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Randomized Clinical Trial

Lymphatic venous anastomosis and complex decongestive therapy for lymphoedema: randomized clinical trial

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Abstract

Background: Lymphatic venous anastomosis is associated with a low incidence of lower extremity lymphoedema-associated cellulitis; however, the exact relationship is unknown. This multicentre RCT evaluated the effect of lymphatic venous anastomosis on prevention of cellulitis.

Methods: Patients with secondary lower extremity lymphoedema who underwent at least 3 months of non-operative decongestive therapy were assigned randomly to lymphatic venous anastomosis or conservative therapy. The primary and secondary outcomes were cellulitis frequency, and assessments of circumference, hardness, and pain respectively.

Results: Overall, 336 patients were divided into two groups: 225 in the full-analysis set (primary outcome 225; secondary outcomes 170) and 156 in the per-protocol set (primary outcome 156; secondary outcomes 110). In both analyses, lymphatic venous anastomosis with non-operative decongestive therapy was more effective in preventing cellulitis than non-operative decongestive therapy alone; the difference between groups in reducing cellulitis frequency over 6 months was −0.35 (95 per cent c.i. −0.62 to −0.09; $P = 0.010$) in the full-analysis set (FAS) and −0.60 (−0.94 to −0.27; $P = 0.001$) in the per-protocol set (PPS) Limb circumference and pain were not significantly different, but lymphatic venous anastomosis reduced thigh area hardness (proximal medial and distal and lateral proximal). Four patients experienced contact dermatitis with non-operative decongestive therapy alone.

Conclusion: Lymphatic venous anastomosis in combination with non-operative decongestive therapy prevents cellulitis.

Registration number: UMIN00025137, UMIN00031462.

Introduction

Lymphoedema is characterized by impairments in lymphatic function that cause lymph to collect in the skin or subcutaneous tissue[1]. Lymphedema is divided into primary lymphedema of unknown cause and secondary lymphedema following cancer treatment. It is estimated to affect approximately 120 million individuals worldwide and is considered incurable[2].

Extremities affected by lymphoedema are prone to cellulitis, which can substantially lower the quality of life of patients[3]. Cellulitis commonly presents when lower extremity lymphoedema involves lymphatic vesicles in the genitalia[4–6]. Some patients experience cellulitis up to 20 times a year, making social life difficult. Unlike ordinary cellulitis, cellulitis associated with lymphoedema can develop and progress in just 1–2 h, covering an extensive range and inducing fever, with temperature reaching 38–40°C. Such rapid progression can eventually lead to sepsis or necrotizing fasciitis[7]. Furthermore, concerns related to cellulitis make work, travel, and exercise difficult for patients with lymphoedema.

Reported strategies for preventing cellulitis include complex physical therapy (complex decongestive therapy, CDT), compression therapy, liposuction, and vascularized lymph node transfer, all of which have been suggested to be effective[8–16]. In the authors' previous prospective study, a lower frequency of postoperative cellulitis was observed among patients who had undergone lymphatic venous anastomosis (LVA) compared with those who had not[17]. During LVA, the

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lymphatic vessels in the affected extremity are anastomosed to nearby veins, allowing the collected lymph to drain[17–20]. Despite requiring advanced supermicrosurgery using a microscope, the procedure is minimally invasive and can be performed under local anaesthesia[21]. Nonetheless, there is little evidence regarding the efficacy of LVA in preventing cellulitis in patients with lymphoedema. Therefore, a randomized trial of LVA and CDT *versus* CDT alone was designed.

Methods

Participants

The present study included patients who first sought consultation either at the Department of Lymphatic and Reconstructive Surgery, Saiseikai Kawaguchi General Hospital (Saitama, Japan) between January 2017 and December 2017, or at the Department of Lymphatic and Reconstructive Surgery, JR Tokyo General Hospital, between February 2018 and September 2019. The trial was registered at UMIN (UMIN00025137, UMIN00031462).

The inclusion criteria were: diagnosis of secondary lower extremity lymphoedema; at least 3 months of conservative (decongestive) therapy; capacity to answer medical questions; informed patient consent presented in writing, of the patient's free will, after receiving a full explanation regarding study participation; and written informed consent obtained from the patient's guardians, in addition to patient consent as above, for underage patients. The exclusion criteria were: expected postoperative follow-up for less than 6 months; oedema complicated by heart failure, renal failure, or similar complications; and inclusion deemed unsuitable by an investigator.

Planned intervention

Patients who met the inclusion criteria were assigned randomly to the LVA or CDT (control) group. In the LVA group, LVA was performed during CDT using a previously described surgical technique[18,19]. Ultrasonography was centred on sites where lymphatic vessels were found during preoperative lymphoscintigraphy/indocyanine green fluorescence lymphangiography. A skin incision was made at the location of the most dilated vessels in one of the lymphosomes with suitable veins located nearby[20–26]. After subcutaneous injection of xylocaine with 1 per cent adrenaline (epinephrine), a skin incision was made using a #15 scalpel. The veins and lymphatic vessels were identified in the subcutaneous fat and anastomosed with 12/0 or 11/0 nylon sutures. Many patients required end-to-end anastomosis. However, end-to-side anastomosis was chosen when the veins were at least twice as thick as the lymphatic vessels, or when lymphatic vessels had a diameter of 1.5 mm or greater and were suspected to have valve dysfunction. Wound closure was performed via a dermal suture with 4/0 absorbable surgical suture. Surgery was followed by fundamentally the same CDT as used before surgery. The need for more intensive CDT after surgery was noted as appropriate.

The conservative therapy (control) group underwent either CDT similar to that at their first visit or intensified CDT. CDT included compression therapy using bandages or elastic stockings, manual lymphatic drainage by the patients themselves, guidance regarding exercise while using compression, and lifestyle guidance.

Outcomes

Assessments were made at the first outpatient visit at least 6 months after the start of intervention. For those living far away who had difficulty visiting the hospital, questions were asked by telephone at least 6 months after the start of the intervention. The primary outcome was the frequency of cellulitis, recorded as the number of times cellulitis occurred over 6 months. For the secondary outcomes, only patients who presented for outpatient consultation at least 6 months later underwent assessments of the circumference of the affected extremities, hardness, and pain. Circumference was measured at six places using a tape measure: 20 cm proximal to the knee joint, 10 cm proximal to the knee joint, at the knee joint, 10 cm distal to the knee joint, at the ankle joint, and at the instep. The sum of values obtained from these six locations was recorded. Measurements were taken by a randomly assigned nurse or therapist during an outpatient visit in the afternoon. Hardness was measured using the sponge method, as described previously[27]. Briefly, three types of sponge with different hardness (Yahata Neji, Aichi, Japan) were prepared. Each sponge was numbered 2, 4, or 6, the first of these being the softest. The stiffness of the oedematous extremities and the sponges was compared, and the number of the sponge that was most comparable to the oedematous extremities in stiffness was recorded. Hardness was measured at a total of eight places by dividing the thigh and lower leg into proximal/distal and medial/lateral, and the sum of the values for the eight locations was used for analysis. Pain was assessed on an 11-point visual analogue scale (0–10).

Sample size determination

The mean frequency of cellulitis was assumed to be 0.59 per year. Surgery was expected to reduce the frequency to 0.17 per year, whereas the control group (CDT only) was expected to have a reduced frequency (0.47 per year). Therefore, the difference in the mean frequency of cellulitis was expected to be 0.30 per year. The standard deviation was expected to be 0.65 per year, based on the values from existing studies[17]. Using Student's *t* test to detect a difference in mean frequency of cellulitis between the two groups with 90 per cent power, the required sample size was calculated to be 200. In the present study, the sample size was calculated based on the assumption that the number of occurrences of cellulitis follows a normal distribution; however, this normality assumption may not hold. Therefore, Welch's *t* test, which is robust to violations of normality, was employed as a statistical test[28,29].

Random assignment

Random assignments were made for each patient. Once patients had been registered, the first or second author arranged the assignments in chronological order of when consent forms were received at the hospital, ensuring the concealment of random assignments.

Based on the blocked random assignment, the statistician prepared an allocation table (1 : 1 ratio) in advance, which was strictly managed by the Clinical Trial Office of the Department of Pharmacology. The block size was determined to be four in advance but not written in the protocol. Owing to the nature of surgical treatment and conservative therapy, blinding was not possible in the present study.

Statistical analysis

Outcomes were evaluated using both the full-analysis set (FAS) and per-protocol set (PPS). The FAS results were interpreted as the main results because FAS is based closely on the intention-to-treat principle. The FAS comprised participants who did not interrupt the treatment of their own accord after randomization and

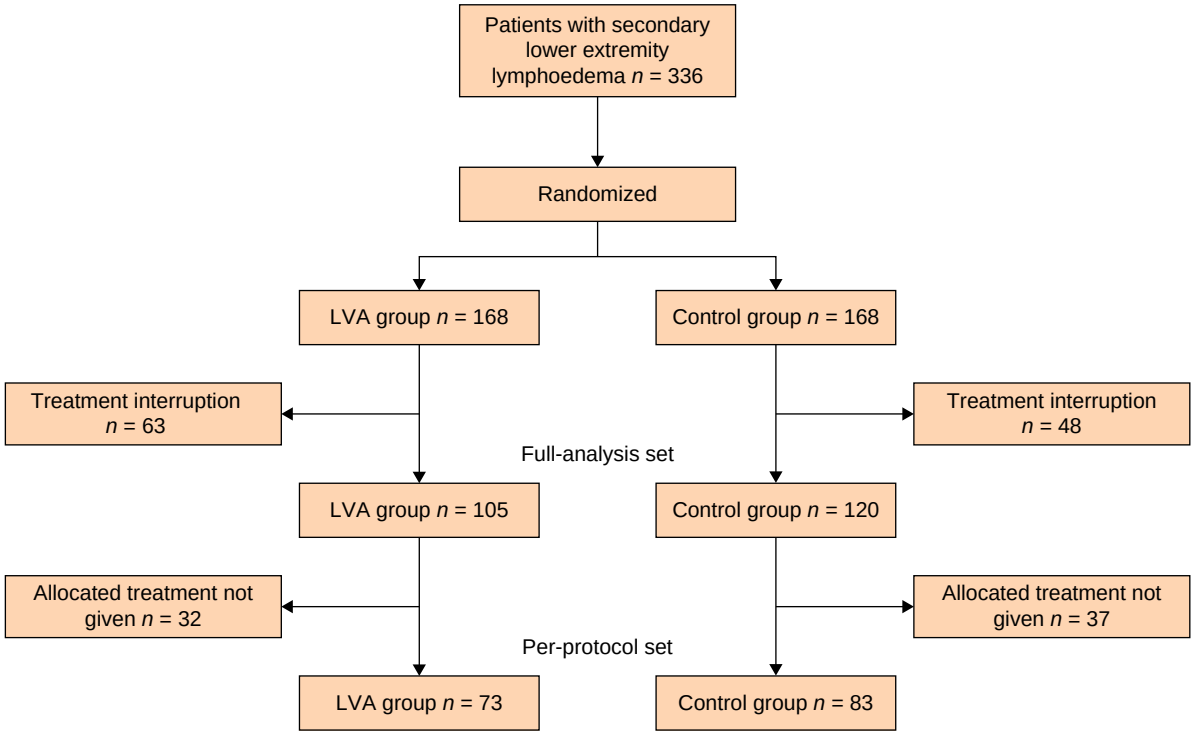

Fig. 1 CONSORT flow diagram for trial

violate the inclusion or exclusion criteria. The PPS consisted of participants in the FAS who were treated as assigned.

Continuous variables are described using means, standard deviations, medians, and interquartile ranges. Categorical variables are described using frequencies and percentages.

For primary and secondary outcomes, the mean difference in the frequency of cellulitis before and after intervention was calculated, with a 95 per cent confidence interval. Welch's t test was employed as a test of statistical significance to assess the mean difference between the two groups because it does not assume equal variances between two variables and minimizes the effects of normality assumption violation on trial outcomes[28,29]. Secondary outcomes were analysed using the same method. The proportion of discontinuations and the incidence of adverse events were compared between groups using χ^2 tests.

Statistical analysis was undertaken using Stata® version 17 (StataCorp, College Station, TX, USA). $P < 0.050$ was considered statistically significant. Given that the intervention group was expected to exhibit a reduction effect 0.4 times greater than that of the control group, a reduction greater than this value was considered clinically significant. Missing values were not manipulated (complete-case analysis was performed).

Table 1 Patient characteristics in full-analysis set

	LVA group	CDT group
Sex ratio (F : M)	104 : 1	118 : 2
Primary disease *3		
Prostate cancer	0 (0)	2 (1.7)
Ovarian cancer	21 (20.0)	22 (18.3)
Fallopian tube cancer	0 (0)	1 (0.8)
Uterine cancer	80 (76.2)	95 (79.2)
Colorectal cancer	1 (1.0)	1 (0.8)
Stomach cancer	0 (0)	1 (0.8)
Ureteral cancer	0 (0)	1 (0.8)
Bladder cancer	1 (1.0)	1 (0.8)
Uterine sarcoma	4 (3.8)	0 (0)
Transverse colonic cancer	1 (1.0)	0 (0)
Malignant lymphoma	1 (1.0)	0 (0)
Anal cancer	1 (1.0)	0 (0)
International Society of Lymphology classification		
1	7 (6.7)	9 (7.5)
2a	27 (25.7)	28 (23.3)
2b	50 (47.6)	62 (51.7)
3	19 (18.1)	21 (17.5)
Missing data	2 (1.9)	0 (0)
Lymphoscintigraphy staging		
1	3 (2.9)	4 (3.3)
2	29 (27.6)	26 (21.7)
3	32 (30.5)	40 (33.3)
4	32 (30.5)	31 (25.8)
5	9 (8.6)	17 (14.2)
Missing data	0 (0)	2 (1.7)

Values are *n* (%). *3 refers to the cancer disease that caused the patient's lymphedema to develop. LVA, lymphatic venous anastomosis. CDT, complex decongestive therapy.

Results

Participant flow and follow-up

A total of 336 patients were allocated into LVA and CDT groups (*Fig. 1*). Of these, 111 individuals with missing data regarding cellulitis were deemed unsuitable and excluded, and the remaining 225 patients (LVA 105, CDT 120) comprised the FAS (primary outcome 225; secondary outcomes 170) (*Table 1*). The 156 participants (LVA 73, CDT 83) remaining after the exclusion of 69 patients who refused to receive the therapy assigned to them comprised the PPS set (primary outcome 156, secondary outcomes 110) (*Table 2*). The LVA group included 8 patients who underwent intensified CDT after surgery and 10 who had lymphatic vesicles removed from the genitalia during LVA. The CDT group included 26 patients who underwent more intensive CDT following the initial session (*Tables 1* and *2*).

Table 2 Patient characteristics in per-protocol set

	LVA group	CDT group
Sex ratio (F : M)	72 : 1	81 : 2
Primary disease *3		
Prostate cancer	0 (0)	2 (2.4)
Ovarian cancer	15 (20.5)	15 (18.1)
Fallopian tube cancer	0 (0)	1 (1.2)
Uterine cancer	55 (75.3)	65 (78.3)
Colorectal cancer	0 (0)	1 (1.2)
Stomach cancer	0 (0)	1 (1.2)
Ureteral cancer	0 (0)	1 (1.2)
Bladder cancer	1 (1.4)	1 (1.2)
Uterine sarcoma	3 (4.1)	0 (0)
Transverse colonic cancer	1 (1.4)	0 (0)
Malignant lymphoma	1 (1.4)	0 (0)
Anal cancer	1 (1.4)	0 (0)
International Society of Lymphology classification		
1	4 (5.5)	7 (8.4)
2a	20 (27.4)	25 (30.1)
2b	35 (47.9)	39 (47.0)
3	13 (17.8)	12 (14.5)
Missing data	1 (1.4)	0 (0)
Lymphoscintigraphy staging		
1	2 (2.7)	2 (2.4)
2	21 (28.8)	21 (25.3)
3	23 (31.5)	28 (33.7)
4	21 (28.8)	21 (25.3)
5	6 (8.2)	9 (10.8)
Missing data	0 (0)	2 (2.4)

Values are *n* (%). *3 refers to the cancer disease that caused the patient's lymphedema to develop. LVA, lymphatic venous anastomosis; CDT, complex decongestive therapy.

Analysis

The results for the FAS are shown in *Fig. 2*. The number of times that cellulitis occurred over the 6 months was −0.57 in the LVA group and −0.21 in the CDT group. Welch's *t* test revealed that the difference of −0.35 (95 per cent c.i. −0.62 to −0.09) times was statistically significant, indicating that LVA with CDT was more effective than CDT alone in preventing cellulitis ($P = 0.010$).

In terms of secondary outcomes, both groups exhibited a decrease in the circumference of the affected extremities at 6 months, and there was no statistically significant difference between the LVA and CDT groups ($P = 0.129$). The hardness of the affected limbs also decreased in both groups. The medial proximal thigh, medial distal thigh, and lateral proximal thigh exhibited statistically significantly greater decreases in hardness in the LVA group than in the CDT group ($P = 0.007$, $P = 0.011$, and $P = 0.052$ respectively). The decrease in pain did not differ significantly between the LVA and CDT groups ($P = 0.611$).

The results of the PPS analysis are shown in *Fig. 3*. The number of times cellulitis occurred over 6 months was −0.72 in the LVA group and −0.11 in the CDT group. Welch's *t* test revealed that the difference of −0.60 (−0.94 to −0.27) times was statistically and clinically significant, indicating that LVA with CDT was more effective than CDT alone in preventing cellulitis ($P = 0.001$).

In terms of secondary outcomes, both groups exhibited a decrease in the circumference of the affected extremities at 6 months, and there was no statistically significant difference between the LVA and CDT groups ($P = 0.051$). The hardness of

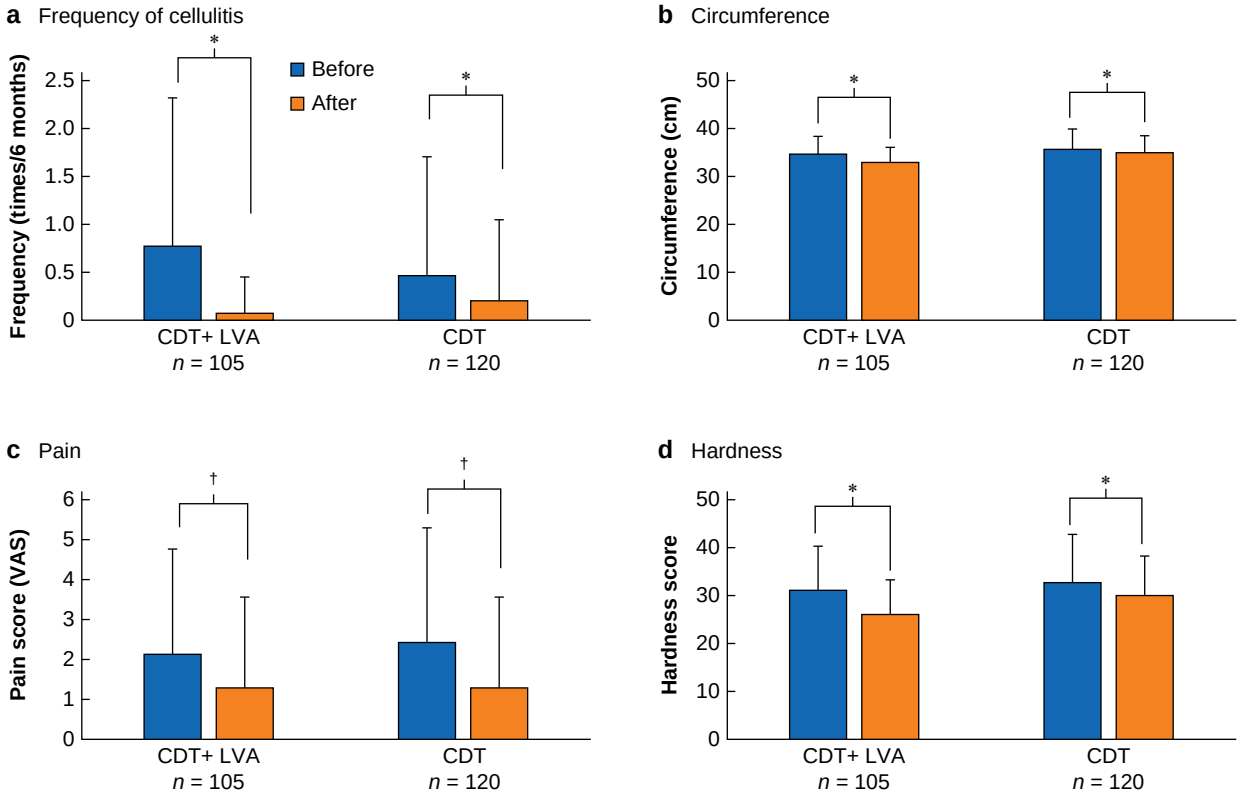

Fig. 2 Results for full-analysis set

a Frequency of cellulitis, **b** circumference, **c** pain, and **d** hardness. Values are mean(s.d.). $P < 0.001$, †$P < 0.050$ (Welch's *t* test).

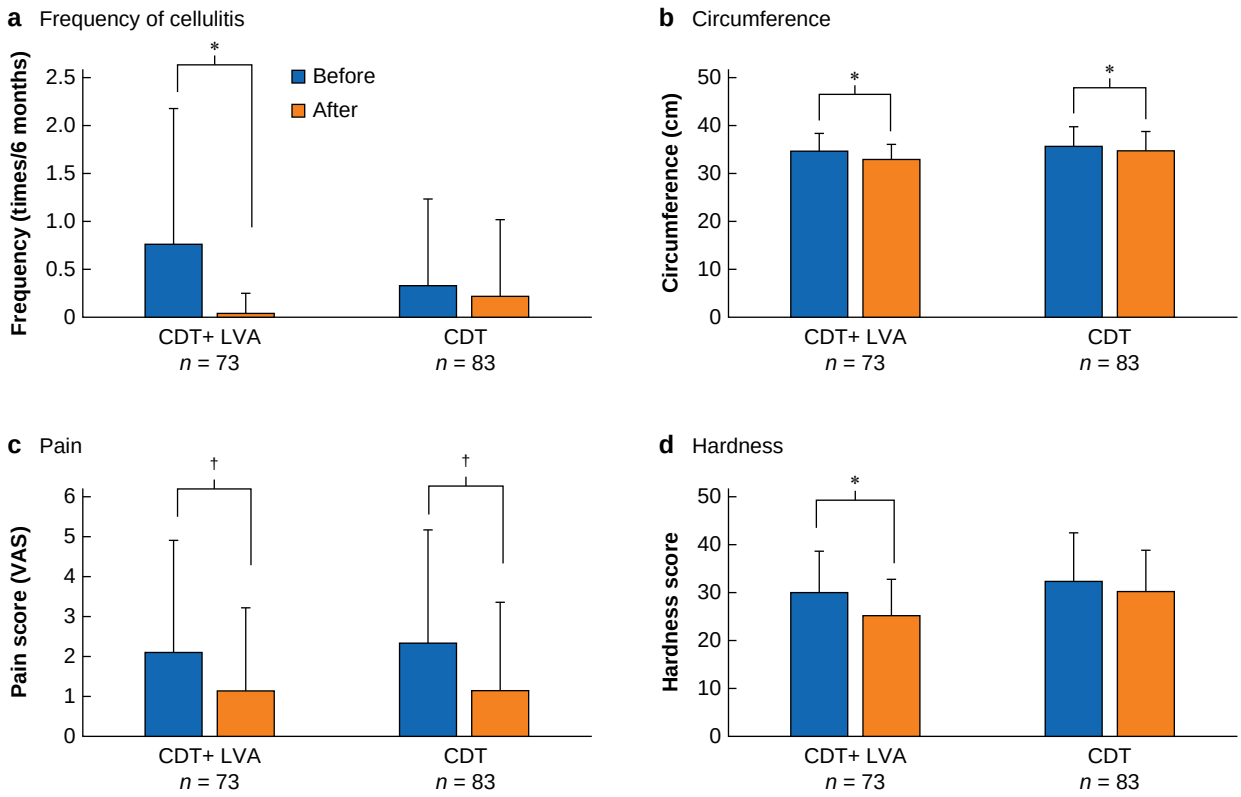

Fig. 3 Results for per-protocol set

a Frequency of cellulitis, **b** circumference, **c** pain, and **d** hardness. Values are mean(s.d.). $P < 0.001$, †$P < 0.050$ (Welch's *t* test).

the affected limbs also decreased in both groups. The medial proximal thigh, medial distal thigh, and lateral proximal thigh exhibited statistically significant greater decreases in hardness in the LVA group than in the CDT group ($P = 0.036$, $P = 0.014$, and $P = 0.038$ respectively). The decrease in pain did not differ significantly between the LVA and CDT groups ($P = 0.844$).

Adverse events

No adverse events were observed in the LVA group. In the CDT group, the elastic clothing caused contact dermatitis in four patients, which improved after treatment with a steroid ointment. A χ^2 test revealed a statistically significant increase in the incidence of adverse events in the CDT group compared with the LVA group ($\chi^2(1) = 3.69$, $P = 0.055$, $\phi = 0.129$).

Discussion

The present study compared the ability of LVA with CDT *versus* CDT alone to prevent cellulitis in patients with lower extremity lymphoedema. Based on previous research, it was postulated that the reduction effect of LVA with CDT compared with CDT alone would be 0.4. However, given that some participants were already aware of the preventive benefits of LVA, those who frequently experienced cellulitis and were allocated to the CDT-only group preferred LVA, leading to their exclusion from the RCT. Consequently, the pretreatment cellulitis count was reduced, potentially diminishing the anticipated reduction. This hypothesis is further bolstered by the results from the PPS analysis, in which clinically significant findings diverged from those of the FAS analysis.

Webb *et al.*[10] conducted an RCT including patients with chronic lower extremity oedema and recurring cellulitis who did and did not undergo compression therapy, and reported that compression therapy effectively prevented cellulitis. Similarly, an RCT by Negussie *et al.*[11] reported a lower frequency of cellulitis in the CDT group than in the non-CDT group. Olszewski and Zaleska[12] noted that long-term treatment with benzathine penicillin prevented cellulitis associated with lymphoedema. Moreover, Dai *et al.*[13] reported a greater frequency of cellulitis among patients with lymphoedema who had poor access to specialists. In terms of surgical treatment, Karlsson *et al.*[14] documented that performing liposuction and controlled compression therapy can reduce the frequency of cellulitis. A surgical review by Sharkey *et al.*[15] also noted that surgical treatments such as LVA, lymph node transfer, liposuction, and Charles' procedure may prevent cellulitis associated with lymphoedema, although the authors commented that no high-quality RCTs have examined this possibility[16]. Thus, despite the various methods reported for preventing cellulitis associated with lymphoedema, there is currently little evidence that can be used to guide surgical treatment.

To address this issue, the present trial included patients who had undergone at least 3 months of CDT. Nonetheless, there were a few patients in whom CDT alone failed to curb cellulitis. This result supports the notion that LVA is more effective in preventing cellulitis, suggesting that LVA should be recommended for patients with recurrent cellulitis in addition to CDT. However, for patients in whom CDT triggers cellulitis or those with lymphatic vesicles, the authors believe that surgery without full CDT should also be considered.

Nearly all patients in the present study underwent pelvic lymph node dissection, and for many of them the medial thigh

was the first site at which symptoms of lymphoedema appeared. This is the site most directly affected by pelvic lymph node dissection; it can thus be inferred that LVA can assist in reconstructing the lymphatic drainage system more readily than CDT, as the latter is a symptomatic treatment only.

In the present study, the CDT group experienced statistically significantly more adverse events than the LVA group. All adverse events were cases of contact dermatitis caused by the elastic clothing, which can be attributed to the greater number of patients who underwent intensified compression therapy in the CDT group compared with the LVA group (26 *versus* 8). Compression therapy is a standard treatment for lymphoedema and is highly effective. However, when first introduced or when changes are made, the fabric of the elastic garments can produce contact dermatitis or medical device-related pressure ulcers[30]. The contact dermatitis observed in the present study was mild and resolved after treatment with an ointment, although this required continued attention. Although no LVA-related adverse events occurred among the patients in the present RCT, the potential for wound dehiscence, long-term lymphorrhoea, drug allergies, and other events highlights the need for caution when implementing the treatment.

Limitations of the present study include the brevity of follow-up, which was only 6 months. Many patients with frequent cellulitis hope to undergo LVA as quickly as possible. Such patients, if assigned to the CDT group, would find it difficult to proceed with CDT only for an extended period of time. Thus, ethical considerations make a long-term study design challenging. In addition, 68 patients (31.8 per cent) refused the assigned treatment and opted for the other treatment, partly for the abovementioned reasons. Some patients also exhibited fear of, or resistance to, surgery despite being assigned to the LVA group, emphasizing the need to provide proper patient education regarding the procedure.

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Author contributions

Makoto Mihara (CRediT contribution not specified), Hisako Hara (Conceptualization, Data curation), Yohei Kawasaki (Formal analysis, Supervision), Toshiharu Mitsuhashi (Supervision), Hideki Origasa (Supervision), Hirohiko Ando (Conceptualization, Data curation, Formal analysis), and Munekazu Naito (CRediT contribution not specified).

Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

Data availability

Raw data were generated at JR Tokyo General Hospital, Tokyo, Japan. The derived data support the findings of this study and are available from the corresponding author on request.

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