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J R O JOURNAL OF RADIOLOGY AND ONCOLOGY
ISSN 2573-7724

Research Article

Reduced Pain Scores during Indocyanine Green Lymphography by using a Different Preparation Formula

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Submitted: March 25, 2025
Approved: March 31, 2025
Published: April 01, 2025

How to cite this article: Wen J, Zhou Z, Marei AE, Yu L, Meng F, Duan L, et al. Reduced Pain Scores during Indocyanine Green Lymphography by using a Different Preparation Formula. J Radiol Oncol. 2025; 9(1): 041-045. Available from: https://dx.doi.org/10.29328/journal.jro.1001078

Keywords: Indocyanine green lymphography (ICG); VAS pain scores; Lymphedema

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Summary

Purpose: The purpose of this study was to investigate whether a different indocyanine green lymphography formula can reduce the severe pain encountered during this investigation.

Methods: Indocyanine green ICG lymphography frequently induces severe and intolerable pain in patients. It is very important to develop a relatively painless lymphography method. This helps reduce patients' apprehension during examination. Our center conducted randomized control groups of 60 patients with limb lymphedema. Cases were divided into experimental and control groups. Patients in the experimental group were injected with indocyanine green solution containing 5% glucose, while patients in the control group were injected with indocyanine green solution with sterile water.

VAS scores were recorded pre-injection, during, and at 10, 20, and 30 minutes post-injection. We recorded possible side effects, e.g. skin redness, itching, subcutaneous bleeding, bruising, severe allergic reactions, and other complications within 24 and 48 hours after imaging, and analyzed the pain score data.

Results: The average pain score of the experimental group was 0-3 points, while the control group was 6-8 points. Disease staging was accurately assessed based on imaging results . No other serious complications occurred.

Conclusion: Pain can be significantly reduced by the new modality. This method does not affect lymphography results and imaging quality, and there are no obvious serious complications.

Introduction

Indocyanine green lymphography is an important investigation used for mapping lymphatics [1], is often required for staging or preoperative evaluation of patients with limb lymphedema [2]. Lymphedema is caused by lymphatic vessel dysfunction, and common causes include malignant tumors, bacterial infections, and chronic venous insufficiency [3]. Clinical examination and lymphography can be used to assess disease severity and determine the most appropriate treatment [4-6]. During Indocyanine Green lymphography (ICG), it was found that the original formula often caused severe pain that was unbearable for the majority of patients. This adverse effect often deters patients from undergoing this crucial diagnostic test . Hence, developing a less painful ICG lymphography method is essential for ICG lymphography.

Patients

This study includes 60 patients who received ICG lymphography between April 2023 and November 2023. This study was written in strict accordance with the CONSORT checklist. Patients were selected randomly. Simple randomization was applied using admission serial

numbers . For the patients who met the inclusion criteria, Patients with odd-numbered admissions were assigned to the experimental group, and those with even admission serial numbers were assigned to the control group. A single-blind protocol was employed . The patients did not know which method they were receiving, while the physicians and the assessment recorders were aware of it. The method of allocation concealment was that the data analyst did not know the specific grouping information of the patients. We clearly demonstrated the situation of the study subjects at each stage from recruitment to the final analysis through the CONSORT flowchart, ensuring the integrity and transparency of the research report.

This study was approved by the Ethics Committee of Peking University Shenzhen Hospital. A written informed consent was obtained from all patients prior to the test.

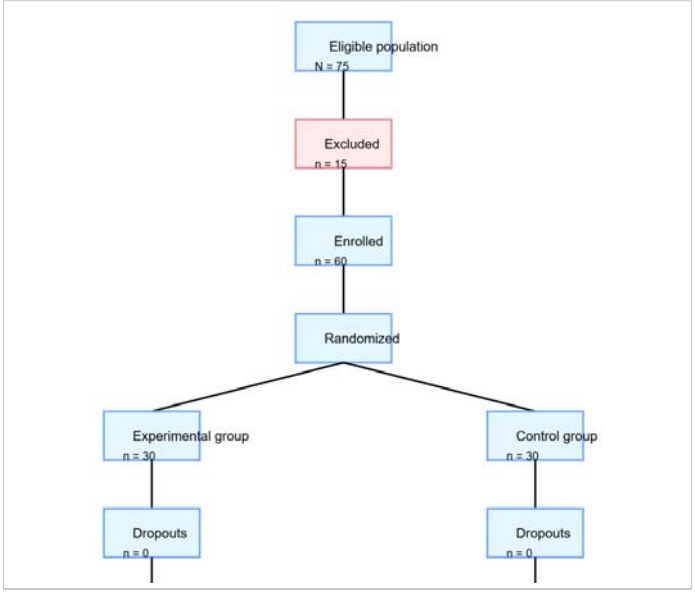
Inclusion criteria

Patients with lymphedema affecting upper or lower extremities were selected for testing. The diagnosis of lymphedema was based on medical history and differences in limb circumference.

Exclusion criteria

Patients with a history of trauma, metastasis, acute limb infection, severe allergies, venous edema, lipedema, deep vein thrombosis, and severe cardiovascular disease were excluded from this study.

Indocyanine green lymph vessel mapping procedure: The formula of the experimental group was 10 ml of 5% glucose solution as solvent [7], coupled with 25 mg of sterile indocyanine green freeze-dried powder preparation (Figure 1). The formula of the control group was 10 ml of sterile water for injection (that comes with the drug as a solvent), and 25 mg of indocyanine green powder preparation (Figure 2).



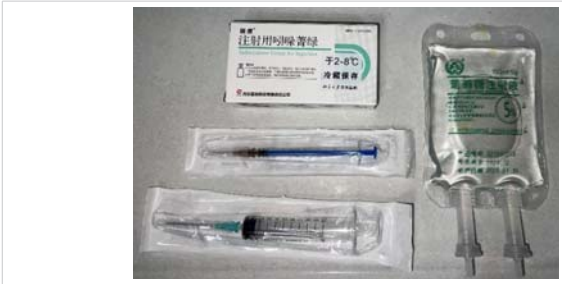


Figure 1: The formula of the experimental group.

Figure 2: The formula of the control group.

The injection method: Seventy five percent alcohol solution was used to sterilize the intended injection site (it was recommended to use alcohol instead of iodophor, as the iodine may affect the judgment of skin allergies). A 10-ml syringe was used to aspirate the solvent for mixing, and a 1-ml syringe was used for intradermal injection. We injected 0.2 ml of ICG solution into each finger web (or toe web) of the affected limb. An ICG camera (a laser lymphatic imaging examiner of Harbin Haihong Jiye Technology Development Co., Ltd., model HH-C-01) was used to perform lymphatic scanning (Figure 3). We used a green marker to map the lymphatic course. We used a blue one to mark areas of contrast leakage and future incisions (Figure 4). The whole procedure took about 30 minutes.

Assessment of pain response: The Visual Analog Scale (VAS) [8] of pain was assessed at different intervals; before injection, during injection, 10 minutes, 20 minutes, and 30 minutes after injection. We observed and recorded other responses including skin rash, itching, and subcutaneous bleeding within 24 hours and 48 hours after injection, ecchymosis, severe allergic reactions such as dyspnea and other complications.

Results

Before injection, the VAS scores of both groups were 0 points. Both groups obtained excellent contrast images of lymphatic system, and we could accurately assess and stage lymphedema based on imaging results. No other serious complications occurred (Tables 1,2).

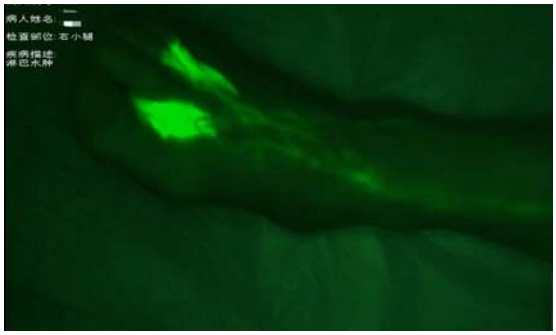


Figure 3: Lymph scanning image.

Figure 4: Edema areas and surgical incision markers. (Green Lines are functional lymphatic vessels, blue markers are areas of edema and future incisions).

Table 1: Baseline characteristics with *p* - values.

Time & Measurement	Group	N	Mean ± Std	t	p
Average VAS during injection	Control	30	6.5 ± 1.306	15.289	0.000
	Experimental	30	2.13 ± 0.86		
Average VAS at 10 minutes after injection	Control	30	3.17 ± 0.834	17.512	0.000
	Experimental	30	0.2 ± 0.407		
Average VAS at 20 minutes after injection	Control	30	0.53 ± 0.776	3.764	0.000
	Experimental	30	0 ± 0		
Average VAS at 30 minutes after injection	Control	30	0.47 ± 0.776	3.294	0.002
	Experimental	30	0 ± 0		

Group Statistics

	group	N	Mean	Std. Deviation	Std. Error Mean
Average VAS before injection	Control	30	.00	.000[a]	.000
	Experimental	30	.00	.000[a]	.000
Average VAS during injection	Control	30	6.50	1.306	.239
	Experimental	30	2.13	.860	.157
Average VAS at 10 minutes after injection	Control	30	3.17	.834	.152
	Experimental	30	.20	.407	.074
Average VAS at 20 minutes after injection	Control	30	.53	.776	.142
	Experimental	30	.00	.000	.000
Average VAS at 30 minutes after injection	Control	30	.47	.776	.142
	Experimental	30	.00	.000	.000

a. t cannot be computed because the standard deviations of both groups are 0.

Table 2: Outcomes with final difference, 95%CI, *p* - values, and effect size.

Statistical analysis

This analysis was performed using SPSS (version X.X) software, and independent samples t-test was used to analyze whether there was a significant difference in VAS scores before and after the experiment in different groups.

The average VAS value before injection, 10 minutes after injection, 20 minutes after injection, 30 minutes after injection, the mean value of VAS in the experimental group was less than that of the control group and the independent samples t-test revealed a statistically significant difference ($p < 0.05$), indicating that there was a significant difference between the Average VAS during injection scores of the experimental and control groups.

There was a significant difference between the Average VAS scores between the experimental and the control groups.

Discussion

Lymphedema is a chronic progressive pathological condition resulting from impaired lymphatic drainage due to injury, infection, congenital or unknown abnormalities of the lymphatic system [9]. Clinical assessment and staging of functional lymphatic vessels has become an important factor in defining surgical indications and postoperative prognosis [10]. In the past decade, ICG lymphography has been widely used and is considered a preliminary examination to confirm diagnosis and determine functional lymphatics, allowing for individualized diagnosis, staging, and treatment planning [11-13]. Many studies have also demonstrated a significant correlation between this test and the clinical outcome of lymphedema [14], and showed that it can be used to determine the most appropriate treatment [15]. There are also several reports on improving ICG lymphangiographic staging, which can introduce a clearer classification system of the condition [16-18]. However, our center currently still uses ICG DB staging [19].

Previous literature has suggested that LVA surgery is effective for stages I-II, and VLNT or VLVT should be considered for stages III and above. However, our treatment center performs LVA treatment for patients with lymphedema of all stages, and the current follow-up results were good. More research is, however, needed to verify the correlation between preoperative angiographic staging, surgical indications and surgical methods.

When doctors at this center completed indocyanine green lymphography in the ward, they found that the original formula often caused severe and unbearable pain. It was very important to develop a relatively painless method of indocyanine green lymphography, which would help reduce patients' apprehension, making them more likely to accept this important examination. Before angiography, all subjects were informed of the benefits and risks associated with this examination. We informed them that lymphedema is a chronic disease, and it was incurable before the development of supermicrosurgery. Although the current surgical treatment of Lymphaticovenous Anastomosis (LVA) has good results and gives us a certain degree of confidence, long-term follow-up is still needed. At the same time, if the diagnosis of lymphedema is confirmed by angiography and the patient

temporarily chooses conservative treatment, we inform the patient that long-term therapy and compliance are required. Modalities include manual massage lymphatic drainage, physical therapy, pressure therapy, standard bandage, elastic sleeves and stockings, and emotional management [20-22].

Searching the relevant literature, the current research on patient experience, pain perception and scoring of ICG lymphography is still in its infancy. Professor Elizabeth Tillotson, N.P.-C. has published an article on improving patients' experience with indocyanine green lymphangiography. It has been mentioned that using 5% glucose solution as a solvent for contrast imaging can significantly reduce the pain of patients and has basically no impact on the results of contrast imaging. However, no controlled groups or standard pain scores have been used in the study methodology. Our center designed a randomized control study, using a formula of 5% glucose solution, and the original formula of sterile water for injection as a control. The experimental results showed that the new formula can significantly reduce pain. The average VAS score of patients was significantly lower than that of the control group. The imaging results did not have a significant impact. Both groups obtained satisfactory lymphography images, and lymphedema could be accurately assessed based on imaging results. However, during the angiography process, it was found that patients' understanding of VAS pain scores varied from person to person. Some patients even had pain scores as high as 10 in the control group. In some cases, the examiner did not perform the test and asked about pain score, some unexpectedly reported a lower pain score, possibly due to apprehension or misinterpretation. Therefore, the accuracy of scoring still requires enrollment of more cases to reduce errors. However, the overall results appear reliable based on statistical outcomes , and the result analysis remains statistically significant. Of course, it is still necessary to continue to expand data, closely monitor the occurrence of complications, and be prepared for severe allergic rescue.

Despite the rigor of this study, several limitations must be acknowledged. Firstly, the relatively small sample size (n = 75) may limit generalizability of the findings. With a larger sample, the findings could potentially be more representative and the statistical power greater, enabling more definitive conclusions. Small sample sizes are more vulnerable to random variation, which may have influenced the observed results. Secondly, as we have mentioned, pain is subjective. Each patient may not have a thorough understanding of the pain score. Different patients have inconsistent pain thresholds and tolerances, and there are numerous factors influencing pain scores. Therefore, more data are needed to support our conclusion.

In conclusion, this study shows that 5% glucose solution can be safely and efficiently used as a solvent for ICG imaging, which can significantly reduce procedural discomfort and patient apprehension during imaging , improve satisfaction, and almost have no effect on imaging results. No serious complications have been found so far, and this formula shows potential for broader clinical adoption .

Ethical statements

This study was approved by the Ethics Committee of Peking University Shenzhen Hospital.

Written informed consent was obtained for each participant according to institutional guidelines.

The study adhered to the principles of the Declaration of Helsinki.

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