Title

Preliminary experience with intraoperative near-infrared fluorescence imaging in percutaneous sclerotherapy of soft-tissue venous malformations

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Running title: NIR Fluorescence Sclerotherapy

Abstract

Background: It has recently been demonstrated that near-infrared (NIR) fluorescence imaging can be used to visualize the blood vasculature. Although sclerotherapy has been successfully used in treating venous malformations, the spread of sclerosant is difficult to monitor during sclerotherapy.

Objective: To evaluate the safety and efficacy of NIR fluorescence imaging in percutaneous sclerotherapy of soft-tissue venous malformations.

Methods and Materials. The use of NIR fluorescence imaging following administration of indocyanine green (ICG) was evaluated in 15 duplex-guided sclerotherapy performed on 15 patients with venous malformations. The involved regions were the lower extremities in seven, the upper extremities in four and the face in four.

Results: In 13 of the 15 procedures, spotty fluorescence images were obtained, and in eight procedures, linear fluorescence images were obtained. In two patients with intramuscular venous malformations in lower extremities, no fluorescence images were obtained. Observational depth seemed to be < 1 cm below the skin surface with an ICG concentration of 0.01 mg/mL. No complications associated with ICG were observed. Adjacent tissue ulceration occurred in one patient.

Conclusion: NIR fluorescence imaging with ICG can be a useful additional monitor for percutaneous sclerotherapy of venous malformations, especially in the face and hands, enabling noninvasive assessment of real-time spread of sclerosant.

Introduction

Sclerotherapy has been a useful alternative to surgical excision of vascular malformations.[1, 2] One of the most common causes of complication during the procedure is extravasation of sclerosant with necrosis of adjacent tissue.[3] Therefore, procedural guidance is required to ensure precise puncture, and the spread of sclerosant should be carefully monitored. Various sclerotherapy techniques have been reported: fluoroscopic guided,[3] duplex guided[4] and magnetic resonance (MR) guided.[5] Recently near-infrared (NIR) fluorescence imaging has been demonstrated to offer real-time visualization, enabling noninvasive assessment of lymphatic and blood vasculature.[6] Kikuchi and Hosokawa reported that intraoperative NIR fluorescence imaging allowed for visualization of sclerosant spreading in varicose veins.[7] We used a real-time NIR fluorescence imaging system with indocyanine green (ICG) as an additional monitor of the spread of sclerosant in duplex-guided percutaneous sclerotherapy of soft-tissue venous malformations. In this report, we describe our clinical experience and evaluate the safety and efficacy of NIR fluorescence imaging.

Patients

The use of NIR fluorescence imaging was evaluated in duplex-guided percutaneous sclerotherapy performed on 15 patients (ages 3–64, average 14.9) with venous malformations from March to August in 2010 at KKR Sapporo Medical Center Tonan Hospital. The lower extremities were involved in seven, the upper extremities in four, and the face in four. Before the procedure, all patients underwent color duplex ultrasound and MR imaging to evaluate the extent, distribution, and character of the lesions. The diagnosis of a venous malformation was made on the basis of clinical history, physical examination, ultrasound and MR imaging. The lesions of all patients in the study met the MR imaging criteria for venous malformations.[8] Follow-up ranged from 1 to 16 months (average 6.3 months). This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Methods

NIR fluorescence imaging

Intraoperatively, venous malformations were visualized through direct injection of a solution of ICG and sclerosant using a NIR fluorescence camera device [Photodynamic Eye (PDE); Hamamatsu Photonics K.K., Shizuoka, Japan] equipped with 760-nm light-emitting diodes within a handheld unit with a charge-coupled device camera as a detector and a bandpass filter to block light below 820 nm.[6] The maximum excitation and fluorescence wave- lengths of ICG in plasma are 765 nm and 840 nm, respectively.[9] Fluorescence within the NIR spectral range (≥ 800 nm) is tissue penetrating, and the PDE provides noninvasive detection of the fluorescence in deeper tissues. This device is portable and easy to use intraoperatively. The fluorescence signals were digitalized for real-time display in monochrome. According to the recorded movies of the procedures, patterns of fluorescence images were classified as linear images, spotty images, or no images obtained. Linear images were defined as more than one vessel-like fluorescence pattern originating from spotty images, which were defined as a local dim fluorescence pattern.

ICG and Sclerosants

ICG (Diagnogreen for injection; Daiichi-Sankyo Co. Ltd., Tokyo, Japan) was used as an NIR fluorophore. Concentrated ICG solution (0.04 mL) was made by dissolving ICG (25 mg) in injection solvent (10 mL) and added to 10 mL of sclerosant solution, resulting in an ICG

concentration of 0.01 mg/mL.[7] The sclerosants were absolute ethanol and 3% polidocanol (Polidocasklerol 3% injection; Zeria Pharmaceutical Co., Ltd., Tokyo, Japan) foamed using the Tessari method.[10] The stable sclerosing microfoam was obtained by mixing 2 mL of polidocanol with atmospheric air at a 1:4 ratio in two syringes attached using a three-way stopcock.

Procedures

All patients were treated under general anesthesia. Direct puncture of the venous malformation was performed using a 22-G angiocatheter with color duplex ultrasound (LOGIQ e; GE Yokogawa Medical Co., Ltd., Tokyo, Japan) to visualize needle placement and facilitate direct cannulation of the vascular channels. Then sclerosant solution mixed with ICG was slowly injected under duplex guidance, and fluorescence images were obtained through the PDE held 15–20 cm from the skin surface to monitor the spread of sclerosant. Operating lights were turned off during the procedure, and room lights were left on to keep light reflection off the skin. In most patients, direct puncture and sclerosis were performed in more than one region of the venous malformation. The sclerotherapy was stopped when the vascular lesion was sufficiently filled according to duplex sonography, when the use of sclerosants reached a maximum dose of 1 mL/kg, or when fluorescence images were obtained at the contralateral side of the treated finger.

Results

Patient characteristics, treatments, and outcomes are summarized in Table 1. Spotty fluorescence images were obtained from the skin surface in 13 of the 15 procedures (87%) and linear fluorescence images in eight (53%). No fluorescence images were obtained in two patients with intramuscular venous malformations in the lower extremities. These intramuscular lesions were located more than 1 cm below the skin surface. Image quality and spatial resolution on PDE were sufficient for visualization of ICG and sclerosant spread. In two procedures (patients 8 and 14), NIR fluorescence imaging was useful in deciding when to stop the sclerotherapy because fluorescence images were obtained at the contralateral side of the treated finger (Figure 1). Linear fluorescence images were more likely to be obtained in the upper extremities and the face than in the lower extremities (Table 2). Linear images seemed to represent the flow in draining vessels, and spotty images seemed to represent the intralesional or extralesional existence of ICG. Fluorescence images were obtained at the end of the procedure, which took approximately 30 minutes, without a decrease in fluorescence. No worsening of the initial clinical situation occurred, and no complications associated with ICG were observed. The volume of ethanol used per treatment session ranged from 0.8 to 36.2 mL (average 14.3 mL) and that of foam polidocanol from 4.0 to 19.8 mL (average 8.5 mL). A local complication occurred as a result of the procedure in one of the 15 procedures. Intraoral ulceration occurred in a 17-year-old man (patient 2) with an extensive venous malformation of the face who had undergone ethanol sclerotherapy of the lip but eventually healed. No other

complications, such as cutaneous necrosis, damage to local nerve, and symptomatic embolism of the sclerosant into the circulation, were observed during follow-up.

Discussion

Percutaneous sclerotherapy has been established as a minimally invasive treatment option for slow-flow vascular malformations.[2] The combination of sonographic and fluoroscopic guidance increases the safety of the procedure by allowing direct imaging of venous drainage.[3] Duplex sonography has been described as a real-time guidance technique providing visualization of the extent of the malformation and assessment of blood flow velocity.[4] MR-guided sclerotherapy allows direct visualization of needle placement and sclerosant distribution.[5] The value of navigation guidance for percutaneous sclerotherapy is based on the additional information derived from visualization of the target lesion. Several recent investigational studies have used NIR fluorescence imaging system after administration of ICG for intraoperative identification of lymph nodes and patency of lymph and blood vessels, as well as noninvasive assessment of lymphatic function.[6, 11]

Duplex-guided sclerotherapy has been our standard method for the treatment of venous malformations. In this trial, we used real-time NIR fluorescence imaging as an additional monitor of the spread of sclerosant intraoperatively. Although observation on duplex sonography is limited to the cross-sectional area contacted by the probe, NIR fluorescence imaging can visualize sclerosant spreading horizontally on the skin surface. Nevertheless,

extravasation of the ICG–sclerosant solution may cause visualization of extravascular space. Given that ICG binds to globulin proteins within tissues, it may be taken up by the lymphatics and visualize lymphatic vessels unexpectedly. Visual interpretation of the spotty fluorescence patterns may be controversial if they reflect intravascular spread or extravasation of sclerosant in this series.

Owing to its sensitivity, fluoroscopic imaging with radiopaque contrast medium is the clinical standard for vascular imaging, but NIR fluorescence imaging may provide noninvasive visualization that can be repeatedly excited without radiation exposure. There is also an advantage for NIR fluorescence imaging that is enhanced by the smaller amounts of contrast agent than with MR- or computed tomography–based angiography procedures.[6] Depth of penetration of NIR fluorescence is estimated to be between 2 and 3 cm below the skin surface.[7] In this series, observational depth seemed to be <1 cm below the skin surface with an ICG concentration of 0.01 mg/mL.

For sclerotherapy of venous malformations, especially those in the face and hands, the risk of necrosis should be carefully considered from an esthetic point of view. Linear fluorescence images were obtained more often in these regions (Table 2), because it was assumed that subcutaneous tissue was thin and vascular vessels well-developed. Because of the limits of its tissue-penetrating depth, NIR fluorescence imaging can be suitable for lesions located in the face and hands (Figures 1 and 2). For lesions located in the fingers, the flow of sclerosant to the contralateral side of the treated finger could lead to total necrosis of the finger.

In duplex-guided sclerotherapy, it is difficult to monitor the spread of sclerosant in the whole finger. NIR fluorescence imaging made it possible to detect flow to the contralateral side of the treated finger.

ICG is a tricarbocynanine dye that has been used clinically for longer than 50 years for hepatic clearance, cardiovascular function testing, and retinal angiography on the basis of its dark green color. ICG associates with albumin, making it an excellent vascular agent for evaluating the blood and lymphatic systems.[6] Most studies have used NIR fluorescence imaging system after administration of mg amounts of ICG.[6, 11] Our ICG concentration of 0.01mg/mL was enough to get visualization of sclerosant spreading. The incidence of adverse mg amounts of ICG injection was reported 0.4%, and 0.05% for severe adverse reactions such as hypotension, arrhythmia, and anaphylactic shock.[12] No suspended matter was found in the mixture of ICG with absolute ethanol or 3% polidocanol, and the mixed solution was stable.

NIR fluorescence images with ICG were obtained in 13 of 15 procedures (87%) without any complications associated with ICG. This technique of NIR fluorescence imaging is safe and noninvasive. The device is portable and easy to use, and real-time fluorescence images can be obtained. The combination of duplex sonography and NIR fluorescence imaging may provide safer, more-efficient sclerotherapy. Although further study is necessary to validate the results of this trial, this method can be used as a useful additional monitor for sclerotherapy of venous malformations, especially those located in the face and hands.

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Tables and Figures

Table 1. Patient characteristics, treatments and outcomes

Patient			*Venous Malformation*			*Sclerosant*	*Pattern of Fluorescence Images*
No	*Age*	*Sex*	*Location*	*Distribution*	*Treated region*		
1	7	M	SC	Upper Extremity	Hand	POL	Linear
2	17	M	SC	Face	Lip	ET	Spotty
3	11	M	IM	Lower Extremity	Thigh	ET	None obtained
4	7	F	SC	Lower Extremity	Thigh	ET	Spotty
5	15	F	SC	Lower Extremity	Thigh, Buttock	ET	Linear
6	11	F	SC	Lower Extremity	Buttock	ET, POL	Spotty
7	17	F	IM	Lower Extremity	Leg	ET	None obtained
8	6	F	SC	Upper Extremity	Fingers	POL	Linear
9	11	F	SC	Face	Cheek	ET	Linear
10	17	F	SC	Upper Extremity	Thumb	ET	Linear
11	9	M	SC	Lower Extremity	Leg	POL	Spotty
12	3	M	SC	Lower Extremity	Foot	ET, POL	Spotty
13	64	F	SC	Face	Lower Eyelid	POL	Linear
14	6	F	SC	Upper Extremity	Finger	POL	Linear
15	22	F	SC	Face	Lip	ET, POL	Linear

M, male; F, female; SC, subcutaneous; IM, intramuscular; POL, polidocanol; ET, ethanol

Table 2. Evaluation of pattern of fluorescence images in 15 patients

Distribution of Venous Malformations	*Pattern, n*		
	Linear Images	*Spotty Images*	*None obtained*
Upper Extremity	4		
Lower Extremity	1	4	2
Face	3	1	

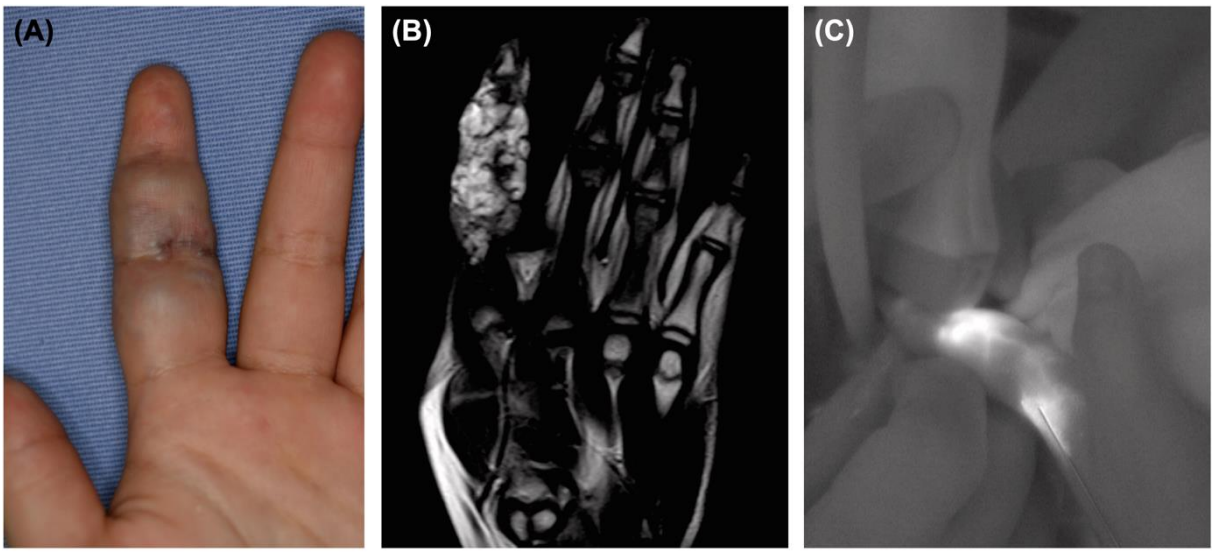

Figure 1. Case 14. Patient with venous malformation in the left index finger. (A) Preoperative view of the left hand. (B) Coronal fat-suppressed T2-weighted magnetic resonance image obtained before sclerotherapy shows a homogenous hyperintense mass in the left index finger. (C) Fluorescence image obtained during sclerotherapy shows unilateral contrast of the treated region of the index finger. Sclerotherapy was stopped when fluorescence images were obtained at the contralateral side of the index finger.

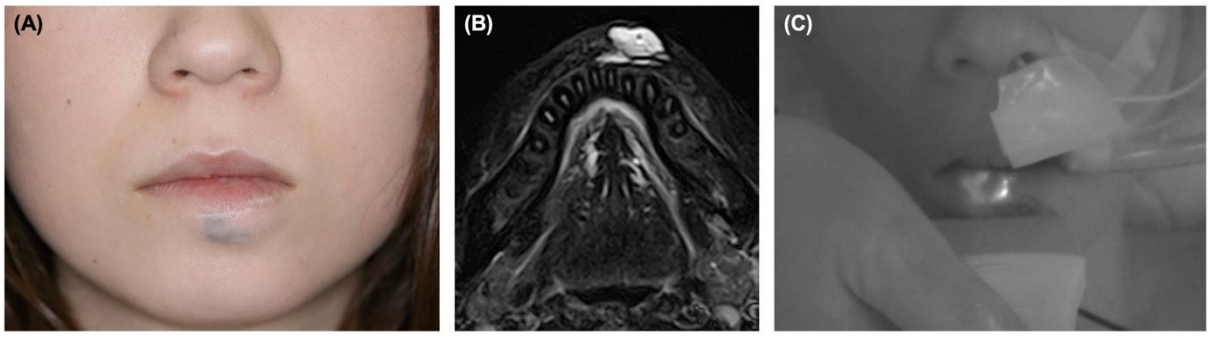

Figure 2. Case 15. Patient with venous malformation in the lower lip. (A) Preoperative view of the face. (B) Axial fat- suppressed T2-weighted magnetic resonance image obtained before sclerotherapy shows a homogenous hyperintense mass in the lower lip. (C) Fluorescence image obtained during sclerotherapy shows the spread of sclerosant in the lower lip.