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ORIGINAL ARTICLE

# Comparing the direct effect of lymphatic dynamic transport after lower-level laser therapy in healthy volunteers: a randomized controlled trial

Hasuk Bae[1] · Jae Yong Jeon[2] · Su Hong Choi[3] · Min-Hyung Rhee[3] · Ye Ji Kim[3] · In Joo Kong[3] · Ju-Ri Eom[3] · Jin A Yoon[4]

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## Abstract

This study is aimed to explore the direct effects of low-level laser therapy (LLLT) at different wavelengths on lymphatic motility int healthy individuals. The goal was to identify the most effective protocol and assess the potential application of LLLT in managing lymphedema. The study included 32 healthy participants (12 males, and 20 females), divided into two groups. Each participant underwent a single session of unilateral upper extremity manual lymphatic drainage (UE MLD), followed by two types of LLLT applied to the ipsilateral axilla region to promote lymphatic drainage. Indocyanine green (ICG) lymphography was used during each treatment session to evaluate the immediate effect of LLLT on lymphatic motility. Additionally, extracellular fluid (ECF) and local tissue water level were assessed before and after the intervention using multiple frequency bioelectrical impedance analysis (MFBIA) and tissue dielectric constant (TDC). The overall reduction in body water content post-intervention was observed across multiple areas in both groups but without consistent statistical significance between groups. After UE MLD, the number of lymph packets significantly increased in both groups (Group A: from 3.20 ± 0.76 to 6.00 ± 1.38; Group B: from 2.80 ± 0.95 to 5.38 ± 1.44). However, during LLLT, the lymph packet count decreased significantly (Group A: to 1.73 ± 0.51; Group B: to 1.96 ± 0.67). Linear mixed model analysis showed that LLLT was associated with a reduction in lymph packet velocity (Estimate = −1.22, 95% CI: −2.08 to −0.36, $p = 0.006$) and count (Estimate = −1.11, 95% CI: −1.57 to −0.66, $p < 0.001$), while UE MLD significantly increased packet count (Estimate = 2.73, 95% CI: 2.28 to 3.19, $p < 0.001$). No significant intergroup differences were observed in lymphatic motility. This study quantitatively assessed lymphatic motility and tissue water content following different types of LLLT in healthy individuals. The findings suggest the need for further clinical studies to evaluate the effect of various LLLT parameters in lymphedema patients.

**Clinical trial number** Not applicable.

✉ Jin A Yoon
yjk5289@naver.com

1 Department of Rehabilitation Medicine, Ewha Womans University Mokdong Hospital, Ewha Womans University College of Medicine, Seoul, Republic of Korea

2 Department of Rehabilitation Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

3 Department of Rehabilitation Medicine, Biomedical Research Institute, Pusan National University Hospital, Busan, Republic of Korea

4 Department of Rehabilitation Medicine, Biomedical Research Institute, Pusan National University Hospital, Pusan National University School of Medicine, Busan, Republic of Korea

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**Graphical Abstract**

LLLT applied to the ipsilateral axilla region to promote lymphatic drainage on ICG lymphography



**Keywords** Lymphedema · Breast cancer lymphedema · Upper extremity · Low-level light therapy

## Introduction

Breast cancer-related lymphedema occurs because of damage to the axillary lymphatic drainage pathways, which can significantly affect the quality of life owing to limitations in the upper limb function [1–3]. In 2006, the United States Food and Drug Administration accepted low-level laser therapy (LLLT) as a treatment option for breast cancer-related lymphedema. It is effective in reducing the volume of the edema site; relieving pain; and improving shoulder range of motion, grip strength, and quality of life [4, 5]. It delivers low energy to the lymphedema site, inducing biochemical changes at the cellular level [6, 7]. In lymphedema, LLLT reduces tissue fibrosis by triggering metabolic energy, thereby decreasing profibrotic transformation growth factor expression and type I collagen deposition, improving lymphatic drainage by enhancing lymphangiogenesis and lymphatic motoricity, and reducing tissue fluid accumulation owing to changes in blood flow [8–10]. LLLT is also known as photobiomodulation, non-invasive light treatment that does not produce heat. Recent systematic reviews concluded that LLLT there are few treatment-related adverse events [11] and is generally considered safe as it does not lead to the tumor safety issues [12]. Various LLLT devices with different wavelengths and depths of penetration are available in the market, and the effects of LLLT may vary depending on the targeted tissue; therefore, optimal wavelengths may differ for each location [11, 13–15]. Otherwise, the optimal protocol of LLLT for lymphedema patients according to clinical severity and application site is still lacking.

Non-invasive imaging methods for monitoring the real-time dynamic movement of the lymphatic system for diagnosing and evaluating treatment effects on the lymphatic system are lacking. Current clinical studies to determine the effectiveness of LLLT mostly focused on reducing limb volume and improving lymphedema symptoms following LLLT [16–20]. However, there was no clinical trials comparing the direct effects of LLTT on the real-time lymphatic motility of superficial lymphatics based on various LLLT protocols for lymphedema. In addition, confirming the effect of LLLT on improving lymphatic motility based on a previous laboratory hypothesis describing LLLT mechanisms on lymphatic function is important to bridge these results of laboratory findings into clinical application [15]. Therefore, this study aimed to investigate the direct effects of LLLT at different wavelengths on lymphatic motility and local fluid reduction in healthy individuals to further determine the appropriate protocol and effectiveness of LLLT in patients with lymphedema.

## Materials and methods

### Participants

This study was a prospective, single-blinded, parallel, randomized controlled trial conducted in a tertiary hospital. Physical therapy trainees aged 20–30 years were enrolled between August 2023 and January 2024. None of the participants had a history of iodine allergy or asthma. None of the participants were pregnant, or had a history of cancer, heart disease, renal failure, pulmonary hypertension, congenital lymphatic obstruction, or had conditions that may cause upper limb edema. All participants received information about the study and provided written informed consent before inclusion. These individuals were not involved in

any system testing or usability, but were instead subjects in a physiological trial of low-level laser therapy. Therefore, feedback collection and iterative system design were not applicable to the study design. Each group was determined to require 15 participants based on a previous study [21], with an effect size of 80% and a significance level of 5%, using the G power 3.1.9 program. A total of thirty-two participants were recruited in the study. The participants were randomly assigned to either Group A (904 nm LLLT) or Group B (650 nm LLLT) (Fig. 1). Randomization was conducted using Microsoft Excel 2019, employing block randomization with a fixed block size of four to ensure balanced group sizes throughout the enrollment period. A random sequence of group allocations (Group A or Group B) was generated in advance using Excel's RAND function and organized into blocks to maintain a 1:1 allocation ratio within each block. Allocation concealment was achieved using sequentially numbered, opaque, sealed envelopes (SNOSE). Each envelope contained the group assignment corresponding to the randomization schedule and was opened only after the participant completed the baseline assessment, ensuring that the assignment was not known beforehand by either the participant or the researcher conducting the assessment. This was a single-blinded study: while participants were aware of receiving low-level laser therapy (LLLT), they were blinded to the wavelength being used. The assessor responsible for evaluating the outcomes was blinded to group allocation throughout the study. The study was approved by the Institutional Review Board (IRB) of Pusan National University Hospital (IRB No. D-2308-023-130).

## Intervention

Treatment protocol of this study is depicted in Fig. 2. In this study, LLLT was performed after the manual lymphatic drainage (MLD) session to follow the conventional treatment protocol for lymphedema and for the intergroup analysis to compare the additional effect of 2 LLLT types after conventional treatment. Three physical therapists in a tertiary hospital who had received standard treatment

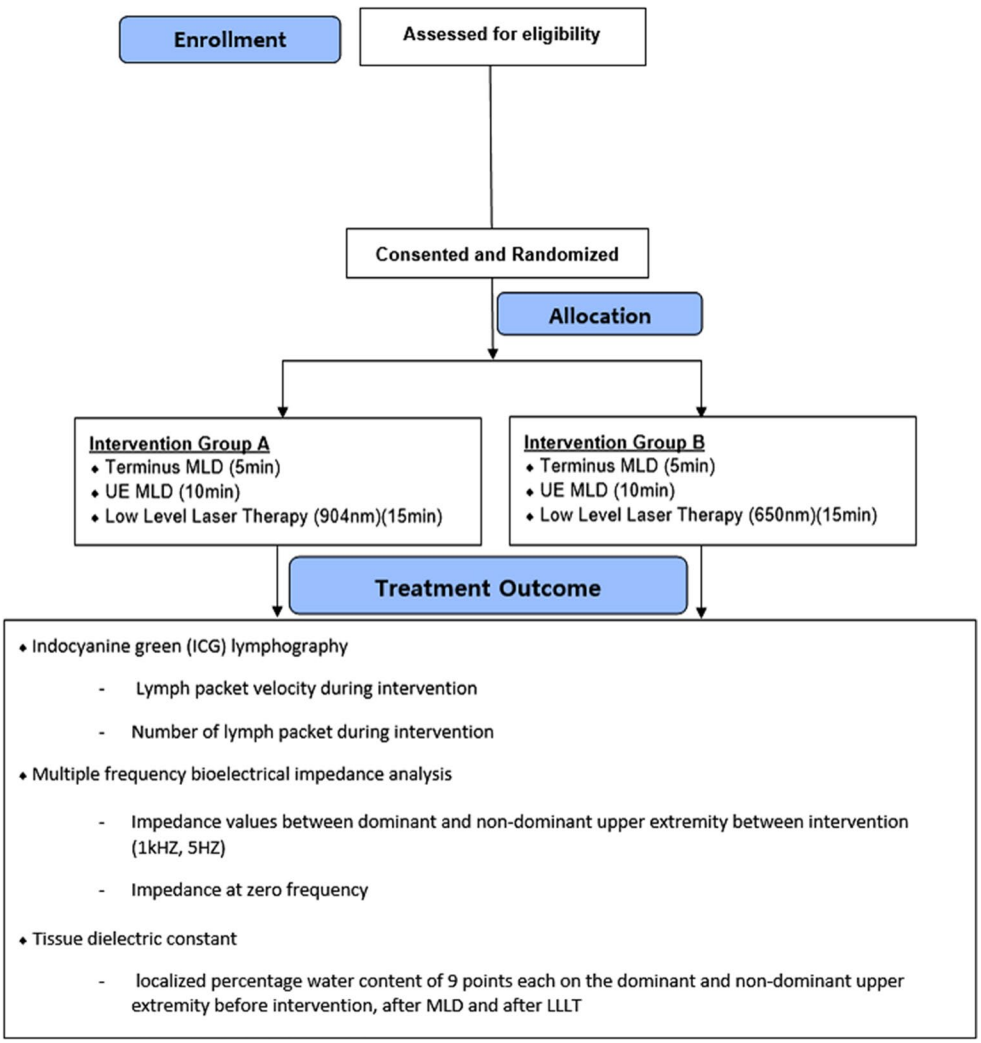



**Fig. 1** Flow diagram outlining participant enrollment, randomization, intervention allocation, and analysis

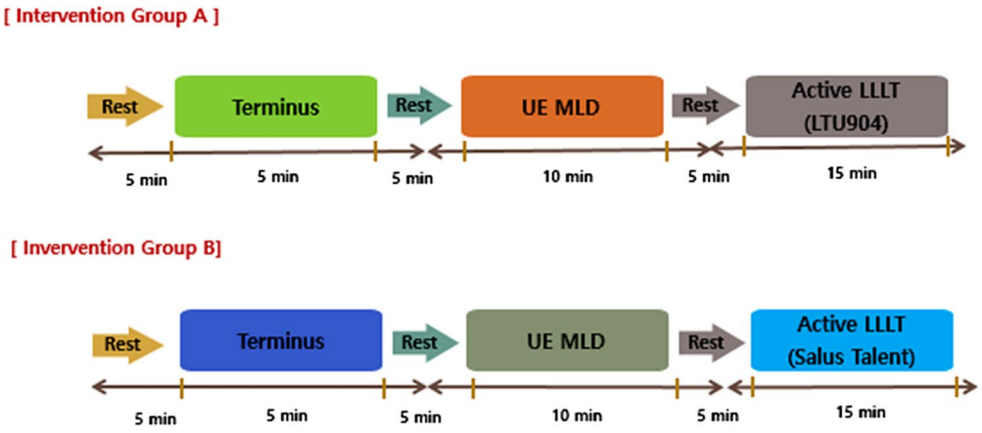



**Fig. 2** Treatment protocol applied to each group, including timing and sequence of manual lymphatic drainage (MLD) and low-level laser therapy (LLLT)

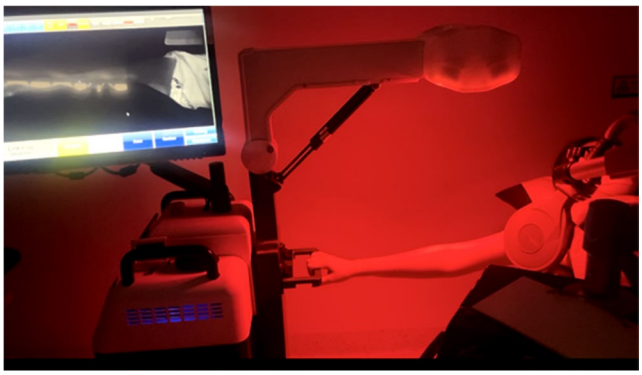


**Fig. 3** Real-time ICG lymphography measurements obtained during low-level laser therapy

education for manual lymphatic drainage (MLD) performed the interventions. In both groups, 5 min of supraclavicular fossa (terminus site) lymphatic drainage followed by 10 min fluoroscopy-guided MLD [22] was performed on the unilateral upper limb. Subsequently, LLLT was applied to the ipsilateral axillary nodes, which involved in key lymph nodes for lymphatic drainage [15, 21]. The participant was placed in a supine position with the dominant hand externally rotated at 90°. The single session was chosen to isolate and observe the immediate effect of LLLT on normal participants, as opposed to cumulative or long-term effects. The laser parameters used for the intervention were fixed values based on the specifications of the LTU-904 device [20]. These parameters were chosen to ensure stability and safety during the therapy. For Group A, LTU-904 (RianCorp, Australia) with a wavelength of 904 nm was used applied to axillary region. 15 points centered at 2 cm intervals in the axilla and treatment time was 1 min for each point. A total dose of 22.5 $Jcm^2$ was administered in the 15-min treatment session. For Group B, Salus Talent (Remed, USA) with a wavelength of 650 nm was applied to the same area, and the same laser output and energy dose were used as in Group A. Five minutes of rest were allocated between each intervention, and intergroup and intragroup analyses were conducted before, after, and between the intervention. After the single session of intervention, indocyanine green (ICG) lymphography was used during each treatment session to evaluate the immediate effect of LLLT on lymphatic motility. (Fig. 3) Extracellular fluid (ECF) and local tissue water level were assessed before and after the intervention using multiple frequency bioelectrical impedance analysis (MFBIA) and tissue dielectric constant (TDC).

## Assessment

### ICG *lymphography* [23–25]

ICG lymphography images were obtained using a near-infrared camera (Lymphoscope, Busan, Korea) to detect 760 nm light-emitting diode and a filter cutting light below 820 nm. In total, 0.2 mL of ICG (Diagnogreen 2.5 mL/mL) was injected subcutaneously into the unilateral upper extremities in the first and third web spaces of the hand. Lidocaine HCL (2%) with epinephrine (1:100,000) was injected before the dye injection to minimize pain. Images were obtained from the time of injection until the intervention period, with participants in a fixed supine position. Images were recorded six times during the intervention period: three resting periods (5 min each), a terminal MLD period (5 min), an upper extremity (UE) MLD period (10 min), and an LLLT period (15 min). Changes in lymphatic function were assessed by calculating the number of lymph packets transported per minute and the lymph packet velocity during the period [26]. The number of lymph packets was determined by measuring the number of packets moving within the lymph vessels at three locations during each intervention period, and the average was calculated. To determine the velocity of the packets, a region of interest (ROI) was placed 10 cm along each vessel, and the time required for continuously moving packets to traverse this distance was measured. The average values measured for the three vessels were calculated.

The number of packets and the velocity measurements were obtained by averaging the values measured by the two examiners (Supplementary Video 1).

### MFBIA

The extracellular fluid volume was measured using MFBIA before and after the intervention using S10 (Inbody, Seoul, Korea). The limb index ratio was derived by comparing the impedance values of the affected and unaffected arms at 1 and 5 kHz (kHZ), generating a proportional value [27]. Additionally, the impedance at zero frequency, which represents the impedance of extracellular water fluid alone, was measured, and R0 ratio (R0 Upper extremity/Lower extremity) was calculated by comparing the impedance values between the upper and lower extremities on the affected side [28].

#### Local tissue water measurement [29, 30]

TDC was measured before and after the intervention to assess the local skin water using a moisture meter-D compact (Delfin Technologies Ltd., Kuopio Finland). A high-frequency electromagnetic wave at 300 MHz signal is generated within a control unit, and the electromagnetic wave is reflected depending on the dielectric constant of the focal tissue, which depends on the amount of free water in the focal tissue relative to the dielectric constant and is calculated for the index of the tissue water. As a reference, pure water has a value of approximately 78.5. The measurement points consisted of 9 points, on the unilateral upper extremity and trunk of the participants, marked with a soft pencil. The device measured TDC using electromagnetic waves and displayed the converted results as the localized percentage water content of the measurement site. The parameters were measured three times per area and the averages were calculated [31].

### Statistical analysis

Continuous variables are presented as means and standard deviations, and categorical variables are presented as frequencies and percentages. Owing to the small sample size of each group, nonparametric tests were conducted. The Wilcoxon rank-sum test was used to compare continuous variables between the two independent groups. The Fisher's exact test was used to analyze categorical variables. The Wilcoxon signed-rank sum test and paired t-test were conducted to compare the differences in the velocity and number of lymph packets, and the F-test was used to examine variance differences. The velocity and number of lymph packets were tracked over time for each participant, and trends were analyzed to identify specific patterns. A linear mixed model was used to evaluate group effects, time effects, and interaction effects to test interaction effects. The mixed model assumed an unstructured covariance structure. Statistical analysis was performed using the language R version 4.3.1 (R Core Team, 2023, http://cran.r-project.org). A $p$-value of $<0.05$ was considered to be statistically significant.

## Result

### Baseline characteristics

A total of 32 participants (16 per group) completed the study. There were no significant differences between Group A (904 nm LLLT) and Group B (650 nm LLLT) in age, gender distribution, BMI, baseline bioimpedance (MFBIA) values, or most tissue dielectric constant (TDC) values (Table 1).

### Changes in tissue water content and bioimpedance

After intervention, both groups showed trends toward reduced extracellular fluid and local water content. Group B showed a significantly greater reduction in ventral forearm moisture (ΔPWC M) compared to Group A (median: −1.83 vs. −0.67; $p=0.027$) (Table 2). No other regions showed statistically significant intergroup differences in TDC or MFBIA changes. Overall, the reduction in body water content post-intervention was observed across multiple areas in both groups but without consistent statistical significance between groups.

### Lymphatic velocity and packet count changes

Intra-group analysis revealed that both groups exhibited an increase in the number of lymph packets after UE MLD, followed by a significant reduction during LLLT. For example, in Group A, the packet count rose from 3.20 after Terminus MLD to 6.00 post-UE MLD, and then declined sharply to 1.73 during LLLT. (Fig. 4) Group B showed a similar trend. Otherwise, intergroup comparisons of velocity and packet count at each time point did not reveal statistically significant differences (Table 3). The greatest observed difference was in lymphatic velocity during Terminus MLD ($\Delta=1.303$, 95% CI: −0.103 to 2.709, $p=0.080$), which did not show statistical significance.

### Linear mixed model analysis

The linear mixed model further explored factors influencing lymph packet velocity indicated that the significantly higher overall lymph packet velocity in the group A compared to

**Table 1** Baseline characteristic of the participants

| Characteristic | Group A ($n=16$) | Group B ($n=16$) | Total ($n=32$) | $P$ value |
|---|---|---|---|---|
| Age (yr), mean (SD) | 23.62 (4.01) | 22.88 (1.59) | 23.25 (3.03) | 0.688 |
| Gender (male: female) | 6:10 | 6:10 | 12:20 | 1.000 |
| BMI, mean (SD) | 22.48 (2.29) | 23.68 (3.37) | 23.08 (2.90) | 0.235 |
| Baseline MFBIA values, median (IQR) | | | | |
| R0 Lo/Up | 0.70 [0.66, 0.82] | 0.71 [0.64, 0.76] | 0.71 [0.65, 0.79] | 0.571 |
| 1 Hz LIR | 1.00 [0.98, 1.01] | 1.01 [0.98, 1.02] | 1.00 [0.98, 1.02] | 0.880 |
| 5 Hz LIR | 1.00 [0.98, 1.01] | 1.01 [0.99, 1.02] | 1.01 [0.99, 1.02] | 0.703 |
| Baseline PWC values, median (IQR) | | | | |
| ventral forearm | 40.83 [36.75, 44.08] | 38.83 [34.92, 43.92] | 39.83 [35.58, 43.92] | 0.336 |
| medial upper arm | 31.50 [29.00, 36.83] | 33.00 [31.42, 35.17] | 32.33 [29.58, 35.83] | 0.473 |
| ventral upper arm | 36.50 [33.92, 40.33] | 33.83 [31.50, 40.08] | 35.83 [32.58, 40.33] | 0.355 |
| shoulder | 43.50 [40.25, 48.00] | 43.17 [38.00, 46.17] | 43.17 [38.75, 47.75] | 0.584 |
| hand | 42.33 [39.58, 44.17] | 37.00 [33.00, 40.67] | 40.33 [36.17, 43.50] | 0.012* |
| dorsal forearm | 43.83 [38.17, 46.75] | 42.67 [40.92, 45.67] | 43.33 [40.08, 45.67] | 0.748 |
| dorsal upper arm | 37.17 [35.17, 39.33] | 37.33 [34.92, 39.75] | 37.17 [34.92, 39.75] | 0.940 |
| trunk | 41.33 [37.58, 46.00] | 42.33 [39.17, 46.50] | 41.67 [38.50, 46.00] | 0.720 |
| breast | 47.83 [45.83, 50.08] | 44.67 [43.00, 46.42] | 46.33 [43.83, 48.83] | 0.017* |

BMI, body mass index; MFBIA, multifrequency bioelectrical impedance analysis; Lo/Up, Lower/Upper extremity; LIR, limb index ratio; PWC, percentage of water content

*$p<0.05$

**Table 2** Changes in MFBIA and TDC values after treatment

| Characteristic | Group A ($n=16$) | Group B ($n=16$) | Total ($n=32$) | $P$ value |
|---|---|---|---|---|
| MFBIA values median (IQR) | | | | |
| Δ R0 Lo/Up | 0.04 [0.03, 0.09] | 0.02 [0.00, 0.06] | 0.03 [0.01, 0.07] | 0.079 |
| Δ 1 Hz LIR | 0.03 [0.00, 0.03] | 0.01 [0.00, 0.03] | 0.02 [0.00, 0.03] | 0.296 |
| Δ 5 Hz LIR | 0.02 [0.00, 0.03] | 0.01 [0.00, 0.02] | 0.02 [0.00, 0.03] | 0.183 |
| Δ PWC values. median (IQR) | | | | |
| ventral forearm (M) | −0.67 [−1.08, 0.25] | −1.83 [−3.00, −0.67] | −1.00 [−2.42, −0.67] | 0.027* |
| (L) | 0.67 [−0.08, 0.75] | 0.17 [−0.08, 1.67] | 0.33 [−0.08, 1.00] | 0.635 |
| medial upper arm (M) | 0.17 [−0.33, 2.08] | −0.17 [−0.75, 0.67] | 0.00 [−0.67, 1.00] | 0.242 |
| (L) | −0.17 [−1.00, 0.33] | 0.00 [−0.42, 0.75] | 0.00 [−0.67, 0.33] | 0.264 |
| ventral upper arm (M) | −0.17 [−0.50, 1.08] | −0.33 [−1.00, 0.33] | −0.17 [−1.00, 0.75] | 0.597 |
| (L) | 0.00 [−0.67, 0.33] | 0.00 [0.00, 0.42] | 0.00 [−0.42, 0.33] | 0.420 |
| Shoulder (M) | 0.67 [−1.00, 2.08] | −0.33 [−1.83, 1.67] | 0.00 [−1.17, 2.00] | 0.282 |
| (L) | −1.67 [−2.33, −0.67 | −0.33 [−2.00, 0.00] | −1.17 [−2.33, 0.00] | 0.085 |
| Hand (M) | 0.33 [−2.17, 3.92] | −1.33 [−3.67, 0.83] | −0.33 [−3.67, 2.00] | 0.185 |
| (L) | −0.50 [−2.25, 1.42] | 0.00 [−0.50, 2.50] | 0.00 [−1.33, 1.83] | 0.185 |
| dorsal forearm (M) | −0.33 [−1.17, 0.83] | 0.50 [−1.08, 1.08] | 0.00 [−1.08, 1.08] | 0.763 |
| (L) | 0.17 [−0.67, 1.42] | 0.00 [−1.00, 0.58] | 0.00 [−0.75, 1.33] | 0.322 |
| dorsal upper arm (M) | 0.00 [−2.83, 3.42] | −0.33 [−4.75, 0.42] | −0.33 [−3.42, 1.25] | 0.258 |
| (L) | 0.00 [−1.83, 1.08] | 0.50 [0.00, 2.75] | 0.33 [−1.17, 1.92] | 0.174 |
| trunk (M) | 4.00 [0.58, 5.92] | 4.67 [2.50, 7.33] | 4.17 [1.00, 6.83] | 0.611 |
| (L) | −3.00 [−4.42, 0.25] | −1.83 [−4.33, 0.00] | −2.33 [−4.33, 0.00] | 0.865 |
| breast (M) | 2.17 [0.67, 4.50] | 1.00 [−0.34, 2.17] | 1.33 [0.58, 3.83] | 0.101 |
| (L) | 0.17 [−1.92, 0.75] | 0.00 [−1.75, 0.50] | 0.00 [−1.75, 0.75] | 0.985 |

MFBIA, multifrequency bioelectrical impedance analysis; Lo/Up, Lower/Upper extremity; LIR, limb index ratio; PWC, percentage of water content

*$p<0.05$

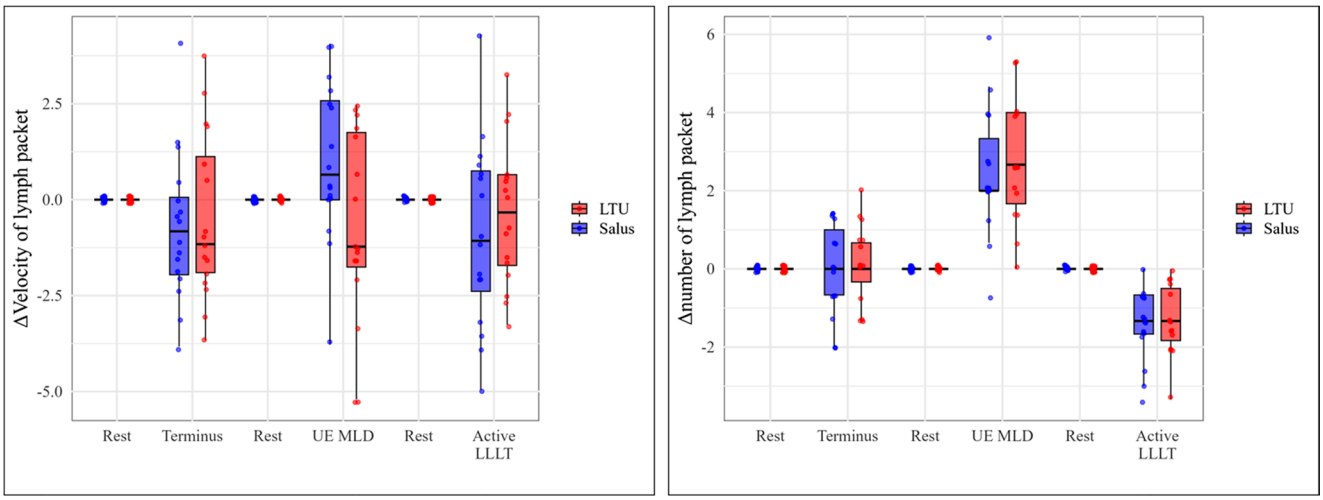



**Fig. 4** Intra group analysis comparison of changes in lymph packet velocity and count across intervention periods

**Table 3** Comparison of velocity and number of lymph packet during each time points between groups

| Group | Velocity of lymph packet | | | Number of lymph packet | | |
|---|---|---|---|---|---|---|
| | Terminus MLD | UE MLD | LLLT | Terminus MLD | UE MLD | LLLT |
| Group A | 9.751 ± 1.992 | 9.455 ± 2.592 | 9.028 ± 1.664 | 3.200 ± 0.764 | 6.000 ± 1.380 | 1.733 ± 0.507 |
| Group B | 8.448 ± 1.9 | 9.024 ± 1.843 | 7.926 ± 2.607 | 2.800 ± 0.950 | 5.377 ± 1.437 | 1.956 ± 0.666 |
| Diff | 1.303 | 0.431 | 1.102 | 0.400 | 0.623 | −0.223 |
| 95% CI | −0.103, 2.709 | −1.200, 2.063 | −0.488, 2.694 | −0.246, 1.046 | −0.431, 1.676 | −0.667, 0.222 |
| *p* value | 0.080 | 0.838 | 0.184 | 0.110 | 0.239 | 0.444 |

MLD, manual lymphatic drainage; LLLT, low level laser therapy

*$p < 0.05$

**Table 4** Linear mixed effect model showing correlation of each treatment with velocity and number of lymph packet during treatment

| | Velocity of lymph packet | | | Number of lymph packet | | |
|---|---|---|---|---|---|---|
| *Predictors* | *Estimates* | *CI* | *p* value | *Estimates* | *std. Beta* | *p* value |
| (Intercept) | 9.142 | 8.204–10.080 | < 0.001 | 2.956 | 2.623–3.288 | < 0.001 |
| Terminus MLD | −0.597 | −1.460–0.267 | 0.174 | 0.044 | −0.410–0.499 | 0.848 |
| UE MLD | −0.457 | −1.320–0.407 | 0.298 | 2.733 | 2.278–3.188 | < 0.001 |
| LLLT | −1.219 | −2.083 – −0.356 | 0.006 | −1.111 | −1.566 – −0.656 | < 0.001 |

MLD, manual lymphatic drainage; LLLT, low level laser therapy

the group B (*Estimate = 1.109*, 95% CI: 0.042 to 2.175, $p = 0.042$); however, this difference was no longer significant in after adjusting for interaction terms. No time × group interactions reached significance, suggesting the effect of LLLT on velocity was consistent across both wavelengths. UE MLD significantly increased the lymph packet count in all with significance. (Estimate = 2.533, 95% CI: 1.894 to 3.171, $p < 0.001$). In addition, active LLLT was associated with a significant decrease in packet count (Estimate = −0.888, 95% CI: −1.527 to −0.250, $p = 0.007$). No significant group or interaction effects were found, indicating that the response in lymph packet number was consistent across both wavelengths. (Table 4)

## Discussion

In this study, extracellular fluid volume measurements using TDC showed significant differences following MLD and LLLT, whereas no differences were observed between different types of LLLT. In addition, confirming the effect on direct lymphatic movement in normal subjects, in the case of UE MLD, an increase in the number of direct lymph packets, that is, an increase in the amount of lymph discharged, was confirmed. In contrast, in the case of LLLT, there was no significant change in velocity and moreover, decrease in number of lymph packet were observed in both groups.

LLLT is proved as an effective treatment modality for various symptoms especially reducing edema of upper limb lymphedema [11]. Although there was various clinical trials to improve these effectiveness, extensive heterogeneity in laser therapy regimens among studies was resulted inconsistent conclusion [32]. Furthermore, confirming the long-term effects of LLLT without continuous treatment is still inconclusive [15]. Therefore, it is necessary to determine by additional clinical studies and objective data to prove the effect of LLLT according to the severity of the patents group, optimal laser parameters for lymphedema and its long-term effect. In this study, the overall TDC values of the participants decreased in body water values in most areas immediately after LLLT. Otherwise, no difference was observed in the effect depending on the laser wavelength. Furthermore, when the direct lymph velocity and number of lymph packets were measured through quantitative analysis, LLLT did not directly affect lymph velocity. In addition, while UE MLD consistently increased lymphatic activity, LLLT was unexpectedly associated with a reduction in both the velocity and number of lymph packets, suggesting a possible short-term suppressive effect. Despite prior assumptions that LLLT would enhance lymphatic flow, our data consistently showed no intergroup advantage and an overall negative correlation between LLLT and lymphatic function, regardless of wavelength. This result can be interpreted as factors related to the characteristics of normal participant rather than a treatment effect. As some amount of lymph fluid was manually drained through UE MLD before LLLT in healthy participants without lymphatic dysfunction, the period right after UE MLD, when no additional lymph production occurred, may have resulted in a temporary decrease in lymph packets during LLLT. In addition, the physiologic rationale for the decrease in lymphatic contraction after LLLT is consistent with nitric oxide (NO) mediated modulation and flow feedback in lymphatics. LLLT is known to increased bioavailable NO which exerts a negative chronotropic effect when shear stress is elevated after UE MLD [33, 34]. Therefore, in healthy participants where lymphatic pumping is adequate, LLLT may have induced rise in NO and transiently suppressed pumping not to decrease net clearing. In contrast, LLLT main exerts anti-inflammatory and lymphangiogenesis on pathologic state in lymphedema, thereby improving pumping capacity [35]. Regarding the mechanistic plausibility and population-specific effect of LLLT, randomized, clinical trial in lymphedema population are warranted.

Recommended wavelength used clinically differs according to the tissue indication of low-power laser treatment. Different wavelengths of LLLT were applied depending on the target tissue in the range of 500–1000 nm, from, skin to collagen formation, subcutaneous fat and mucosa. Recent systematic reviews related to LLLT treatment parameters used for lymphedema the wavelengths are mostly around 900 nm [15]. As a result, the pooled effect size within-group and between-groups in the fixed-effect model for volume reduction was moderately reduced. However, if we look back at the effects of various low-level lasers in lymphedema, we can see differences in the tissue targeting even within lymphedema, that is, whether skin fibrosis or the lymph node, superficial and deep lymphatics therefore the optimal wavelength of LLLT could be different depending on targeting tissue. The evidence for the effect of reducing edema at the endpoint immediately after treatment is valid. Our data confirmed a decrease in body water content immediately after LLLT at both wavelengths, but no significant difference was observed between the groups. Therefore, extended clinical research can be conducted to evaluate the difference in LLLT effects by various parameters, including wavelength, targeting tissues, energy density, pulse duration, and spot size during treatment in the patient group.

Lastly, this study is the first clinical trial to confirm the effectiveness of LLLT through the quantitative assessment of dynamic lymphatic motility using ICG lymphography. No significant results related to the effect of LLLT were found in this study. This requires further validation through additional proves with objective imaging modality in the patient group to determine whether LLLT applied to the axillary lymph nodes ultimately improves lymphatic drainage by enhancing lymphatic motoricity. Furthermore, the imaging modality can be used to evaluate the effect of LLLT applied to various areas of lymphedema in the patient group. Clinical studies, such as those on the status of dermal backflow and the appearance of collateral pathways, could be conducted to verify the effectiveness of treatment through various outcome measurements of ICG lymphography.

This study had some limitations. First, comprehensively evaluating the treatment effects was challenging because only healthy participants were included, and only a single intervention was administered to each participant. Consistent treatment would have provided a better comparison of treatment efficacy. Second, the results cannot be directly applied to patients or interpreted because this study was conducted on healthy volunteers. This study is the first randomized controlled trial to simultaneously derive quantitative data from ICG lymphography after LLLT; hence, the data from this study can serve as baseline values for future research involving patient groups. In addition, we were unable to set up a sham-control group in this study in the discussion. Otherwise, resting period were allocated between each intervention for intragroup analysis to compare the status of lymph flow before, after, and between the intervention. As a result, the changes in lymphatic flow during LLLT did not show difference or superiority over other

interventions without LLLT. Finally, this study did not compare the effectiveness of LLLT on the various parts of the upper extremities. A future study should be conducted to compare the effectiveness of LLLT in various areas, targeting patient groups in addition to the axillary area. In this study, LLLT was applied to the axillary site, the most commonly applied region, because of its mechanism of facilitating lymphatic drainage of the axillary area and preventing lymph node fibrosis. To apply the best practice of LLLT to patients with lymphedema, further verification of the effect of LLLT depending on the target area and severity of lymphedema is necessary. Additionally, a protocol for targeting focal fibrosis in patients with chronic lymphedema and its effectiveness based on the treatment session could be applied.

### Conclusion

In this study, we quantitatively evaluated the lymphatic motility and tissue water content after different types of LLLT in healthy participants. A single application of LLLT to the healthy subjects showed no direct effect on lymphatic motility. Therefore, to validate the reliability of the treatment effects of LLLT on lymphedema, it is essential to verify its impact in patient groups using ICG lymphography. In addition, clinical studies to prove the differences in LLLT effects by wavelength in patient groups and the effectiveness of LLLT based on various targeted areas of lymphedema is needed.

**Data availability** All data supporting the findings of this study are available within the paper and its figures & tables.

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### Declarations

**Informed consent** All patients signed an informed written consent for participation and photography.

**Competing interests** The authors have no competing interests to declare that are relevant to the content of this article.

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