Side-to-End Lymphaticovenular Anastomosis through Temporary Lymphatic Expansion

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Abstract

Objective: The number of bypasses is the most important factor in lymphaticovenular anastomosis (LVA) for lymphedema treatment. Side-to-end (S-E) LVA, which can bypass bidirectional lymph flows via one anastomosis, is considered to be the most efficient bypass, but creation of lateral window to a small lymphatic vessel is technically demanding. To overcome the difficulty, we introduced S-E anastomosis through temporary lymphatic expansion (SEATTLE) procedure in S-E LVA.

Methods: This was a retrospective observational study set in a teaching hospital. Forty eight lower extremity lymphedema (LEL) patients underwent LVA. S-E LVAs were performed with (SEATTLE group) or without (non-SEATTLE group) temporary lymphatic expansion. S-E LVAs were evaluated to compare anastomosis result in SEATTLE and non-SEATTLE groups.

Results: S-E LVAs resulted in 44 anastomoses in SEATTLE group (n = 25) and 37 anastomoses in non-SEATTLE group (n = 23). LEL index reduction in SEATTLE group was significantly greater than that in non-SEATTLE group (16.5±14.5 vs. 10.9±11.8, P = 0.041). Success rate of S-E LVA in SEATTLE group was significantly higher than that in non-SEATTLE group (95.5% vs 81.1%, P = 0.040). Thirty seven of 44 (84.1%) lymph vessels in SEATTLE group were successfully dilated by temporary lymphatic expansion maneuver. All of 9 failed S-E LVAs used a lymphatic vessel with diameter of 0.35 mm or smaller.

Conclusions: The SEATTLE procedure facilitates S-E LVA by a simple and easy maneuver. When the diameter of the lymphatic vessel is 0.35 mm or smaller even after the temporary lymphatic expansion maneuver, S-E LVA is not recommended due to relatively high failure rate.

Introduction

Treating lymphedema refractory to conservative therapies is a great challenge [1–5]. With development of supermicrosurgery which allows anastomosis of vessels less than 0.5 mm in diameter, supermicrosurgical lymphaticovenular anastomosis (LVA) is becoming the treatment of choice for refractory lymphedema due to its effectiveness and minimal invasiveness [6–14]. Treatment efficacy of LVA has been reported to correlate with the number of lymphaticovenular anastomoses (LVAs) [10,11,13]. It is important to make bypasses not only with normograde distal-to-proximal lymph flow, but also with retrograde proximal-to-distal lymph flow; abnormal retrograde lymph flow always exists in lymphedema patients due to valve insufficiency of the lymphatic vessels [13].

Among various types of LVAs, side-to-end (S-E) anastomosis is considered to be the most efficient bypass, because S-E anastomosis can bypass both normograde and retrograde lymph flows with one anastomosis [11,13]. However, S-E anastomosis is technically more challenging than end-to-end (E-E) or end-to-side (E-S), and cannot be performed by a microsurgeon with less experience of LVA. The procedure’s highest hurdle is creation of a lateral window in the wall of a small lymphatic vessel. In this study, we introduced a new method, temporary lymphatic expansion technique, to facilitate S-E LVA for lower extremity lymphedema (LEL), and evaluated its effectiveness by comparing anastomosis results between S-E LVA with and without the method.

Methods

From July 2009 to August 2010 under the University of Tokyo Hospital ethical committee-approved protocol, 48 bilateral LEL patients (3 males and 45 females) underwent LVA surgery at The University of Tokyo Hospital, Japan. All patients included in this study received compression therapy using elastic stockings, and suffered from progressive lymphedema refractory to conservative therapy. The etiology of LELs consisted of primary lymphedema (n = 6), uterine cervical carcinoma (n = 18), uterine corpus carcinoma (n = 13), ovarian cancer (n = 6), rectal carcinoma (n = 2), prostatic carcinoma (n = 1), malignant lymphoma (n = 1), and bladder cancer (n = 1). Patients’ age ranged from 25 to 71.
years old (median, 49 years old), duration of edema ranged from 8 to 216 months (median, 66 months), International Society of Lymphology stage ranged from 1 to 3 (11 in stage 1, 34 in stage 2, and 3 in stage 3) [15]. All patients gave written consents to this retrospective observational study.

LVA Procedures

Incision sites were decided based on preoperative indocyanine green (ICG) lymphography findings, and 2-cm long incisions were usually made around the inguinal regions, the knees, and the ankles along the greater saphenous veins [16–21]. After detection of lymphatic vessels and venules suitable for anastomoses, lymphatic vessels were anastomosed to venules using 11-0 or 12-0 nylon [11,13,22–25]. Successful LVA is defined by confirmation of patency under an operating microscope, in which lymph-blood border movement across the site of anastomosis is observed. All S-E LVAs were performed by one surgeon (T.Y.). One week after LVA surgery, patients resumed the same conservative therapies as performed preoperatively. After January 2010, side-to-end anastomosis through temporary lymphatic expansion (SEATTLE) procedure was employed in S-E LVA.

SEATTLE Procedures (Video S1)

Shortly before performing a S-E anastomosis, the lymphatic vessel was clamped proximal to the anastomosis site, and the limb distal to the site was manually massaged to bring lymph fluid to the region, thus expanding the lymphatic vessel (Figure 1A & 1B). The lymphatic vessel became dilated to 0.70 mm in diameter via clamping and the massage, allowing easier creation of a window for S-E anastomosis, one of the most difficult procedures in S-E anastomosis (Figure 1C). A window for anastomosis is created using microscissors (D). Successful creation of the window appropriate for anastomosis allows safe and easy S-E anastomosis (E). After completion of the SEATTLE procedure, patency of the anastomosis is confirmed by observing movement of lymph-blood border under an operating microscope (F). In this anastomosis, blood temporarily flowed into the lymphatic vessel (arrow heads), then the lymph-blood border moved to the venule (arrow).

Data Collection and Statistical Analysis

Patient characteristics, operative findings, and pre- and post-operative lymphedematous volume were collected and evaluated retrospectively. Forty eight LEL patients who underwent S-E LVAs were divided into SEATTLE group and non-SEATTLE group; patients who underwent S-E LVAs with temporary lymphatic expansion maneuver were classified into SEATTLE group, and patients who underwent S-E LVAs without temporary lymphatic expansion maneuver into non-SEATTLE group. Edematous volume was evaluated preoperatively and 6 months after the operations using lower extremity lymphedema (LEL) index [26]. A summation of squares of circumferences C1, C2, C3, C4, and C5 (cm) divided by body mass index (BMI) is defined as the LEL index. C1 denotes circumference at 10 cm above the superior border of the patella, C2 circumference at the lateral malleolus, and C3 circumference at the dorsum of the foot. LEL index reduction after LVA surgery in SEATTLE group and non-SEATTLE group, success rate of S-E anastomosis and successful dilatation of lymph vessels by temporary lymphatic expansion maneuver in the SEATTLE group were evaluated. Chi-square
test, paired Student’s t test, and Mann-Whitney U test were used appropriately for statistical analysis. The numbers after the plus-minus signs are the standard deviations. Statistical significance was defined as a P-value <0.05.

**Results**

Patient demographics were shown in Table 1. S-E LVAs resulted in 37 S-E LVAs without temporary lymphatic expansion maneuver on 23 patients (non-SEATTLE group), and 44 S-E LVAs with temporary lymphatic expansion maneuver on 25 patients (SEATTLE group). In non-SEATTLE group, LEL index 6 months after LVA ranged from 190 to 288, and significantly decreased compared with preoperative LEL index (240.2±25.1 vs. 251.0±28.6, \( P<0.001 \)) (Figure 2). LEL index reduction in SEATTLE group was significantly greater than in non-SEATTLE group (16.5±14.5 vs. 10.9±11.8, \( P=0.041 \)). There was no statistically significant difference in LEL index reduction between primary and secondary lymphedema cases (18.2±15.9 vs. 13.2±13.1, \( P=0.316 \)).

Comparison of intraoperative findings between non-SEATTLE and SEATTLE groups revealed significant differences in diameter of lymph vessel after expansion maneuver (0.492±0.177 vs. 0.602±0.230, \( P=0.017 \)) and success rate of S-E anastomosis (81.1% vs. 95.5%, \( P=0.040 \)) (Table 2). Thirty-seven of 44 (84.1%) lymph vessels in SEATTLE group were successfully dilated by temporary lymphatic expansion maneuver, and diameter of lymph

![Figure 2. A 54-year-old female suffered from International Society of Lymphology stage 2 lower extremity lymphedema (LEL), whose LEL index of the left leg was 284 (left). Two side-to-end lymphaticovenular anastomoses were performed with temporary lymphatic expansion technique on the left leg. Six months after the operation, her left leg decreased in size, resulting in decrease of LEL index to 258 (right).](diagram.png)
vessels after expansion were significantly larger than those before the maneuver (0.602 ± 0.230 vs. 0.481 ± 0.195, \( P < 0.001 \)). No obvious adverse effect was observed due to temporary lymphatic expansion maneuver, such as obstruction or stenosis of a lymphatic vessel at the site of clamping. Nine of 81 S-E LVAs resulted in anastomosis failure; 7 of which were in non-SEATTLE group, and 2 of which were in SEATTLE group (Table 3). All of 9 failed S-E LVAs used a lymphatic vessel with diameter of 0.35 mm or smaller, and were re-anastomosed in an E-E or E-S fashion; 6 of which were successfully re-anastomosed, but 3 of which resulted in re-anastomosis failure. The main reason for the re-anastomosis failure was the shortness of vessels’ length after removal of the failed anastomosis sites.

### Discussion

This study revealed that SEATTLE procedure improved success rate of S-E LVA, and that volume reduction in SEATTLE group was significantly greater than that in non-SEATTLE group. SEATTLE procedure successfully dilates less-sclerotic lymphatic vessels by a simple and easy maneuver, which only requires clamping and manual massage without harmful effect on lymphatic vessels. Although dilatation of a lymphatic vessel is temporary, this temporary lymphatic expansion maneuver dilates the vessel by about 0.12 mm, making creation of a lateral window in a lymphatic vessel much easier.

LVA requires superspecialized techniques, and anastomosis of vessels with diameter of around 0.5 mm. To facilitate technically demanding superspecialized anastomosis, several stenting methods have been reported; a nylon thread is inserted into a lymphatic vessel to keep the vessel’s lumen open [11,13,22]. Using stenting methods, a surgeon can anastomose lymphatic vessels with more ease and confidence. Although several technical refinements in anastomosis have been reported, no technique for lymphotomy in S-E LVA has been reported. For microsurgeons with experience of LVA surgery, anastomosing lymphatic vessels is not especially difficult, but lymphotomy, creating a window on a lymphatic vessel is challenging. It is difficult to create a window in a small lymphatic vessel, so a larger lymphatic vessel is favorable to be used in a S-E LVA [11,13]. Successful window creation is the key to establishment of a successful S-E LVA. If the window is too large relative to the diameter of the lymphatic vessel, the

### Table 1. Patient demographics in SEATTLE and non-SEATTLE group.

|                | non-SEATTLE (n = 23) | SEATTLE (n = 25) |
|----------------|----------------------|-----------------|
| Age (years old)a | 25–71 (48)          | 26–70 (52)      |
| Gender          | female               | female          |
|                | 21 (91.3%)           | 24 (96.0%)      |
|                | male                 | male            |
|                | 2 (8.7%)             | 1 (4.0%)        |
| Duration of edema (months)a | 8–192 (60) | 12–216 (72) |
| ISL stage       | stage 1              | stage 1         |
|                | 6 (26.1%)            | 5 (20.0%)       |
|                | stage 2              | stage 2         |
|                | 16 (69.6%)           | 18 (72.0%)      |
|                | stage 3              | stage 3         |
|                | 1 (4.3%)             | 2 (8.0%)        |
| Etiology of lymphedema | primary            | secondary       |
|                | uterine cervical carcinoma | 8 (34.8%) | 10 (40.0%) |
|                | uterine corpus carcinoma | 5 (21.7%) | 8 (32.0%) |
|                | ovarian cancer       | ovarian cancer  |
|                | 4 (17.4%)            | 2 (8.0%)        |
|                | other cancersb       | other cancersb  |
|                | 2 (8.7%)             | 3 (12.0%)       |

SEATTLE, side-to-end anastomosis through temporary lymphatic expansion. ISL, International Society of Lymphology. Data are counts (percentages) otherwise indicated.
aData are ranges (medians).
bOther cancers include rectal carcinoma, prostatic carcinoma, malignant lymphoma, and bladder cancer.
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### Table 2. Comparison of intraoperative findings between non-SEATTLE and SEATTLE groups.

|                | non-SEATTLE (n = 37) | SEATTLE (n = 44) | P-value |
|----------------|----------------------|-----------------|---------|
|                | Mean ± SD            | Mean ± SD       |         |
| Elapsed time (minute) for anastomosis | 10.6 ± 3.5 | 10.3 ± 3.8a | 0.739   |
| Diameter of lymphatic vessel before expansion maneuver (mm) | 0.492 ± 0.177 | 0.481 ± 0.195 | 0.787   |
| Diameter of lymphatic vessel after expansion maneuver (mm) | -- | 0.602 ± 0.230 | 0.017b  |
| Diameter of venule (mm) | 0.461 ± 0.223 | 0.443 ± 0.244 | 0.735   |
| Success ratec | 30/37 (81.1%) | 42/44 (95.5%) | 0.040   |

SEATTLE, side-to-end anastomosis through temporary lymphatic expansion; SD, standard deviation.
aIncluding time for clamping and manual massage.
bCompared with diameter of lymph vessel before expansion maneuver in non-SEATTLE group.
cData are counts (percentages).
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disposition of the vessels tends to be tortuous, resulting in poor patency. Higher success rate of S-E LVA in SEATTLE group than that in non-SEATTLE group suggests that the temporary expansion maneuver plays an important role in improving anastomosis result of S-E LVA. S-E LVA is the most recommended type of anastomoses and should be considered as the first choice whenever possible, because it can make bidirectional lymph flow bypasses in one anastomosis, preserve a native recipient lymph flow, and show less venous backflow after anastomosis [10,11,13]. However, S-E LVA is technically difficult, especially when diameter of a lymphatic vessel is 0.35 mm or less. As shown in Table 3, all failed S-E LVAs used lymphatic vessels with diameter of 0.35 mm or less. Failure in primary S-E LVA makes secondary end-to-end (E-E) or end-to-side (E-S) anastomosis more difficult than the primary anastomosis. This is because the lymphatic vessel and the venule become shorter after removal of the failed anastomosis site.

We recommend following strategy in selecting anastomosis type. First, temporary expansion maneuver should be performed. Then, a S-E LVA should be employed when diameter of a lymphatic vessel is larger than 0.35 mm; otherwise an E-E or E-S LVA should be selected.

Major limitations of this study are that this study was a retrospective observational study, and that the effectiveness of our technique is not supported by long-term results or anastomosis patency. Our previous reports revealed short-term and long-term effectiveness of LVA surgery using various types of anastomoses [7–9,12,13]. Since volume reduction after LVA surgery results from bypassing congested lymph into venous circulation, anastomosis patency would be the most important prognostic factor, and should be evaluated postoperatively. Although this study revealed significant positive effect on volume reduction by SEATTLE procedure compared with S-E LVA without temporary lymphatic expansion, further prospective controlled studies are needed to clarify long-term effectiveness of the procedure evidenced with long-term anastomosis patency.

Conclusions
The SEATTLE procedure facilitates successful S-E LVA by a simple and easy maneuver. To avoid anastomosis failure, S-E LVA should not be employed when diameter of the lymphatic vessel is 0.35 mm or smaller after temporary lymphatic expansion maneuver.

Supporting Information

Video S1 A lymphatic vessel with diameter of 0.45 mm and a venule with diameter of 0.60 mm are prepared for anastomosis. The lymphatic vessel is clamped proximal to the anastomosis site, and the limb distal to the anastomosis site is massaged to expand the lymphatic vessel. The lymphatic vessel becomes dilated to 0.70 mm in diameter via clamping and the massage, allowing easier creation of a window for S-E anastomosis. A window for anastomosis is created using microscissors. Successful creation of the window appropriate for anastomosis allows safe and easy S-E anastomosis. After completion of the SEATTLE procedure, patency of the anastomosis is confirmed by observing a movement of lymph-blood border under an operating microscope. In this anastomosis, blood temporally flowed into the lymphatic vessel, then the lymph-blood border moved to the venule.

(WMV)

Author Contributions
Conceived and designed the experiments: TY HY. Performed the experiments: TY HY MN NY TI IK. Analyzed the data: TY NY. Contributed reagents/materials/analysis tools: TY NY. Wrote the paper: TY NY.

References
1. Szuba A, Cooke JP, Yousef S, Rockson SG (2000) Decongestive lymphatic therapy for patients with cancer-related or primary lymphedema. Am J Med 109: 296–300.
2. Warren AG, Bronson H, Borud LJ, Slavin SA (2007) Lymphedema: a comprehensive review. Ann Plast Surg 59(4): 464–72.
3. Armer J (2000) The problem of post-breast cancer lymphedema: impact and measurement issues. Cancer Invest 23: 76–83.
4. Devoogdt N, Van KM, Geraerts I, Coremans T, Christiaens MR (2010) Different physical treatment modalities for lymphedema developing after axillary lymph node dissection for breast cancer. Eur J Obstet Gynecol Reprod Biol 149(1): 3–9.
5. McNeely ML, Peddle CJ, Yuick JL, Days IS, Mackey JR (2011) Conservative and dietary interventions for cancer-related lymphedema: a systematic review and meta-analysis. Cancer 117(6): 1136–48.
6. Yamada Y (1969) Studies on lymphatic-venous anastomoses in lymphedema. Nagoya J Med 32: 1–21.
7. Koshima I, Inagawa K, Urushibara K, Morijuchi T (2000) Supermicrosurgical lymphaticovenular anastomosis for the treatment of lymphedema in the upper extremities. J Reconstr Microsurg 16: 432–7.

8. Koshima I, Nanba Y, Tsutsui T, Takahashi Y, Itoh S (2003) Long-term follow-up after lymphaticovenular anastomosis for lymphedema in the leg. J Reconstr Microsurg 19: 209–15.

9. Koshima I, Nanba Y, Tsutsui T, Takahashi Y, Itoh S, et al. (2004) Minimal invasive lymphaticovenular anastomosis under local anesthesia for leg lymphedema: is it effective for stage III and IV? J Reconstr Microsurg 20: 261–6.

10. Nagase T, Gonda K, Inoue K, Higashino T, Fukuda N, et al. (2005) Treatment of lymphedema with lymphaticovenular anastomoses. Int J Clin Oncol 10: 304–10.

11. Narushima M, Mihara M, Yamamoto Y, Iida T, Koshima I, et al. (2010) The intravascular stenting method for treatment of extremity lymphedema with multiconfiguration lymphaticovenous anastomoses. Plast Reconstr Surg 125: 935–43.

12. Chang DW (2010) Lymphaticovenular bypass for lymphedema management in breast cancer patients: a prospective study. Plast Reconstr Surg 126(3): 752–6.

13. Yamamoto T, Narushima M, Kikuchi K, Yoshimatsu H, Todokoro T, et al. (2011) Lambda-shaped anastomosis with intravascular stenting method for safe and effective lymphaticovenular anastomosis. Plast Reconstr Surg 127(3): 1907–92.

14. Yamamoto T, Koshina I, Yoshimatsu H, Narushima M, Mihara M, et al. (2010) Simultaneous multi-site lymphaticovenular anastomoses for primary lower extremity and genital lymphedema complicated with severe lymphorhea. J Plast Reconstr Aesthet Surg 64(6): 812–5.

15. International Society of Lymphology (2009) The diagnosis and treatment of peripheral lymphedema. 2009 consensus document of the international society of lymphology. Lymphology 42(2): 51–60.

16. Yamamoto T, Narushima M, Doi K, Oshima A, Ogata F, et al. (2011) Characteristic indocyanine green lymphography findings in lower extremity lymphedema: the generation of a novel lymphedema severity staging system using dermal backflow patterns. Plast Reconstr Surg 127(5): 979–96.

17. Yamamoto T, Iida T, Matsuda N, Kikuchi K, Yoshimatsu H, et al. (2011) Indocyanine green (ICG)-enhanced lymphography for evaluation of facial lymphoedema. J Plast Reconstr Aesthet Surg 64(11): 1541–4.

18. Yamamoto T, Yamamoto N, Doi K, Oshima A, Yoshimatsu H, et al. (2011) Indocyanine green-enhanced lymphography for upper extremity lymphedema: a novel severity staging system using dermal backflow patterns. Plast Reconstr Surg 128(4): 941–7.

19. Yamamoto T, Matsuda N, Doi K, Oshima A, Yoshimatsu H, et al. (2011) The earliest finding of indocyanine green lymphography in asymptomatic limbs of lower extremity lymphedema patients secondary to cancer treatment: the modified dermal backflow stage and concept of subclinical lymphedema. Plast Reconstr Surg 128(4): 314e–21e.

20. Yamamoto T, Narushima M, Yoshimatsu H, Yamamoto N, Oka A, et al. Indocyanine green velocity: Lymph transportation capacity deterioration with progression of lymphedema. Ann Plast Surg (in press).

21. Yamamoto T, Narushima M, Yoshimatsu H, Yamamoto N, Kikuchi K, et al. Dynamic indocyanine green lymphography for breast cancer-related arm lymphedema. Ann Plast Surg (in press).

22. Yamamoto T, Yoshimatsu H, Narushima M, Yamamoto N, Koshima I Split intravascular stents for side-to-end lymphaticovenular anastomosis. Ann Plast Surg (in press).

23. Yamamoto T, Narushima M, Yoshimatsu H, Seki Y, Yamamoto N, et al. (2012) Minimally invasive lymphatic supermicrosurgery (MILS): indocyanine green-guided simultaneous multi-site lymphaticovenous anastomoses via millimeter skin incisions. Ann Plast Surg Dec 13 [Epub ahead of print].

24. Yamamoto T, Yoshimatsu H, Narushima M, Seki Y, Yamamoto N, et al. (2012) A modified side-to-end lymphaticovenular anastomosis. Microsurgery Sep 14 [Epub ahead of print].

25. Yamamoto T, Yoshimatsu H, Narushima M, Yamamoto N, Shim TWH, et al. (2012) Sequential anastomosis for lymphatic supermicrosurgery: multiple lymphaticovenular anastomoses on one vein. Ann Plast Surg Dec 13 [Epub ahead of print].

26. Yamamoto T, Matsuda N, Todokoro T, Yoshimatsu H, Narushima M, et al. (2011) Lower extremity lymphedema index: a simple method for severity evaluation of lower extremity lymphedema. Ann Plast Surg 67(6): 637–40.