The most common causes of lower extremity pain are of neurological origins, such as lumbar disk herniation and spinal stenosis or of orthopedic origins, such as trauma and osteoarthritis. Cases of lymphedema-associated pain are seldom reported and are often confused with postmastectomy pain syndrome. Studies done in the 1960s suggest the use of antidepressant drugs for symptomatic treatment of lymphedema-associated pain. Vascularized lymph node transfer has also been reported to be effective for reducing upper extremity pain after mastectomy.

In this retrospective study, we evaluated and compared the degree of lower extremity pain before and after the LVA procedure in LEL patients who presented persistent pain over their clinical course. The purpose of this study is to investigate the effectiveness of LVA in reducing lymphedema-associated pain.

**PATIENTS AND METHODS**

We performed a retrospective analysis of the effectiveness of LVA in reducing LEL-associated pain. Subjects of this study included LEL patients who visited the Department of Vascular Surgery, Saiseikai General Hospital, between April 2010 and May 2014 and who presented with persistent and constant degree of pain in their lower limbs for a period of 3 months or longer before the surgery, despite conservative therapy having been performed. Patients who presented with inconsistent degree of pain or whose pain was of orthopedic origin were excluded from this study. Orthopedic surgeons examined...
the patients who formerly had orthopedic diseases and diagnosed the origin of the pain. Additionally, vascular ultrasonography was performed to rule out any venous anomaly.

Lymphoscintigraphy\textsuperscript{11,12} and indocyanine green (ICG) lymphography\textsuperscript{13,14} were used for diagnosing LEL. The results of the lymphoscintigraphy were classified based on the Maegawa classification (Table 1).\textsuperscript{11} The results of the ICG lymphography were classified based on the Yamamoto classification (Table 2).\textsuperscript{15} and patients were labeled as “c” if any dilatation of collateral lymphatic vessels were observed (Table 3). We applied LVA when there were abnormal findings in either ICG lymphography or lymphoscintigraphy. Regions where linear patterns were observed under ICG lymphography were also marked. The pathological classification of the lymphedema was done based on the Classification of International Society of Lymphology.\textsuperscript{15} Moreover, we performed preoperative venous ultrasonography to identify and mark the subcutaneous veins suited for the LVA procedure.

The LVA procedure was performed under local anesthesia in all cases. Skin incisions were made at sites of possible lymph congestion as identified by lymphoscintigraphy and ICG lymphography, and the subcutaneous collecting lymphatic vessels were identified and anastomosed to nearby veins under a surgical microscope using 11-0 or 12-0 nylon microsutures. Additionally, we also classified the collecting lymphatic vessels identified during the surgery using the normal, ectasis, contraction, and sclerosis type (NECST) classification\textsuperscript{16,17} based on intraoperative microscopic visual observations.

Both preoperative lower extremity pain and postoperative lower extremity pain of each patient were surveyed and recorded using the visual analog scale (VAS) on a score from 0 to 10. The preoperative and postoperative circumferences of the affected limbs were also recorded as a secondary outcome measure of the LVA procedure. Limb circumferences were measured essentially at 6 pre-defined sites: dorsum of foot, the ankle, 10 cm below the Limb circumferences were measured essentially at 6 pre-defined sites: dorsum of foot, the ankle, 10 cm below the patella, the patella, 10 cm above the patella, and 20 cm above the patella. Because the number of sites measured was not always consistent before and after the surgery, only measurements that were measured both preoperatively and postoperatively were used in the analysis. To decrease the influence of body weight, we applied LEL index to evaluate the change in circumference.\textsuperscript{18,19} LEL index is calculated as follows: $\text{LEL index} = \frac{\sum \text{(circumference)}^2}{\text{body mass index}}$. The preoperative and postoperative changing rates of the LEL index were then calculated using the equation: changing rate (%) = $\left( \frac{\text{postoperative LEL index} - \text{preoperative LEL index}}{\text{preoperative LEL index}} \right) \times 100$. Statistical analysis about preoperative and postoperative VAS scores and limb circumferences was performed using Student’s $t$ test. All reported $P$ values were based on 2-sided tests, and $P<0.05$ was regarded as significant.

This clinical study was conducted with the approval of the ethical committees at Saiseikai Kawaguchi General Hospital. All patients have provided written informed consent.

### RESULTS

Among a total of 86 LEL cases diagnosed by using lymphoscintigraphy and ICG lymphography during the study period, 8 patients (16 lower limbs) were selected as subjects to this study using the selection criteria mentioned in the Patients and Methods section.

Detailed patient summary is shown in Table 3. The subjects included 1 man and 7 women, with age ranging from 61 to 80 years; their average age was 72 years. Four patients presented with primary lymphedema and the other 4 patients presented with secondary lymphedema whose etiology is shown in Table 1. Pelvic computed tomography imaging or magnetic resonance imaging was performed except for case 8, and pelvic abnormalities such as venous compression or nerve inflammation that may cause limb pain were ruled out. The average postoperative follow-up period was 17 months. CEAP (Clinical manifestation, Etiologic factors, Anatomic distribution, Pathophysiologic dysfunction) level of case 8 was 3 and she did not have skin change.

Preoperative lymphoscintigraphy revealed that 15 out of 16 limbs were in stage 1, of which 12 presented with dilatation of collateral lymphatic vessels (Table 3).

ICG lymphography revealed 14 out of 16 limbs with dilatation of collateral lymphatic vessels. One patient presented diffused pattern in the crus, which indicates severe lymphedema, in addition to the stardust pattern, which indicates mild lymphedema, accompanied by dilatation of the collateral lymphatic vessels in the thigh area (case 7).

A total of 46 collecting lymphatic vessels were used for the LVA procedure, of which 40 were classified as ectasis.

### Table 1. Lymphoscintigraphy Classification of Lower Lymphedema Cases (Maegawa Classification)

| Characteristic Appearance | Normal |
|---------------------------|--------|
| 1 | No lymph stasis or dermal backflow is detected. |
| 2 | Lymph stasis in the lymphatics and visible dermal backflow on the thigh can be seen. The inguinal lymph nodes are reduced in number. |
| 3 | Dermal backflow in the leg and thigh can be seen. |
| 4 | Dermal backflow and lymph stasis in the lymph vessels in the leg can be seen. |
| 5 | There is no obvious dermal backflow in either the leg or the thigh. |

### Table 2. ICG Lymphographic Classification of Lower Lymphedema Cases (Yamamoto Classification)

| Characteristic Appearance | 0 | 1 | 2 | 3 | 4 | 5 |
|---------------------------|---|---|---|---|---|---|
| 0 | No edema or dermal backflow images are detected. |
| 1 | There is a splash pattern around the groin region. |
| 2 | Lymph stasis in the lymphatics and visible dermal backflow on the thigh can be seen. The inguinal lymph nodes are reduced in number. |
| 3 | The stardust pattern extends distally beyond the superior border of the patella. |
| 4 | The stardust pattern is observed throughout the whole limb. |
| 5 | A diffuse pattern becomes evident with presence of the stardust pattern. |
type (87%) via intraoperative microscopic visual observations (Table 4).

Six of the 8 patients used low-pressure compression stockings (nonmedical use) before the surgery; one patient was able to stop their use due to improvement in pain after the LVA procedure. Of the remaining 2 patients, one (case 2) did not use any preoperative compression stockings due to severe pain and did not start their use after the surgery and the other (case 7) used high-pressure compression stockings (medical use) preoperatively and continued their use after the surgery.

The average preoperative and postoperative VAS scores were 5.3 and 1.8, respectively (Table 5), and the scores were significantly reduced postoperatively ($P = 0.0003$). Moreover, 7 patients who had records of their lower extremity circumference observed an average changing rate of $-4.7\%$ in LEL index after the surgery (Tables 5 and 6), which is statistically nonsignificant ($P = 0.182$). The relationship between the difference of preoperative and postoperative VAS scores and the changing rate of preoperative and postoperative LEL indices is shown in Figure 1. The correlation index was $-2.7$, which indicated low correlation ($P = 0.45$).

Table 4. The Intraoperative Microscopic Visual Observations of the Lymphatic Vessels Identified for LVA

| Case | Limb  | No. LVA | NECST Classification |
|------|-------|---------|----------------------|
| 1    | R     | 1       | N E C S               |
| 2    | L     | 2       | 0 1 0 0               |
| 3    | R     | 4       | 0 0 1 0               |
| 4    | L     | 3       | 1 2 0 0               |
| 5    | R     | 3       | 0 3 0 0               |
| 6    | R     | 3       | 0 3 0 0               |
| 7    | R     | 2       | 0 2 0 0               |
| 8    | R     | 2       | 0 1 0 0               |

Each vessel was classified based on the NECST classification. C, contraction type; E, ectasis type; L, left; N, normal type; NECST, normal, ectasis, contraction, and sclerosis type; R, right; S, sclerosis type.

Table 5. The Post-LVA Results

| Case | Location of Pain | VAS Score | Changing Rate (%) | Follow-up (mo) |
|------|-----------------|-----------|-------------------|---------------|
| 1    | Left limb       | 5         | -19.40            | 47            |
| 2    | Left limb       | 7         | -2.7              | 13            |
| 3    | Bilateral limb  | 5         | -0.6              | 17            |
| 4    | Left limb       | 5         | -12.7             | 92            |
| 5    | Bilateral limb  | 5         | -2.3              | 16            |
| 6    | Bilateral limb  | 3         | -0.1              | 12            |
| 7    | Left limb       | 4         | -8.2              | 12            |
| 8    | Bilateral limb  | 5         | NA                | 18            |

Changing rate was calculated using the equation: changing rate (%) = (postoperative LEL index - preoperative LEL index) / preoperative LEL index) × 100. NA, not applicable.
**Fig. 1.** The relationship between the difference of preoperative and postoperative VAS scores and the changing rate of preoperative and postoperative LEL indices. The vertical scale indicates the changing rate of LEL index and the horizontal scale indicates the difference in VAS scores.

**Table 6. Preoperative and Postoperative Circumference Measurement of All Cases**

| Case   | Pre/Post | 20 cm above Knee | 10 cm above Knee | 10 cm below Knee | Ankle | Dorsum Foot |
|--------|----------|------------------|------------------|------------------|-------|-------------|
| 1-Right| Pre      | *                | *                | 40.5             | *     | 22.5        | 22           |
|        | Post     | *                | *                | 36               | *     | 20.5        | 20.2         |
| 1-Left | Pre      | *                | *                | 40               | *     | 22          | 22           |
|        | Post     | *                | *                | 35.5             | *     | 21.2        | 20           |
| 2-Right| Pre      | *                | *                | 36               | *     | 20.7        | 22.7         |
|        | Post     | *                | *                | 35.6             | *     | 21.2        | 23.5         |
| 2-Left | Pre      | *                | *                | 36.7             | *     | 24.5        | 24.5         |
|        | Post     | *                | *                | 36.5             | *     | 21.4        | 23.5         |
| 3-Right| Pre      | *                | *                | 45.3             | 39.3  | 41.2        | 24.4         | 25.1         |
|        | Post     | *                | *                | 48             | 40.5  | 39          | 24           | 26           |
| 3-Left | Pre      | *                | *                | 45.3             | 41.9  | 39.8        | 25.6         | 26.3         |
|        | Post     | *                | *                | 45              | 41    | 29.5        | 25           | 26           |
| 4-Right| Pre      | *                | *                | 45              | 40    | 33.8        | 23.4         | 23.5         |
|        | Post     | *                | *                | 38.5             | 34.5  | 29.5        | 20.5         | 20.5         |
| 4-Left | Pre      | *                | *                | 44.2             | 40.3  | 32.6        | 27           | 25.3         |
|        | Post     | *                | *                | 39.5             | 37    | 30.5        | 21           | 21           |
| 5-Right| Pre      | *                | *                | 43              | 38.2  | 35.2        | 23.6         | 22.7         |
|        | Post     | *                | *                | 43.2             | 35.8  | 34.1        | 21.7         | 21.6         |
| 5-Left | Pre      | *                | *                | 41.7             | 38    | 35.5        | 24.6         | 23           |
|        | Post     | *                | *                | 42.3             | 37.2  | 34          | 22           | 21.2         |
| 6-Right| Pre      | 48.3             | 41               | 35.3             | 32.7  | 33          | 21.3         | 21.5         |
|        | Post     | 49               | 41               | 36               | 33    | 22          | 21.2         |
| 6-Left | Pre      | 54.4             | 48.7             | 39.6             | 34.9  | 22.5        | 21.5         |
|        | Post     | 54               | 44               | 39.8             | 34.5  | 23           | 22.8         |
| 7-Right| Pre      | 50               | 45.6             | 39               | 34.8  | 22           | 23           |
|        | Post     | 49.2             | 41.5             | 38.4             | 34.4  | 25           | 21.4         |
| 7-Left | Pre      | 55.8             | 45.3             | 40.9             | 41    | 26.5        | 23           |
|        | Post     | 58.9             | 49.7             | 42.5             | 42.2  | 24.5         | 20.5         |
| 8-Right| Pre      | *                | *                | *               | *     | *           | *            |
|        | Post     | *                | *                | *               | *     | *           | *            |
| 8-Left | Pre      | *                | *                | *               | *     | *           | *            |
|        | Post     | *                | *                | *               | *     | *           | *            |

Limb circumferences were measured at 6 predefined sites: dorsum of foot, the ankle, 10 cm below the patella, the patella, 10 cm above the patella, and 20 cm above the patella. Because the number of sites measured was not always consistent before and after the surgery, only measurements that were measured both preoperatively and postoperatively were used in the analysis.

* Not applicable.
Case 3

Case 3 was a 69-year-old female patient with no history of previous illness. The patient presented with LEL and associating lower extremity pain (VAS score: 5) 10 months before the surgery. The patient also consulted the orthopedics department and the possibility that the pain originated from orthopedic causes such as knee or spinal disorders was ruled out. Lymphoscintigraphy (Fig. 2A) and ICG lymphography of her lower extremities revealed bilateral lymphatic vessel dilatation and formation of collateral lymphatic vessels (Fig. 2B). Dermal backflow was not observed. From these results, the patient was diagnosed with lymph congestion in both her lower limbs and was indicated for the LVA procedure. Surgery was performed under local anesthesia and LVA was performed at a total of 4 sites on the right and 3 sites on the left (Fig. 3A). During the procedure, the lymphatic vessels identified at all 4 sites on the right limb were classified as ectasis type (Fig. 3B). Lymphatic vessel identified at one of the 3 sites on the left limb was classified as normal type and the ones at the other 2 sites were classified as ectasis type. There were no postoperative complications and the pain subsided gradually from 5 to 1 on the VAS over a 17-month postoperative period. The changing rates of limb circumference were −2.0% on the right and −0.6% on the left, indicating a decrease in tissue edema in both limbs. Postoperative lymphoscintigraphy also showed improved lymph flow and decreased lymph congestion in the regions (Fig. 2C).

Case 7

Case 7 was a 64-year-old female patient with a history of ovarian cancer 3 years prior, who had undergone total hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy. The patient received postoperative chemotherapy but was not given any radiation treatments. Bilateral LEL appeared 1.5 years after the surgery along with gradual pain (VAS score: 4) centralized around the left ankle. Her symptoms failed to show improvement despite massage therapies and the use of compression stockings. Lymphoscintigraphy revealed normal lymph flow in the

Fig. 2. The lymphoscintigraphy result of case 3 30 minutes after the isotope injection. A, Preoperative lymphoscintigraphy results; lymph congestion and lymphatic vessel dilatation can be observed in the bilateral lower extremities. B, Preoperative ICG lymphography results. C, Postoperative lymphoscintigraphy results; improvement in both lymph congestion and vessel dilatation can be observed.
right limb; however, the left limb presented dermal backflows that were centralized below the knee (Fig. 4A). ICG lymphography revealed splash pattern on the right limb and a mixture of stardust and diffuse patterns on the entire left limb, with a higher ratio of diffuse pattern in the crus and a higher ratio of stardust pattern in the thigh area (Fig. 4B). The abdominal area also presented splash pattern under ICG lymphography. Surgery was performed under local anesthesia and LVA was performed at a total of 2 sites on the right and 3 sites on the left. The lymphatic vessels identified at both sites on the right were classified as ectasis type. On the other hand, the lymphatic vessels identified at one of the 3 sites on the left were of ectasis type and the ones at the other 2 sites were of sclerosis type. There were no postoperative complications, and the pain gradually but completely disappeared from 4 to 0 on the VAS over a 12-month postoperative period. The changing rates of limb circumference were −3.2% on the right and +8.2% on the left limb, indicating an improvement in lymph flow on the right only.

**DISCUSSION**

We performed LVA in lymphedema patients presenting with lower extremity pain and observed a significant decrease in the degree of pain in most patients after the surgery.

It is commonly known that lower extremity pain is often associated with blood congestion or varicose veins; however, the detailed pain-causing mechanism is still poorly understood. Some articles have been published to report pain accompanying upper limb lymphedema, and conservative therapy, physiotherapy, or surgical treatment was applied. In some articles, the cause of pain in upper limb lymphedema is presumed to be neurogenic; however, it has not yet been proven. Similarly, much study has yet to be done to fully understand the physiology behind the pain caused by lymphedema and the pain-reducing mechanism of LVA.

One possible theory suggests that lymph congestion results in an increase of lymph pressure within the lymphatic vessels, which may stimulate the nearby sensory nerves to cause pain. This is supported by our experience that patients often feel pain as the contrast medium is injected into their lymphatic vessels during lymphangiography, suggesting possible existence of nociceptors in the lymphatic vessel walls or in nearby tissues. Moreover, in a previous study done by Hara et al, among the lymph-
edema patients who had undergone LVA, only 26% of the lymphatic vessels found during the procedure were of ectasis type, whereas our study showed an obviously high 87%. This result may imply that ectasis-type lymphatic vessels are observed more frequently in lymphedema patients with associating pain, which may be the result of increased lymph pressure.

Furthermore, pain still manifested in patients who did not show any significant dermal backflow under lymphoscintigraphy. ICG lymphography is an examination with a high sensitivity as described in several papers, and it can detect the lymphatic dysfunction presented as splash pattern which cannot be detected by lymphoscintigraphy. However, even if there is not a splash pattern, stage 1 in lymphoscintigraphy indicates lymphatic stasis or increased lymphatic inner pressure.11 The morphologic changes in the collecting lymphatic vessels, which are caused by increased lymphatic inner pressure, have already started even in the linear pattern area.16,17,28 In fact, we observed the abnormally dilated lymphatic vessels intraoperatively. Stage 1 in lymphoscintigraphy is thought to indicate this condition and seems to be sufficient for diagnosing lymphedema. From the results of this study, it may be feasible to infer that a lack of dermal backflow in a lymphedema region suggests a buildup of lymph pressure within the lymphatic vessels, which may have been released as the lymph congestion aggravates and overflows out of the vessels, causing the dermal backflow to appear, resulting in a decrease in lymph pressure and reliev-

Fig. 4. The preoperative lymphoscintigraphy and ICG lymphography results of case 7. A, The lymphoscintigraphy result; the right limb appears normal, but the left limb presents dermal backflow centralized in areas below the knee. B, The ICG lymphography result; splash pattern can be seen near the interior of the thigh on the right limb; a mixture of diffuse and stardust patterns is observed on the entire left limb with a higher ratio of diffuse pattern in the crus and a higher ratio of splash pattern in the thigh area; the lower abdominal area shows a splash pattern.
ing the pain caused by elevated lymph pressure. LVA can improve lymph flow in a lymphedema region by releasing the elevated lymph pressure via the venous bypass, thus relieving the pain in the region.

Another theory suggests that lymph congestion may create tension forces upon the subcutaneous tissue and the epidermis, which is recognized subjectively by the patient as pain. Therefore, performing LVA to reduce the lymph pressure may result in relieving the stress on the surrounding tissue, causing a positive effect in reducing pain in the region. This may be supported by the fact that manual lymph drainage using complex physical therapy is known to have an effect in reducing pain in patients.

Because most patients subjected to this study did not present with severe cases of edema before the LVA procedure, the increase in the circumference was originally very small, which may be the reason why there was no significant correlation between the change in VAS scores and the change in LEL indices.

Usually, sensitivity of ICG lymphography is higher than that of lymphoscintigraphy, but the description was completely opposite (Table 1). One reason for this result may be the physical appearance of the patients. Most of the patients were obese (an average body mass index of 28.8) and the subcutaneous tissue was so thick that ICG lymphography could not make images of lymphatic vessels. On the contrary, lymphoscintigraphy can draw the lymphatic vessels in deep layer, although the resolution is lower than that of ICG lymphography. A combination of ICG lymphography and lymphoscintigraphy is thought to be the best way to diagnose early-stage lymphedema.

Our limitations were that because of the retrospective nature of the study we were unable to evaluate pain in individual sites of the affected limb or the duration of the pain and thus were not able make proper assessment of the LVA effectiveness. Also, evaluating patient pain based on the VAS score inevitably relies on the patient’s subjective symptoms. Preintervention and postintervention analog scale of pain may be somewhat biased for the intervention itself and should have been compared with another intervention. Although we do not have any data to show preconservative and postconservative treatment VAS scores, all of the present cases did not experience improvement in their pain with conservative treatment and thus proceeded to LVA. At least, pain in their lymphedematous limbs decreased after LVA and the patients could reduce the amount of antidepressant drugs. Further studies must be pursued prospectively with a larger number of subjects and with an objective method to measure pain to improve the reliability of the results.

There is another limitation in this study. The changing rates in the right leg of case 2 and the left leg of case 7 were positive, which indicates the worsening of lymphedema. The pain in lymphedema often occurs in the very early stage and decreases when lymphedema deteriorates. It is difficult to know whether the postoperative pain relief is due to LVA or deterioration of lymphedema. In the future, a study in which 2 groups, postoperatively improved lymphedema group and postoperatively worsening lymphedema group, will be compared is needed.

In conclusion, the LVA procedure was effective in reducing the degree of lower extremity pain in lymphedema patients.

Makoto Mihara, MD
Department of Lymphatic and Reconstructive Surgery
Saiseikai Kawaguchi General Hospital
5-11-5 Nishi-Kawaguchi, Kawaguchi-Shi
Saitama 332-0021, Japan
E-mail: mihara.plasticsurgery@gmail.com

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