicts of interest to declare for this research. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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