Evaluation of custom-made indocyanine green lymphography system for preoperative planning of lymphovenous anastomosis in secondary lymphedema patients

Original Article

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ABSTRACT

Background: Lymphedema is a chronic and progressive disease that can result from the loss of lymphatic pathways or congenital lymphatic malformations. When treating lymphedema, complete decongestive therapy is the initial line of treatment. Lymphatic surgery steps in when conservative treatment fails. Indocyanine green (ICG) lymphography is a precise, and sensitive technique that is frequently utilized in lymphatic imaging for lymphovenous anastomosis (LVA) preoperative planning. Many fluorescence imaging systems for lymphatic vessel mapping have been developed in past decades.

Objective: This study will evaluate the feasibility of a custom-made ICG fluorescence lymphography system for preoperative identification of the lymphatic vessels in cases of secondary lymphedema.

Patients and Methods: A small-scale clinical trial to assess the feasibility of a custom-made ICG lymphography system for preoperative mapping of lymphatic vessels on 10 patients who underwent lymphoveonus anastomosis at Ain Shams University hospitals between May 2022 and May 2023.

Results: Ten Patients with secondary lymphedema underwent preoperative mapping of lymphatic vessels using custom-made ICG lymphography system, then LVA were done for all cases. Four to seven linear lymph vessels were visualized in each case with mean 5.11±1.27 SD. Two lymphovenous anastomoses were done in 6 cases, three LVA were done in 3 cases while 1 LVA was done one patient. The patients were followed-up for 6 months after the operation, Seven cases were improved, however, 3 cases showed no improvement. Improvement was measured by gradual decrease in limb circumference in comparison to measurements before the operation.

Conclusion: This study showed that the custom-made lymphography system, with affordable price is feasible for visualizing the lymphatic vessels before LVA. LVA has been proved to be a good method of treatment of chronic leg ulcers.

Key Words: Indocyanine green lymphography, lymphedema, lymphovenous anastomosis.

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INTRODUCTION

Lymphedema is a chronic illness with a progressive course, which arises when the body's lymphatic drainage system fails to adequately drain the afflicted area. It could be related to inflammation or oncological cancer treatment, or it could be congenital due to a lymphatic system defect[1]. For the progression of lymphedema, numerous grading systems, such as Cheng grading and Campisi stagging, have been established. In 2016, the International Society of Lymphology (ISL) developed a staging method to determine the degree of this disease based on information regarding the state of the skin and tissues at each stage and the degree of edema. Stage 0 refers to a subclinical or latent condition in which lymph transport deficiencies are present but swelling is not visible. The first stage of edema improves with limb elevation. Stage 2 is defined as pitting edema that is not alleviated by elevation. Stage 3 is characterised by non-pitting edema and fibroadipose deposition.

Complete decongestive therapy (or CDT) is the first line of treatment for lymphedema; it involves skin care, exercise, compression, and manual lymph drainage. Surgical intervention is required for those who do not respond to these therapies[2].

Lymphovenous anastomosis (LVA) links lymphatic collecting vessels (LCVs) with vein to improve lymphedema. Vascularized lymph node transfer (VLNT) aids in the restoration of the drainage function by introducing lymph nodes into the afflicted limb[3].

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Prior to surgery, mapping the lymphatic system facilitates a smaller incision and reduces the amount of time needed for lymphatic vessel dissection. In the past, lymphoscintigraphy was the gold standard for assessing lymphatic systems. However, because of the risks associated with radiation, other modalities, such as magnetic resonance lymphangiography (MRL), indocyanine green (ICG) lymphangiography, ultra-high frequency ultrasound, and single photon emission computed tomography (SPECT), improve preoperative planning[4].

ICG is a water-soluble tricarbocyanine dye. Tricarbocyanine dye, or ICG, dissolves in water. It was previously utilized for cardiac output diagnostics in medicine, liver function, detecting sentinel lymph nodes in breast cancer patients. Recently, ICG lymphograhpy is considered as functional and ideal preoperative planning for LVA[5].

When ICG is injected into superficial tissues, it binds to plasma proteins in lymph. ICG fluoresces with near-infrared (NIR) light when the dye is exposed to specific wavelengths of light. Skin is relatively transparent to ICG fluorescence, enabling the visualization of the lymphatic vessels[6].

During the past decade, only a few fluorescence imaging systems have been introduced and evaluated, including the Fluorescence-Assisted Resection and Exploration (FLARE) system (Center for Molecular Imaging, Boston, MA)[7], the Photodynamic Eye (PDE) (Hamamatsu, Japan, and Pulsion, Munich, Germany)[8], the SPY System (Novadaq, Toronto, Canada)[9], and the IC-View System (Pulsion, Munich, Germany)[10].

Yamamoto showed that findings on ICG lymphography changed from a linear to a splash pattern and then to a diffuse pattern as the severity of lymphedema aggravated[11].

In this study we will evaluate the efficiency of a custom-made ICG lymphography system in visualizing the lymphatic vessels in patients with secondary lymphedema before doing lymphovenous anastomosis.

PATIENTS AND METHODS:

The study included 10 patients with International Society of Lymphology (ISL) grade I and II secondary lymphedema, between May 2022 and May 2023 at Ain Shams University hospitals. A custom-made ICG lymphography system for preoperative mapping of lymphatic vessels before LVA was evaluated after obtaining the approval of the Ethical Committee and informed consent from all participants. All the patient data are confidential.

The study included all patients with secondary lymphedema between 18 and 65 years from both sex, of grade I and II lymphedema according to ISL, either upper or lower limb lymphedema. However, patients with primary lymphedema, below 18 years and above 65 years, grade 0 or grade 3 lymphedema according to ISL were excluded from the study.

Preoperative clinical photos are taken for the limb with lymphedema and the normal limb. Two cases out of the ten included in the study had associated chronic lower limb ulcers. Limb Circumference is measured using a tape measure and compared with normal limb at different locations throughout the limb starting by a point at 10 cm from the first web space distally then at every 5 cm proximally through the limb. Postoperatively, these measurements were done in the same points.

Mapping of lymphatic vessels using custom-made ICG lymphography system

A 0.2 ml of ICG is injected intradermally just proximal to the 1st and 4th web spaces in cases of lower limb lymphedema and near medial and latera malleolus of the foot. In cases of upper limb lymphedema 0.2 ml of ICG is injected intradermally proximal to 2nd and 4th web spaces, over anterior border of the styloid process of radius, and at the anterior border of the styloid process of ulna. The limb was then massaged manually to facilitate dye uptake into the lymphatics.

Fluorescent Imaging of superficial lymphatic flow is obtained within few minutes after the injection. The skin surface is illuminated with Near Infrared (NIR) light source which is directed from STORZ 20133720 D-Light *P* Fluorescence Imaging system as shown in (Fig. 1).

Fig. 1: STORZ 20133720 D-Light *P* Fluorescence Imaging system.

Light emitted by ICG, absorbed in lymph vessels, is imaged using a custom-made grey scale M2S Series USB2.0 5 megapixel Area Scan Camera (M2S500M-H) and C-mount 12mmF1-4 (C-Mount Lens 12 mm and focal length 1.4 mm) connected by USB to a laptop used for monitoring video and images and recording them in digital format. ICG maximum Emission filter is between 810 nm and 855 nm and software will be supplied for capturing stills and video and analyzing images as shown in (Fig. 2).

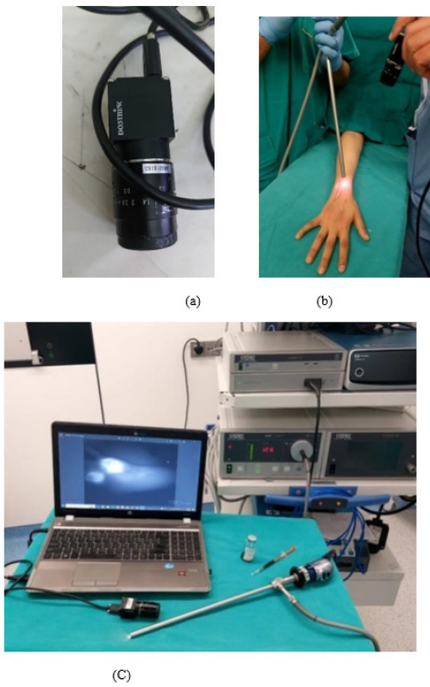


Fig. 2: (a) Custom-made ICG lymphography camera : M2S Series USB2.0 5 megapixel Area Scan Camera (M2S500M-H) and C-mount 12mmF1-4 (C-Mount Lens 12 mm and focal length 1.4 mm) (b) Mapping of upper limb lymphatic vessels in a patient with breast cancer-related lymphedema (BCRL) (c) Custom-made ICG lymphography camera connected to laptop by USB and STORZ 20133720 D-Light P Fluorescence Imaging system NIR source of light.

Identification of lymphatic vessels with linear pattern using the custom-made camera and marking their sites on the skin was done, then marking the sites of incision over the clearest linear lymph channels pattern as shown in (Fig. 3). Super microsurgery was done under local anesthesia using microscope with (26x times) magnification power. The marked linear superficial lymph vessels and a nearby superficial venules were dissected and explored. Finally lymphovenous anastomosis was done at two or three levels using 11-0 Nylon.

Fig. 3: Two linear patter lymph vessels were seen over dorsum of left foot after injection of ICG fluorescence dye using the custom made lymphography system.

RESULTS:

Ten cases suffering from secondary lymphedema underwent preoperative mapping of lymphatic vessels using custom-made ICG lymphography system at Ain Shams University Hospital, then LVA were done for all cases. Six cases were females, while four were males. The mean age of the patients was 44±8.82. 30% of the cases were 40 years old or below, while seventy percent of the cases were above 40 as shown in (Table 1).

Three patients who suffered from secondary lymphedema were breast cancer-related lymphedema due to axillary lymph node clearance after breast tumor excicison, four cases were post traumatic, while three cases were secondary to cellulitis. Ninety percent of the cases had grade II lymphedema according to the International Society of Lymphedema (ISL) while ten percent had grade I lymphedema. (70%) of the cases had lower limb lymphedema while (30%) had upper limb lymphedema. Six cases had lymphedema on the right side while 4 patients had lymphedema on the left side. The circumferential difference between lymphatic limb and normal limb was between 20 to less than 40% in 6 cases, however, the circumferential difference was less than 20% in 4 cases. Two out of 10 cases had associated chronic non healing ulcers, while the rest of cases had no ulcers.

Using the custom made ICG lymphography system, four to seven linear lymph vessels were visualized in each case with mean 5.11±1.27 SD. Two lymphovenous anastomoses were done in 6 cases, three LVA were done in 3 cases while 1 LVA was done one patient as shown in (Table 2).

Table 1: Demographic data of the studied patients

	Number=10 [*n* (%)]
Age	
Mean±SD	44.20±8.82
Range	35–60
Age≤40	3 (30.0)
Age>40	7 (70.0)
Sex	
Female	6 (60.0)
Male	4 (40.0)

Table 2: No. of liner lymph vessel and no. of Lymphovenous anastomosis of the studied patients

	No.=10
No of Linear lymph vessel	
Mean±SD	5.11±1.27
Range	4–7
No of LVA	
1 LV	1 (10.0)
2 LV	6 (60.0)
3 LV	3 (30.0)

Most of the cases (90%) did end to end LVA, however one case that did end to end LVA and one end to side LVA. The mean time of operation was 2.69±0.48 hours. The diameter of lymphatic and venous vessels used for LVA ranged from 0.2 to 0.7 ml with mean 0.39 ml ± 0.15. Venous backflow after LVA occurred in 60% of the cases. 90% of the patients were compliant on Lymphatic massage after the operation.

The patients were followed-up for 6 months after the operation, Seven cases were improved, however, 3 cases showed no improvement. Improvement was measured by gradual decrease in limb circumference in comparison to measurements before the operation, up to 6 months after the operation.

The two patients with the associated chronic lower limb ulcers after doing LVA, the ulcer contracted gradually till healing was completed within 2 months.

The study showed a statistically significant difference in the relationship between the age of the patient and the improvement after LVA, as patients with secondary lymphedema with mean of age 40±3.5 SD were most likely to be improved unlike patients with mean of age 53.7±10 SD showed no improvement. On the other hand, there is no statistically significant relationship difference between either the sex, the cause, limb, ISL grade, number of anastomoses, the pattern of anastomoses done, diameter of anastomosed vessels and intraoperative venous backflow and postoperative improvement.

Case presentation

Thirty eight years old male patient, medically free, nonsmoker with secondary lymphedema over right lower limb post traumatic open Pott's fracture since 2 years. The patient suffered from resistant ulcer over medial and lateral and posterior aspect of same leg for 18 months as shown in (Figs 4 and 5).

Pre-operative mapping of Lymph vessels using ICG lymphography system was done showing linear lymphatic vessels as shown in (Fig. 6).

Exploration over superficial lymph vessels and venules was done and two lymph venous anastomoses were done as shown in (Fig. 7).

Following up the patients showed gradual decrease in ulcer size till it completely healed after 4 months as shown in (Figs. 8–10).

In addition, Limb circumference showed marked decrease gradually in 4 months as shown in (Fig. 11).

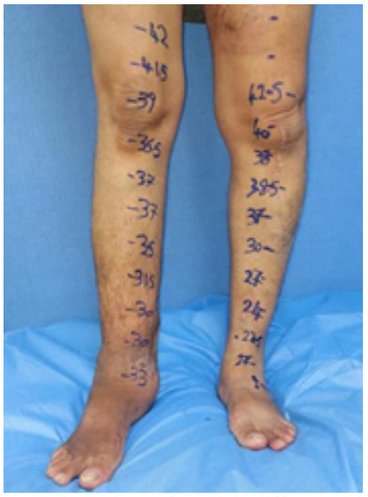
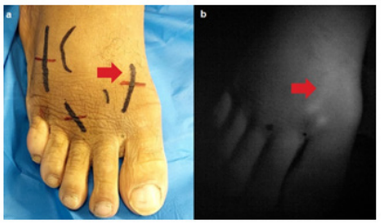


Fig. 4: Preoperative circumferential difference between the normal and lymphedematus limb.

Fig. 5: Resistant ulcer over medial and lateral and posterior aspect of same leg for 18 months.



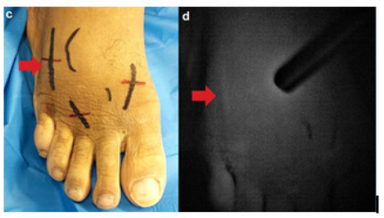


Fig. 6: (a,b) linear lymph vessel seen at level of first metatarsal by ICG lymphography system and marked on skin (c,d) linear lymph vessel seen at lateral aspect of foot and marked on skin.

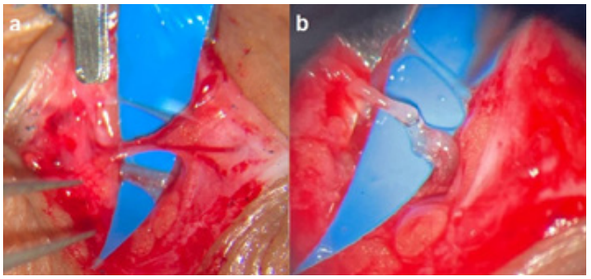


Fig. 7: (a) exploration over superficial lymph vessel and superficial venules of same size (b) lymphovenous anastomosis between proximal end of lymph vessel and distal end of venule.

Fig. 8: (a-d) photos of posterior aspect of left leg showing chronic ulcer healing. (preoperatively and 1, 2, and 4 months, respectively).

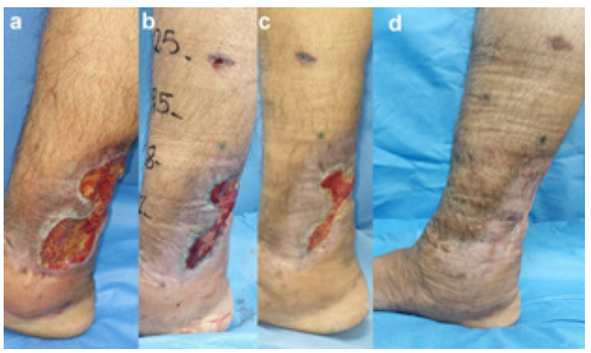


Fig. 9: (a-d) photos of medial aspect of left leg showing chronic ulcer healing. (preoperatively and 1, 2, and 4 months after the operation, respectively.

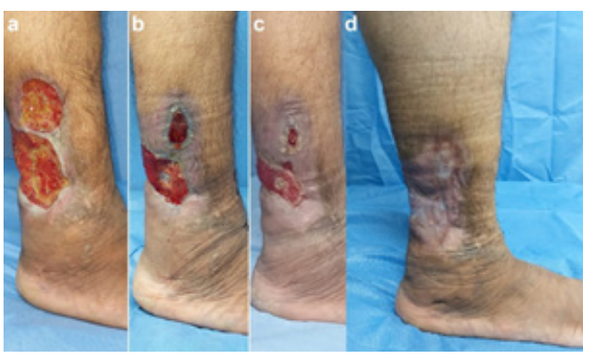


Fig. 10: (a-d) photos of lateral aspect of left leg showing chronic ulcer healing. (preoperatively and 1, 2, and 4 months after the operation, respectively.

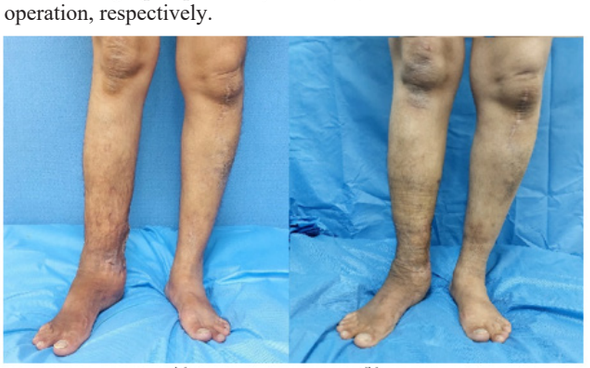


Fig. 11: Preoperative photo and six months postoperation photo showing decrease in limb circumference of left leg.

DISCUSSION

Lymphedema is a common problem that causes pain, disfigurement, recurrent infections, physical disability, and affects quality of life. Secondary lymphedema is more common than primary lymphedema. While the most common cause of lymphedema worldwide is filariasis caused by infection by Wuchereria bancrofti, in developed countries, the most secondary lymphedema cases are due to malignancy or related to the treatment of malignancy[12]. Conventionally, lymphedema is treated with conservative methods and/or pressure garment; however, these therapies are not always effective and may need a long period of treatment[13]. In 1970, LVA has been attracting attention as a new treatment method for early grades of lymphedema[14] However, late-stages of lymphedema are not good candidates for LVA as the lymphatic vessels appear as stardust patterns or diffuse patterns[15].

In comparison to other fluorescence imaging systems, the FLARE imaging system (Fluoptics, Grenoble, France) and the Spy-System (Novadaq, Toronto, Canada) are fixed to portable-carts. However, Fluobeam 800, Photodynamic Eye (PDE) (Hamamatsu, Japan, and Pulsion, Munich, Germany) and IC-View system (Pulsion, Munich, Germany) have hand held probes. On the other hand, the custom-made lymphography system has a hand held camera in addition to NIR light source directed from STORZ 20133720 D-Light P on a portable cart.

As regards to the Lighting of the room, the room and OR light had to be switched off during ICG navigation using the custom-made lymphography system as well as the Fluobeam 800 and the SPY System due to interference with NIR light[16]. In contrast, The FLARE system and the PDE photo-Dynamic-Eye can be applied under room light conditions, but xenon and halogen bulbs had to be switched off[17].

The custom-made lymphography system has a range of 25 to 35 cm working distance which is similar to SPY lymphography camera. In contrast, the Fluobeam 800 has 20 cm working distance, and PDE has a range of 15 to 25 cm working distance. However, the FLARE system has 45 working distance.

The mean number of lymphovenous anastomoses done in the study was 2.2 which is close to the study done using NIF florescence by Shan *et al*. in which the majority of patients with secondary lymphedema post mastectomy and axillary clearance underwent a LVA with a mean number of 2.7. In addition, Onoda *et al*. in 2022 that also proved that increasing number of lymphovenous anastomoses between the lymphatic ducts and veins did not seem to improve the outcomes of surgery for lymphedema in the upper and lower

extremities. On the other hand Chen in 2018 did 42 lymphovenous anastomoses in 5 patients with mean number of lymphovenous anastomoses 8.4[18–20].

Many anastomotic techniques such as; end-to-end, end-to-side and side-to-end was reported[21]. Chen and colleagues introduced the 'octopus' technique in which lymphovenous anastomoses were between several lymphatic vessels and a single venule, and as a result, maximizing the number of anastomoses[22]. The study showed a statistically significant difference in the relationship between the age of the patient and the improvement after lymphovenous anastomosis, as patients with secondary lymphedema with mean of age 40±3.5 SD were most likely to be improved unlike patients with mean of age 53.7±10 SD showed no improvement. On the other hand, in primary lymphedema cases, Mihara *et al*. in 2014 proved that lymphedema significantly decreased after doing LVA in patients with an onset age older than 11 years, unlike the patients develop lymphedema before 11 years of age[23]. Our study revealed no statistically significant relationship difference between the venous back flow and postoperative improvement and decrease in limb circumference after the operation. In contrast, Yamamoto and Koshima in 2014 clarified that venous back flow is considered a negative factor for the success of the LVA and may be associated with anastomosis site thrombosis, and it is important to use a vein with an intact valve as a recipient vein to prevent venous back flow[24]. Moreover, Akita *et al*. in 2020 proposed a strategy to prevent venous reflux before LVA. Dilated perforating veins were ligated, external valvuloplasty in the small vein was performed to eliminate venous reflux pre and post LVA and compared the result with a control group undergoing conventional multiple LVAs. A significant reduction in lymphedemtus limb, frequency of cellulitis was noticed when venous reflux was prevented preoperatively[25].

Due to the pathophysiological and immunological effects of lymphedema, resistant ulcers and delayed wound healing are occasionally linked to lymphedema. Localized peripheral edema that compresses the lymphatic and microvasculature and hinders tissue remodeling is the pathophysiological hallmark of lymphedema. An imbalance in the immune cells' differentiation that are involved is another theory. Deep suppression of T helper (Th)1 cells is believed to raise the risk of infection, and excessive Th2 cell differentiation, including polarization of M2 macrophages, may encourage fibrosis, which throws off the meticulously planned wound healing process[26]. Patients who experienced many episodes of recurrent cellulitis with lymphorrhea and developed severe ulcers that did not respond to skin grafts, flaps, or conservative therapy were treated with lymphaticovenular anastomoses[26].

In our study, two cases had associated chronic lower limb ulcers, they previously underwent coverage by split thickness skin grafts and the grafts were lost. The two patients underwent mapping of lymphatic vessels, LVA was done, the ulcer contracted gradually and healing was completed after 2 months, which is similar to the case report published by Emanuele *et al*. in 2021 in which the LVA allowed resolution of lymphatic leakage and complete wound healing of the chronic ulcer with no recurrence[27].

Although LVA is believed to be not suitable for treating moderate-to-severe grades of lymphedema, Chia-Shen *et al*. in 2020 did a retrospective study included the patients with unilateral lymphedematous lower limbs who underwent LVA. Patients were divided into two groups; Group I with mild lymphedema and Group II with moderate-to-severe lymphedema. And revealed that there were no differences in the percentages of post-LVA volume reduction[28].

Some limitations with our study would be the small sample size and therefore inability to compare the results of LVA with more advanced studies. In addition, differences in patient selection, body mass index, different causes of secondary lymphedema and the compliance of patients to physiotherapy and compression garment, made the results not been consistently reproducible.

CONCLUSION

ICG lymphography is a safe and convenient method for preoperative mapping of secondary lymphedema patients. This study showed that the custom made lymphography system is a feasible for visualizing the lymphatic vessels before LVA. The ICG has been excited and detected as it travelled within the lymphatic system. Two to three competent LVA are sufficient for having a good postoperative reduction in limb circumference measurement. In addition, LVA is a promising procedure to treat chronic leg ulcers and therefore improves the quality of life.

CONFLICT OF INTEREST

There are no conflicts of interest.

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