

Lymphaticovenular anastomosis to prevent cellulitis associated with lymphoedema

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Background: One of the complications of lymphoedema is recurrent cellulitis. The aim was to determine whether lymphaticovenous anastomosis (LVA) was effective at reducing cellulitis in patients with lymphoedema.

Methods: This was a retrospective review of patients with arm/leg lymphoedema who underwent LVA. The frequency of cellulitis was compared before and after surgery. The diagnostic criteria for cellulitis were a fever of 38.5°C or higher, and warmth/redness in the affected limb(s).

Results: A total of 95 patients were included. The mean number of episodes of cellulitis in the year preceding surgery was 1.46, compared with 0.18 in the year after surgery ($P < 0.001$).

Conclusion: LVA reduced the rate of cellulitis in these patients with lymphoedema.

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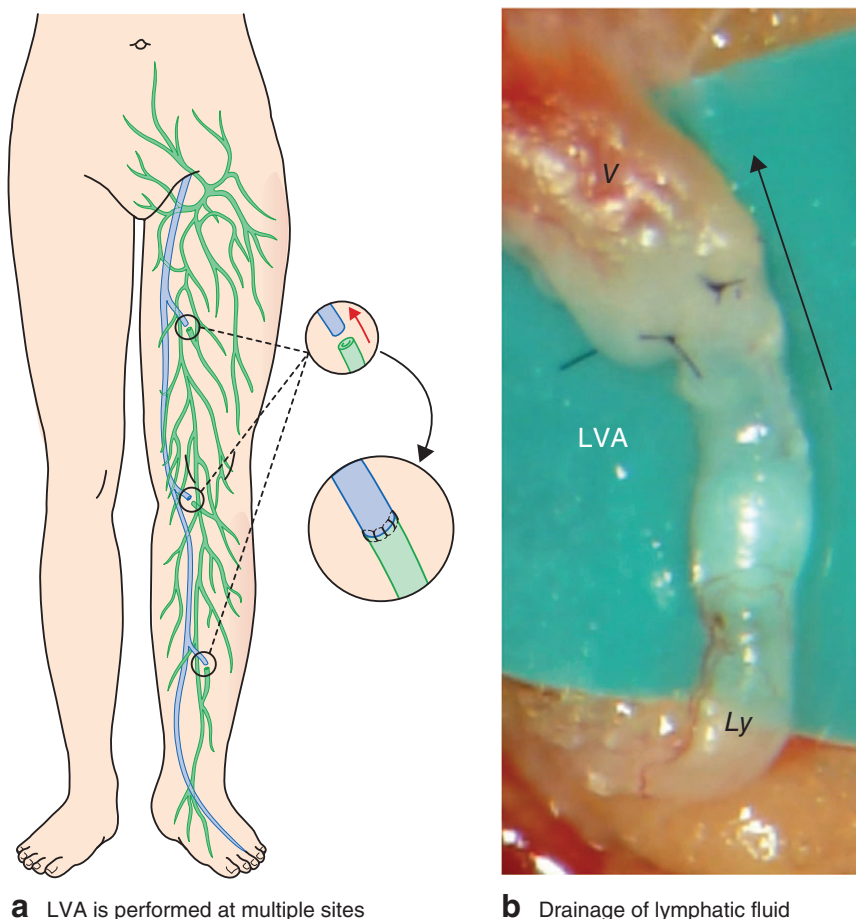
Introduction

Lymphoedema consists of a subcutaneous accumulation of protein-rich fluid caused by dysfunction of the lymphatic system. Primary lymphoedema is caused by congenital hypoplasia or aplasia of lymphatic vessels^{1,2}. Secondary lymphoedema is caused by constriction, stenosis or obstruction of the lymphatic vessels associated with cancer therapy, direct tumour infiltration or infection^{3,4}. Secondary lymphoedema affects 6–63 per cent of patients who have undergone lymph node removal during cancer surgery, or who have received radiotherapy⁵. Worldwide, the most common cause of secondary lymphoedema is infection with a parasitic filarial nematode *Wuchereria bancrofti*, leading to filariasis. This affects nearly 90 million people in 81 countries worldwide, primarily in Africa and South-East Asia⁶.

Although lymphoedema itself is not life-threatening, externally visible changes cause psychological distress⁷. If untreated, significant worsening of oedema can interfere with quality of life, and rarely can lead to lymphangiosarcoma (Stewart–Treves syndrome), which has a poor prognosis⁸.

Another severe complication of lymphoedema is repeated cellulitis of the affected limb, which often requires admission to hospital⁹. Inflammation increases damage to the lymph vessels and causes worsening of the lymphoedema, rendering the patient ever more susceptible to recurrent cellulitis¹⁰. Approximately 23–35 per cent of patients with lymphoedema have this pattern of recurrent, progressive cellulitis^{10,11}. Effective prevention has yet to be determined. Prophylactic antibiotics may protect against cellulitis, but it is not uncommon for cellulitis to reappear the moment they are discontinued, and in some instances cellulitis may occur despite their use^{12,13}.

Efficient lymphatic drainage is considered an important measure for preventing cellulitis. Complex physical therapy (CPT) is now a routine treatment for lymphoedema of the extremities; it not only reduces limb circumference, but also may prevent cellulitis^{14,15}. A surgical treatment that improves lymphatic drainage is lymphaticovenous anastomosis (LVA), where collecting lymphatic vessels are anastomosed to a cutaneous vein under surgical microscopy using 11/0 or 12/0 nylon sutures. LVA is reported to reduce limb diameter and avoid dermal sclerosis^{16–20}. Few reports have addressed the effect of LVA on the rate of cellulitis¹⁷. The



a LVA is performed at multiple sites

b Drainage of lymphatic fluid

Fig. 1 **a** Lymphaticovenous anastomosis (LVA) for leg lymphoedema is usually done at a minimum of three sites. **b** A collecting lymphatic vessel (Ly) is sutured to a cutaneous vein (V) under microscopy. The arrow indicates the direction of lymphatic flow

concomitant use of CPT and LVA may have a synergistic effect on improving lymphatic stasis.

The present study compared the frequency of cellulitis before and after LVA in patients with arm/leg lymphoedema.

Methods

This was a retrospective review of clinical data from the medical records, and information from telephone interviews, concerning the number of preoperative and post-operative episodes of cellulitis among consecutive patients who underwent LVA for lymphoedema at the University of Tokyo Hospital or Saiseikai Kawaguchi General Hospital from September 2005 to April 2012. The diagnostic criteria for lymphoedema were based on the findings from indocyanine green lymphography, as well as limb girth^{21,22}. Lymphoedema was staged using the lymphoedema staging

classification recommended by the International Society of Lymphology²³. The diagnostic criteria for cellulitis were a fever of 38.5°C or higher, and warmth/redness in the affected limb(s). Exclusion criteria were: follow-up of less than 1 year; previous LVA; and use of additional specialized compression therapy (for example multilayer bandaging), but not simple compression after surgery. Where clinically necessary, deep vein thrombosis was excluded by ultrasonography.

LVA was conducted using a previously reported method¹⁶. Briefly, several 0.2–5-cm skin incisions were made in the affected limb, to identify the collecting lymphatic vessels and cutaneous veins of approximately 0.3–1 mm in diameter beneath the skin, followed by end-to-end or end-to-side anastomosis (Fig. 1). Based on previous patency data²⁴, at least three anastomoses were made in each limb. The duration of the operation is about 3–4 h.

Table 1 Patient characteristics and results of lymphaticovenous anastomosis for lymphoedema

	No. of patients	Mean no. of episodes of cellulitis in the year before LVA	Mean no. of episodes of cellulitis in the year after LVA	<i>P</i> *
All patients	95	1.46	0.18	< 0.001
Sex				
M	6	0.67	0.67	–
F	89	1.52	0.15	< 0.001
Location				
Upper limb	11	0.82	0.09	0.100
Lower limb	84	1.55	0.19	< 0.001
International Society of Lymphology stage				
0	3	0.00	0.00	–
1	14	0.00	0.00	–
2a	38	1.39	0.08	0.007
2b	27	1.26	0.22	0.016
3	13	4.00	0.62	0.020
Aetiology				
Primary	7	0.57	0.57	–
Secondary	88	1.53	0.15	< 0.001
Underlying cause				
Cervical cancer	44	2.34	0.18	< 0.001
Uterine cancer	23	0.57	0.09	0.020
Breast cancer	10	0.8	0.10	0.152
Ovarian cancer	4	1.25	0.25	0.250
Other cancer	7	0.86	0.14	0.280
Radiotherapy				
Yes	29	2.72	0.28	0.001
No	59	1.89	0.15	0.003

LVA, lymphaticovenous anastomosis. *Paired *t* test.

Standard CPT^{14,15} for lymphoedema, involving skin care, manual lymph drainage and compression garments, was conducted until just before surgery, and was continued after the operation, depending on the severity of lymphoedema. CPT was discontinued in mild lymphoedema if there was improvement after surgery, but was continued in severe cases. The same antibiotic schedules were used for cellulitis before and after LVA.

Written informed consent was obtained from all patients following the approval of each facility's ethics committee regarding indocyanine green lymphography.

Statistical analysis

The frequency of cellulitis in the year immediately before surgery was compared with that in the following year. A paired two-way Student's *t* test was performed to compare the rates of cellulitis. The significance level was set at 0.050. Patients with longer follow-up were also studied for the mean number of episodes of cellulitis per year thereafter.

Results

Of 124 patients who underwent LVA, 24 had less than 1 year of follow-up and five received additional specialized

compression therapy after surgery, resulting in 95 patients in the present study (*Table 1*). The study included six men and 89 women with a mean age of 57.8 (range 31–90) years; mean follow-up was 27.3 (range 12–57) months. There were 84 patients with leg lymphoedema and 11 with arm lymphoedema; 88 had secondary lymphoedema following cancer treatment, and seven had primary lymphoedema. Three, 14, 38, 27 and 13 patients had lymphoedema stages 0, 1, 2a, 2b and 3 respectively. Three patients underwent simultaneous resection of excess tissue and LVA.

The mean number of episodes of cellulitis in the year preceding surgery was 1.46 (range 0–12), whereas that in the year after surgery was 0.18 (0–3) ($P < 0.001$) (*Table 1*).

The number of episodes of cellulitis following LVA was significantly reduced in women more than in men, the leg compared with the arm, more advanced lymphoedema, secondary compared with primary lymphoedema, and was unaffected by whether or not radiotherapy had been used (*Table 1*). Other subgroups did not reach statistical significance, chiefly owing to smaller sample sizes.

The results of surgery appeared to be sustained, as there was a trend towards reduced cellulitis rates with longer follow-up, although the numbers were small (data not shown).

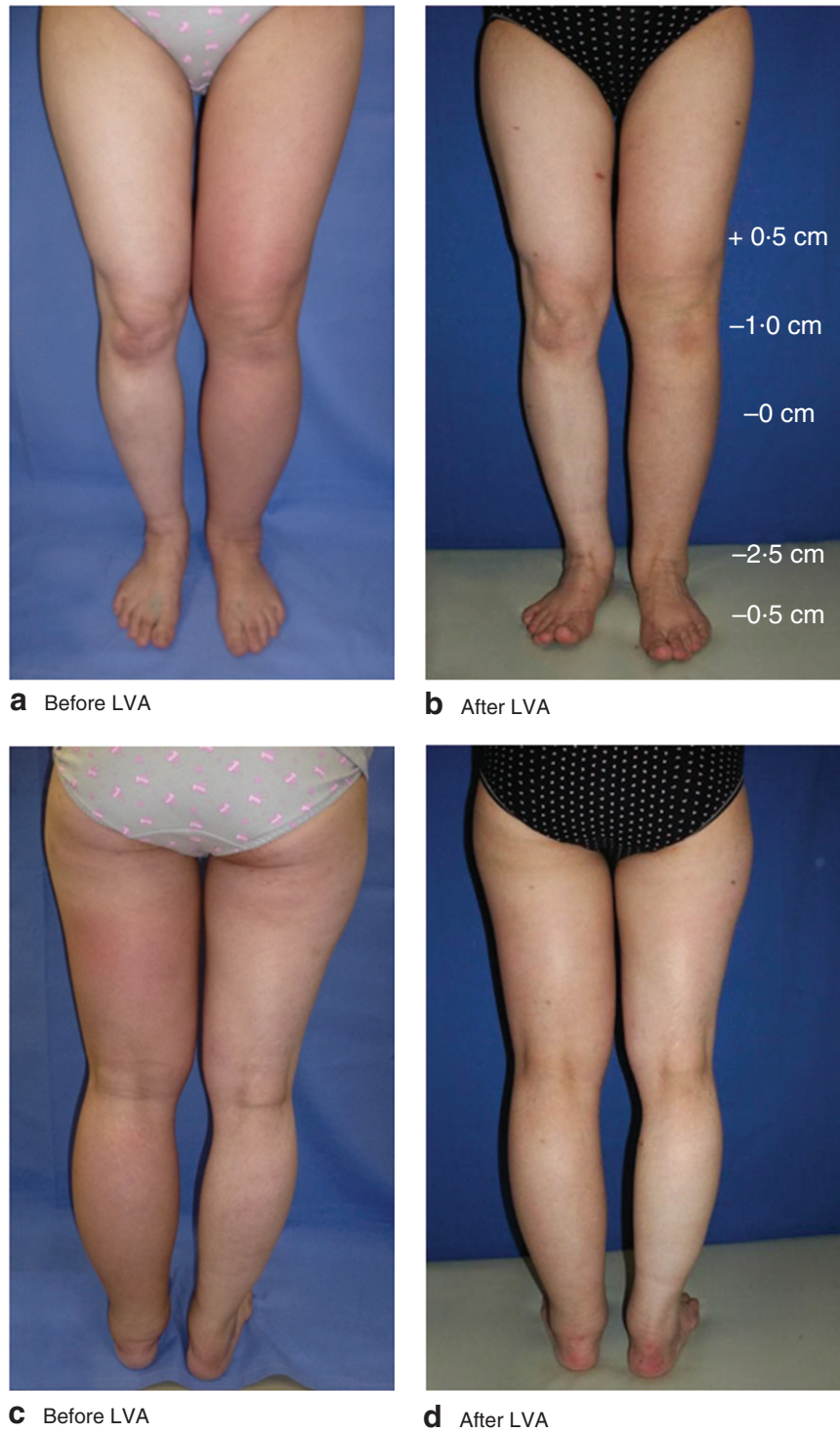


Fig. 2 Clinical appearance **a,c** before and **b,d** 1 year after lymphaticovenous anastomosis (LVA) for lymphoedema of the left leg. Changes in limb diameter are shown in **b**. This patient had 12 episodes of cellulitis in the year before LVA, and none in the year afterwards

Discussion

LVA was first reported as a treatment for chyluria in 1962¹⁹. Since then, it has been reported as a treatment for extremity lymphoedema^{16–20}, facial lymphoedema²⁵, lymphocyst²⁶ and lymphorrhoea²⁷. The procedure is technically challenging, even for surgeons trained in conventional microsurgery. Lymphatic intraoperative fluorescence angiography using indocyanine green has made it possible to find lymph vessels that have retained function²⁸. In addition, newly developed surgical instruments have made possible reliable anastomosis of the lymph vessels and veins^{16,17,29}. The present study demonstrates the effectiveness of LVA for lymphoedema, where surgery resulted in a significant decrease in the rate of cellulitis (Fig. 2).

Definitive prevention of cellulitis in lymphoedema remains uncertain. Standard clinical practice has been to offer prophylactic antibiotics, yet some patients continue to suffer from cellulitis despite the use of penicillin^{12,13}. Cellulitis often recurs after prophylactic penicillin is discontinued. Reduction of oedema through physiotherapy may reduce the frequency of cellulitis¹⁵, but relief may be temporary or limited. In the present study, the number of episodes of cellulitis per year was reduced from a mean 1.46 before LVA to 0.18 after LVA. Initial concerns that the invasiveness of the procedure, or redirecting the lymph into the veins peripherally, might increase the rate of cellulitis or cause systemic bacterial infection seem unfounded.

Bacteria invading the skin are normally detected by dendritic cells and macrophages, leading to their activation and transport along lymphatics to initiate an immune response. In lymphoedema, there is a diminished transport function of the lymph vessels, leading to inefficient priming of the immune system³⁰. LVA may decrease the frequency of cellulitis by restoring lymph circulation in the peripheral tissue. Cellulitis provokes fibrosis of the lymph vessels³¹ and subcutaneous tissue, thus triggering a vicious cycle in which the lymphoedema worsens and cellulitis becomes even more likely to develop; LVA can interrupt this cycle.

Limitations of the present study include its retrospective nature. Further investigation with a controlled study should be conducted. The effects of this treatment for lymphoedema caused by filariasis, which affects a greater number of patients worldwide, will also need to be validated.

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