ORIGINAL PAPER

Nagoya J. Med. Sci. **87**. 632–643, 2025
doi:10.18999/nagjms.87.4.632

A new pneumatic lymphatic drainage device enhancing lymphatic flow in lower limbs with lymphedema: a single-center, single-arm, prospective, open-label, non-randomized, exploratory study

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ABSTRACT

Lymphedema is the swelling of tissues caused by lymphatic stasis. Intermittent pneumatic compression (IPC), a treatment device for lymphedema, improves lymphatic flow using multiple donut-shaped air chambers with graduated compression from the distal. However, the lymphatic pathway has complicated three-dimensional networks; thus, a simple donut-shaped air chamber cannot adapt to the anatomy. A new pneumatic lymphatic drainage (PLD) device consisting of multiple round air chambers located according to the lymphatic pathways was collaboratively developed with a company. The device's air chambers simulate a therapist's manual lymphatic drainage (MLD) movements; however, the efficacy of this novel PLD is unknown. This feasibility study evaluated the lymphatic flow change by lymphoscintigraphy under PLD in 18 lower limbs with lymphedema and showed that the PLD enhanced lymphatic flow, especially in limbs with mild lymphedema. Previous reports have shown that in patients with lymphedema, improving lymphatic flow requires IPC with a high pressure (~100 mmHg). Although the PLD in this study only utilized mild pressure (50 mmHg) for 10 min, the tracer injected into the distal leg moved stably to the inguinal region. MLD promotes flexible lymphatic flow in response to anatomical variations; however, technical heterogeneity, labor costs, and other problems exist. PLD that can imitate MLD would solve these problems derived from human power.

Keywords: intermittent pneumatic compression, complex decongestive therapy, side effect, safety, lymphoscintigraphy

Abbreviations:
IPC: intermittent pneumatic compression

Received: December 6, 2024; Accepted: February 17, 2025
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ISL: International Society of Lymphology
MLD: manual lymphatic drainage
PLD: pneumatic lymphatic drainage

INTRODUCTION

Lymphedema is a chronic swelling of tissues due to lymphatic stasis, and its treatment involves complex decongestive therapy, which combines manual lymphatic drainage (MLD), exercise, and compression to stimulate lymphatic flow. In addition to directly reducing edema volume, complex decongestive therapy is reported to reduce secondary problems such as cellulitis and improve the quality of life of patients, especially in early-stage cases.[1,2]

An intermittent pneumatic compression (IPC) device consisting of multiple donut-shaped air chamber was developed in 1960 and was initially developed as a treatment device for venous stasis.[3] Subsequently, it has been applied to the treatment of lymphedema, and many IPCs already exist worldwide. Systematic reviews have reported that IPCs can promote lymphatic flow in patients with lymphedema[4-7] and are effective for its treatment.[8-10] IPC has already been evaluated as a therapeutic device for lymphedema based on reputable guidelines that recommend its use in a limited number of patients[11]; however, IPCs require a high pressure that is close to 100 mmHg to work sufficiently in patients with lymphedema.[12]

Recent reports have shown that anatomical lower limb lymphatic flow can be divided into two pathways, medial and lateral.[13-15] Healthy individuals and those with early-stage lymphedema have mainly medial lymphatic flow, but as the stage worsens, the lymphatic flow direction changes to lateral flow.[16-17] Based on new lymphatic anatomical findings, we developed a novel pneumatic lymphatic drainage (PLD) device (Fig. 1) that promotes lymphatic flow according to stage-based lymphatic flow changes, similar to MLD with controlled round air chamber placement and behavior. While most existing IPCs have ring-shaped air chambers that promote lymphatic flow in an axial direction, the PLD has round air chambers arranged according to an individual's leg shape and lymphatic anatomy, allowing for more localized compression and more flexible drainage directions similar to a therapist's MLD (Fig. 2).

Fig. 1 Pneumatic lymphatic drainage (PLD) device
The PLD consists of three units. Control units (a) have a touch panel to select and confirm the mode and air pumping systems. Sleeves connect to a control unit with air tubes and consisted of two parts (b and c), and these two sleeves can be overlapped to place on the patient's thigh. The sleeve for foot-thigh (b) include 12 air chambers covered with solid cloths. Sleeves for thigh-lower abdomen have four air chambers.

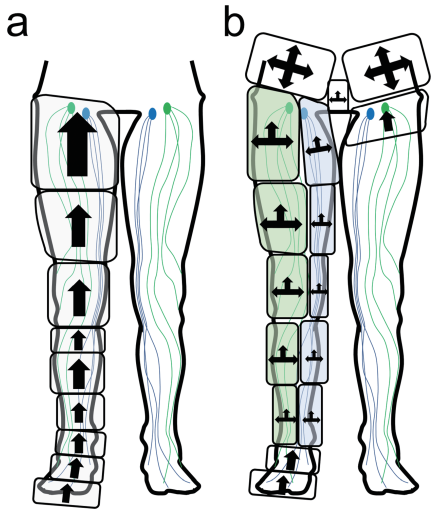

Fig. 2 Air chamber arrangement of conventional IPCs and PLD on lymphatic anatomy
Conventional IPC air chambers are arranged in a ring shape (a), whereas PLD air chambers are arranged according to the limb parts and lymphatic pathways (b). Thus, PLD can apply pressure to lymphatic drainage in any direction, whereas IPCs can only apply to the proximal direction, regardless of the lymphatic anatomy. The arrows indicate the direction of lymphatic flow caused by the air chamber compression. The arrows with blue background indicate the medial lymphatic pathway, whereas the green background represents the lateral pathway.
PLD: pneumatic lymphatic drainage
IPC: intermittent pneumatic compression

The main purpose of this clinical trial was to conduct an exploratory evaluation of the lymphatic flow-promoting effect of the PLD prototype in patients with lymphedema using lymphoscintigraphy to measure changes in lymphatic flow during use. The evaluation of lymphatic flow using lymphoscintigraphy has previously been reported.[18] Similar to the previous study, we analyzed the change in tracer-counts in the lower extremity using lymphoscintigraphy.

MATERIALS AND METHODS

Study design and patients

This was a single-center, single-arm, prospective, open-label, non-randomized, exploratory study (performed between April 12, 2022 and December 31, 2023). Study subjects were recruited between April 12, 2022 and January 31, 2023 at Okayama University Hospital. The main inclusion criteria of subjects were patients who had physical examination findings of lymphedema in at least one leg, aged >20 years, and who underwent lymphoscintigraphy for diagnosis and longitudinal assessment. The main exclusion criteria were the following: patients with a fever (>38 °C); a body mass index <18 or >30 kg/m^2; who may have edema other than lymphedema; and whose wounds or other injuries at the location of the sleeve, which consists of multiple air cambers and covering cloths of PLD. This PLD was developed by authors and TECNO TAKATSUKI CO, LTD's researchers with funding from the Japan Agency for Medical Research and Development. Written informed consent was obtained from all patients. Patients provided informed consent on the first day of the study and underwent scintigraphy on the second day. This clinical trial was approved and implemented by the Okayama University Clinical Review

Board (CRB 6180001), and was conducted in 20 patients. The trial was registered in the Japan Registry of Clinical Trials (jRCTs062220002).

Schematic of PLD

The PLD sleeve pressurized the affected lower limb by supplying air in a set sequence to 16 air chambers. The air in the chambers was then exhausted to relieve pressure. This repeated pressurization and decompression promoted the flow of the congested lymphatic fluid.

The direction of the predominant lymphatic flow in patients with lymphedema changes from medial to lateral, depending on the severity of the condition[16-17]; hence, the PLD had two main compression modes, a lateral-to-medial mode for patients with mild lymphedema and a medial-to-lateral mode for those with severe lymphedema (Fig. 3). In the present study, the PLD was used for lymphedema patients with mild condition (stage 0 to early-stage 2) and severe condition (late-stage 2 to stage 3) based on the International Society of Lymphology (ISL) lymphedema staging, with lateral-to-medial and medial-to-lateral modes, respectively. The device was used in the weakest pressure mode (maximum pressure of 50 mmHg at the peripheral site) for 10 min, which was the shortest possible setting, to ensure that it was effective in promoting lymphatic flow, even at minimal settings.

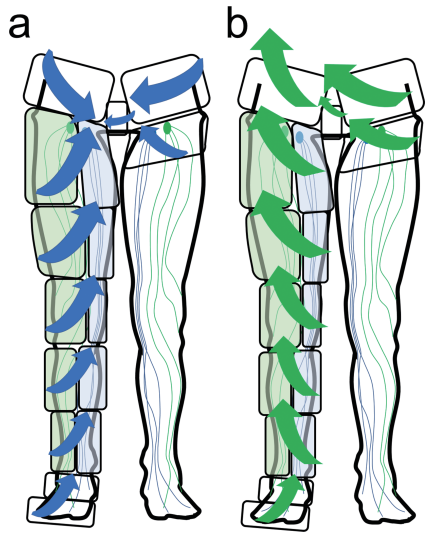

Fig. 3 Lymphatic flow showing the lateral-to-medial and medial-to-lateral modes
Lower limbs in early-stage lymphedema have medial lymphatic flow to the inguinal lymph nodes. As lymphedema progresses, the lymphatic flow direction changes to lateral, and finally to axillary lymph nodes. In this study, the lateral-to-medial mode (a) was applied to mild condition of lymphedema (ISL lymphedema staging 0 to 2 early) and the medial-to-lateral mode (b) was applied to severe condition of lymphedema (ISL lymphedema staging 2 delay to 3).
ISL: International Society of Lymphology

Flow and methodology of the scintigraphy

The scintigraphy treatment flow chart is presented in Fig. 4. The patients rested at the imaging table at least 30 min, and then the radioisotope (RI) (Tc-99mHSAD; Poolscinti injection, Nihon Medi-Physics, Tokyo) was subcutaneously injected. Three RI injections per limb were made using

a 26G needle attached to a 1 mL syringe just below the medial and lateral malleoli on the dorsal-plantar border and midpoint on the line between the fifth metatarsal head and the lateral phalanx, for a total of six injection sites per patient. The RI was administered at 80.0 MBq per injection site. The sleeve was attached to the affected limb just before performing lymphoscintigraphy. If both lower limbs had edema, the sleeve site was determined based on which limb had more severe edema measured by volume that was calculated from circumference. The sleeve fitting and setting were done by one lymphedema therapist who had 20 years of experience.

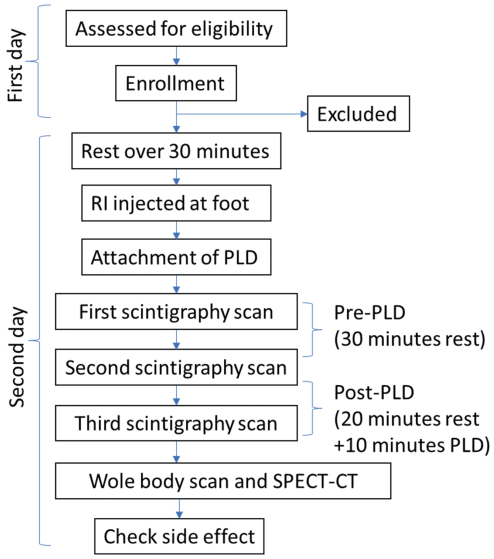

Fig. 4 Study flow chart

Before performing lymphoscintigraphy, patients were kept in a resting position for at least 30 min to calm any lymphatic hyperfiltration. Then, the RI was injected subcutaneously at three locations on one leg and the PLD was immediately applied to begin the first spot scan of scintigraphy. The second spot scan of scintigraphy was performed 30 min after the RI injection, during which the PLD was operated for 10 min. The third spot scan of scintigraphy was performed 60 min after the RI injection.

PLD: pneumatic lymphatic drainage

RI: radioisotope

SPECT-CT: single-photon emission computed tomography-computed tomography

The subject was placed with their limb position in supine rest at the time of imaging, and the subject was lightly immobilized with a restraint band and mat for fixation to prevent displacement. Immediately after the administration, the first spot scan of scintigraphy was performed. The spot images at inguinal region and popliteal fossa were scanned in two directions, anterior or posterior, for 5 min per area. The sensor and sleeve surface were positioned at the shortest possible distance without contacting each other, and the subjects were fixed for all images. The second spot scan of scintigraphy was initiated 30 min after the administration, followed by PLD for 10 min immediately after the imaging session was completed. After the PLD was completed, the third spot scan of scintigraphy was started 60 min after the injection. The period between the first and second spot scan was defined as pre-PLD, and the period between the second and third spot scan was defined as post-PLD. Whole-body scan (matrix size, 256×1024; speed, 10 cm/min) and single-photon emission computed tomography-computed tomography lymphoscintigraphy

were performed 120 min post-injection. Whole-body scan was used for Maegawa classification, and single-photon emission computed tomography-computed tomography was used to confirm lymph node locations.

Endpoints

The primary endpoint was the differences in tracer-count change in the inguinal region and popliteal fossa in same lower limb by lymphoscintigraphy between pre- and post-PLD. The secondary endpoints included the differences: (i) in tracer-count change between mild condition (ISL lymphedema staging 0 to 2 early) and severe condition (ISL lymphedema staging 2 delay to 3), (ii) in tracer-count changes between mild condition (Maegawa classification[19] type 1–2) and severe condition (Maegawa classification type 3–5), and (iii) failures and adverse events.

Image and statistical analysis

Total four spot images of the scintigraphy were obtained from the anterior and posterior sensor at two locations: inguinal region and popliteal fossa, and analyzed and processed on a workstation (SYNAPSE VINCENT V6.7.0007, FUJIFILM, Tokyo) (Fig. 5). The region of interest was specified in a fixed area (popliteal fossa, 200×300 mm; inguinal region, 50×200 mm) such that the lymph nodes were included, and the tracer-count average was calculated per area. The averages in each anterior and posterior spot image were added as each location's tracer-count. Finally, the counts were corrected for attenuation from the imaging time.

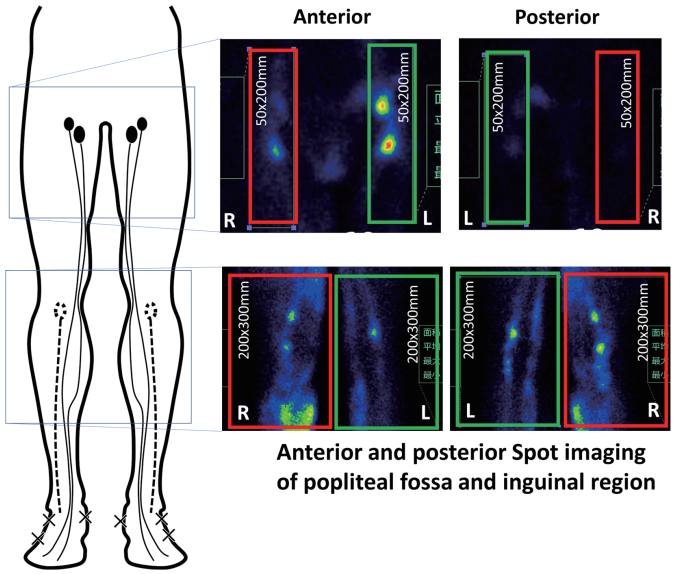

Fig. 5 Schema of scintigraphy scan image analysis

Spot images of scintigraphy were obtained from the anterior and posterior scintigraphy sensors for two fixed locations which included the inguinal and popliteal lymph nodes: inguinal region and popliteal fossa. For each spot image tracer-counts were averaged per fixed area (popliteal fossa, 200×300 mm; inguinal region, 50×200 mm), and the average of the tracer-counts in each anterior and posterior spot image were added as each location's tracer-count. For example, tracer counts in the anterior and posterior images of the right inguinal region were 12560 and 2670 counts, and the averages were 12.56 and 0.267 counts per mm^2, respectively. The combined average was used as the total tracer-count in the right inguinal (12.827). Crosses in foot mean injection sites of the RI. RI: radioisotope

The resulting data were entered into a dedicated database for tabulation and analysis. Differences in tracer-counts and confidence intervals were statistically examined using a Wilcoxon signed-rank test (one-sided). The significance level α was set at <0.05. Data are presented as means ± standard deviations (median). Statistical analyses were performed using EZR version 2.6-1 (https://www.r-project.org/).[20]

RESULTS

Patient characteristics

Twenty patients with lymphedema in their lower limbs were initially enrolled (Table). Two patients were excluded from the study because they had a body mass index of ≥30 kg/m^2 during the study period. Finally, 18 patients comprising 18 limbs were analyzed. The patients had a mean age of 56.3±9.4 years and a mean body mass index of 24.1±3.4 kg/m^2. All patients were female. In the study population, 16 of 18 patients had lymphedema secondary to gynecological surgery and 2 of 18 patients had primary lymphedema. ISL lymphedema stages, judged by a lymphedema therapist who had 20 years of experience and a plastic surgeon who had 15 years of experience, were as follows: stage 0 (0 of 18 limbs), stage 1 (7 of 18 limbs), stage 2 early (3 of 18 limbs), stage 2 delay (6 of 18 limbs), and stage 3 (2 of 18 limbs). The Maegawa classification were as follows: type 1 (10 of 18 limbs), type 2 (2 of 18 limbs), type 3 (3 of 18 limbs), type 4 (2 of 18 limbs), and type 5 (1 of 18 limbs).

Table Patients characteristics

		n = 18
Sex female, %		100 (18 limbs)
Age, years old		56.3 ± 9.4
BMI (body mass index), kg/m^2		24.1 ± 3.4
Secondary or primary, %		88.9 (16 limbs)
ISL lymphedema staging, %		
	Stage 0	0 (0 limbs)
	Stage 1	38.9 (7 limbs)
	Stage 2 early	16.7 (3 limbs)
	Stage 2 delay	33.3 (6 limbs)
	Stage 3	11.1 (2 limbs)
Maegawa classification, %		
	Type 1	55.6 (10 limbs)
	Type 2	11.1 (2 limbs)
	Type 3	16.7 (3 limbs)
	Type 4	11.1 (2 limbs)
	Type 5	5.6 (1 limbs)

ISL: International Society of Lymphology

Primary endpoint

The tracer-count changes in the inguinal region and popliteal fossa using lymphoscintigraphy at pre- and post-PLD were analyzed (Fig. 6). Tracer-count changes in the inguinal region at pre- and post-PLD were 1.20±1.28 (0.95) and 3.30±2.07 (2.77), respectively (95% CI, –2.96, –1.24; P<0.001). Conversely, the tracer-count changes in the popliteal fossa at pre- and post-PLD were 2.51±5.01 (1.08) and 5.53±4.88 (3.58), respectively (95% CI, –5.30, –0.71; P=0.0011).

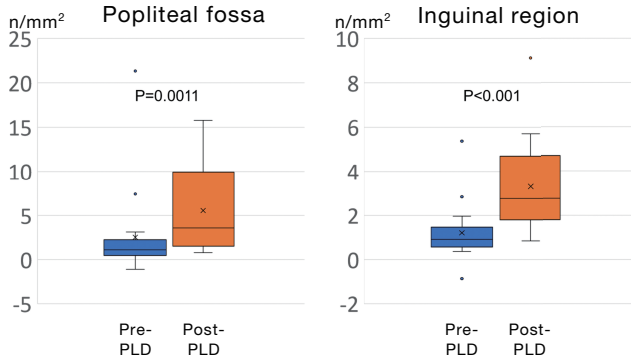

Fig. 6 Differences in the tracer-count changes between pre- and post-PLD
Compared with the rest position, the PLD promoted lymphatic flow, with statistically significant differences in both the inguinal region and popliteal fossa. Whiskers in the graph represent the maximum and minimum.
PLD: pneumatic lymphatic drainage

Secondary endpoints

(i) Differences in tracer-counts by ISL lymphedema stage (mild vs severe). In patients with mild condition (stage 0–2 early), the tracer-count changes in the inguinal region at pre- and post-PLD were 0.81±0.68 (0.91) and 3.61±1.53 (3.43), respectively (95% CI, –3.81, –1.80; P<0.001; Fig. 7). In patients with severe condition (stage 2 delay–3), the tracer-count changes in the inguinal region at pre- and post-PLD were 1.69±1.71 (0.94) and 2.91±2.65 (2.05), respectively (95% CI, –2.67, 0.22; P=0.039).

In patients with mild condition, the tracer-count changes in the popliteal fossa at pre- and post-PLD were 1.63±2.27 (1.08) and 5.81±4.83 (4.13), respectively (95% CI, –7.09, –1.26; P=0.0012). In patients with severe condition, the tracer-count changes in the popliteal fossa at pre- and post-PLD were 3.63±7.21 (1.00) and 5.18±5.24 (2.81), respectively, with no statistically significant difference (95% CI, –5.79, 2.69; P=0.15).

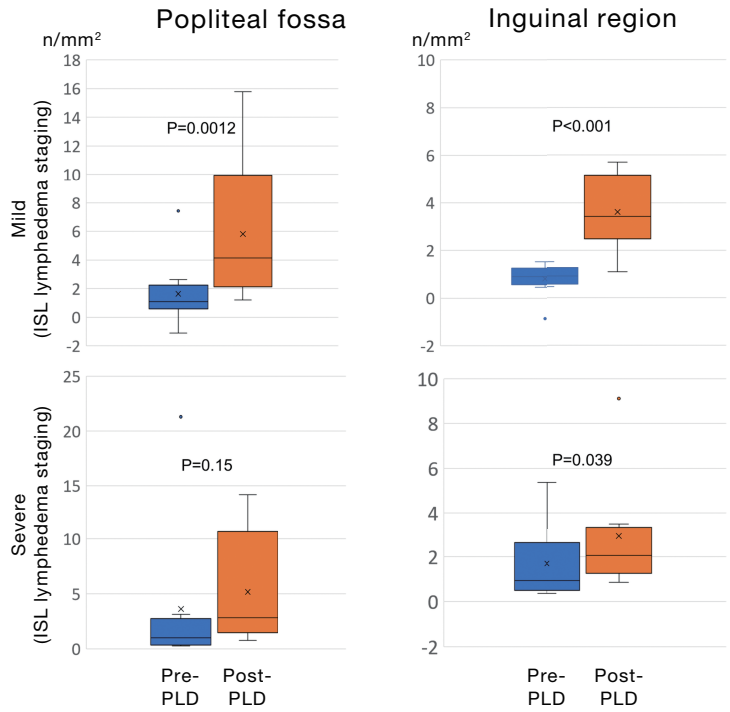

Fig. 7 Differences in tracer-count changes by ISL lymphedema staging (mild vs severe)
In the mild condition (stage 0–2 early), lymphatic flow was enhanced in both the inguinal region and popliteal fossa; however, in the severe condition (stage 2 delay–3), the lymphatic flow was not enhanced in the popliteal fossa. Whiskers in the graph represent the maximum and minimum.
PLD: pneumatic lymphatic drainage
ISL: International Society of Lymphology

(ii) Differences in tracer-counts by Maegawa classification (mild vs severe). In patients with mild condition (type 1–2), the tracer-count changes in the inguinal region at pre- and post-PLD were 0.87±0.71 (0.91) and 3.44±1.45 (2.87), respectively (95% CI, –3.53, –1.61; P<0.001; Fig. 8). In patients with severe condition (type 3–5), the tracer-count changes in the inguinal region at pre- and post-PLD were 1.85±1.93 (0.94) and 3.02±3.13 (1.78), respectively, with no statistically significant difference (95% CI, –3.21, 0.868; P=0.11).

In patients with mild condition, the tracer-count changes in the popliteal fossa at pre- and post-PLD were 1.42±2.11 (0.77) and 5.42±4.54 (4.13), respectively (95% CI, –6.42, –1.58; P<0.001). In patients with severe condition, the tracer-count changes in the popliteal fossa at pre- and post-PLD were 4.72±8.18 (1.45) and 5.74±5.95 (2.82), respectively, with no statistically significant difference (95% CI, –7.07, 5.02; P=0.16)

(iii) Adverse events and failures. No adverse events nor device failures occurred during this study.

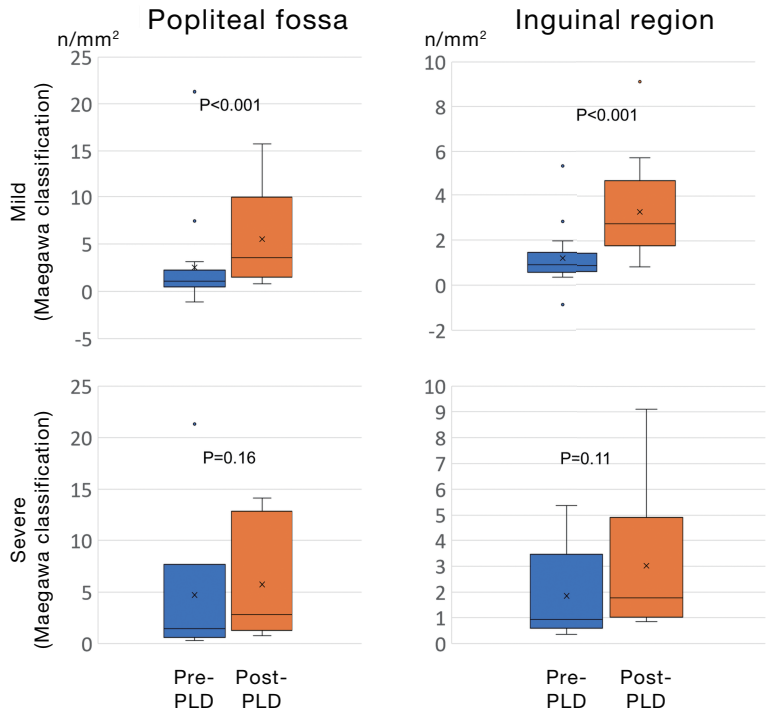

Fig. 8 Differences in tracer-count by Maegawa classification (mild vs severe)
In the mild condition (type 1–2), lymphatic flow was enhanced in both the inguinal region and popliteal fossa; however, in the severe condition (type 3–5) the lymphatic flow was not enhanced in either the inguinal region or popliteal fossa. Whiskers in the graph represent the maximum and minimum.
PLD: pneumatic lymphatic drainage

DISCUSSION

The present study showed that PLD can enhance lymphatic flow in patients with lymphedema compared to resting conditions, especially in those with a mild lymphedema condition. In this study, PLD was safe without any adverse events, such as skin redness.

The results of this study suggest that air chambers set up according to the network of the lymphatic vessels were able to promote lymphatic flow compared with resting conditions. However, patients with severe lymphedema condition, especially those with Maegawa classification type 3–5, did not move the tracer sufficiently. Previous reports indicated that patients with lymphedema in their lower limb require higher compression pressures.[12] It is possible that the pressure used in the study was insufficient, because the compression used was only ~50 mmHg. In addition, the medial-to-lateral mode for patient with a severe condition might be unsuitable. It was reported that even in severe cases, the lymphatic flow change does not occur easily.[21] Thus, the lateral-to-medial mode might be more suitable for patients with a severe condition. In addition, the RI tracer is a large molecule, and its movement may not be indicative of water movement.[22] In the future, when imaging with even smaller molecules becomes possible, actual water movement will become clearer.

Although the PLD could provide more localized compression and simulate movement more

similar to MLD than IPCs, PLD could not imitate all MLD processes. MLD not only promotes lymphatic flow in affected limbs but also involves several processes, such as targeting healthy lymph nodes that are not in affected limbs. However, MLD has limitations, including technical heterogeneity and labor costs. Thus, assistance from PLD would reduce the labor limitation and its costs.

The air chamber and compression pressure did not cause any skin damage; however, some minor side effects, such as discomfort, have been reported in the past IPC studies.[23-26] The air chamber used in this study was applied at a relatively low pressure, and patient safety was ensured. In different situations, such as cellulitis or lymphatic leakage, injury could possibility occur. To prevent issues, patients should be screened for skin or musculoskeletal abnormalities prior to the application of PLD.

This is the first study to report the use and lymphopoietic effects of a PLD device with non-ring-shaped air chambers in patients with lymphedema. However, this study had several limitations. This was a single-arm study, and evaluation of treatment effect compared to IPCs, such as limb volume changes, were not measured. Because this study provided only 10 min of pressure with PLD, side effects might be underestimated. Further comparative research is required to investigate PLD and confirm these results.

DECLARATION OF CONFLICTING INTERESTS

A.S. is a member of the Joint Research Department supported by TECHNO TAKATSUKI CO, LTD. The other authors declare no conflicts of interest associated with this manuscript.

FUNDING/SUPPORT

Supporting for this study was provided to Department of Lymphatics and Edematology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Science through HAMAMATSU PHOTONICS KK and TECHNO TAKATSUKI CO, LTD; grant jp20he0122004 from Japan Agency for Medical Research and Development (AMED).

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