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Long-term Results of Microvascular Lymph Node Transfer: Correlation of Preoperative Factors and Operation Outcome

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Background: Our objective was to analyze whether a correlation could be observed between preoperative factors and microvascular lymph node transfer outcome after long-term follow-up.
Methods: We included 67 patients in this retrospective case series. The incidence of cellulitis, the difference of arm circumference, the use of the compression garments both preoperatively and postoperatively, and subjective symptoms, such as pain, were analyzed. Volumetry and lymphoscintigraphy results were also analyzed in a subgroup of patients. We correlated preoperative factors with postoperative results.
Results: After 70 ± 17 months of follow-up, 42% of the patients were able to discontinue the use of compression garments. The subjective pain symptoms were reduced in 75% of the patients. The incidence of cellulitis was reduced from preoperative 0.20 ± 0.55/y to postoperative 0.02 ± 0.08/y. As a novel finding, the patients with preoperative cellulitis were more likely to continue the use of the compression garments.
Conclusions: The surgery is beneficial to most studied lymphedema patients, although it is not the cure for all patients. The incidence of cellulitis was reduced, and further, the presence of preoperative cellulitis seems to affect the outcome of the operation. *(Plast Reconstr Surg Glob Open 2021;9:e3354; doi: 10.1097/GOX.0000000000003354; Published online 22 January 2021.)*

INTRODUCTION

Lymphedema is a progressive disease characterized by the accumulation of interstitial fluid leading to pitting edema of the affected limb, later accompanied by the proliferation of irreversible fibroadipose tissue and nonpitting edema.[1] Lymphedema may occur after breast cancer surgery-related axillary lymph node dissection (incidence: 19.9%), sentinel node biopsy (incidence: 5.6%), radiation therapy, or trauma.[2] The dissection of lymphatic vessels and lymph nodes during surgery may impair the lymphatic fluid flow and thereby induce lymphedema.[1,3] Lymphedema has a negative influence on the quality of life of affected patients.[4]

Treatment of lymphedema is based on manual lymphatic drainage and compression garments, which are effective in early-stage lymphedema.[5] Patients at later stages do not respond well to conservative treatment because of the hypertrophic tissue.[6] Microvascular lymph node transfer (VLNT) is a fairly new reconstructive surgical method.[7–9] The aim is to induce the regeneration of the lymphatic pathways by surgically removing scar tissue and bringing healthy lymphatic tissue, lymph nodes, and fat tissue from the groin area into the axilla. Other donor and recipient sites can also be used.[10] Lymphatic vessels have been proven to have tremendous ability to regenerate and can be formed without surgical intervention.[11,12] There have been studies suggesting that effective scar removal alone may improve the lymphatic flow. Compression of the axillary vein, due to a scar contracture, may be a cause of postoperative edema.[13] Even though VLNT is gaining popularity, results are varying as well as difficult to analyze and compare due to the

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variability in operation techniques, compression treatment protocols, and patient material.[14]

Our aim was to evaluate the long-term results of the influence of VLNT surgery. Further we analyzed preoperative factors to improve the patient selection process to gain the best possible result for patient management.

PATIENTS AND METHODS

Patients

We performed a retrospective case series that included a total of 67 patients. The patients were operated on either in Turku University Hospital (TYKS) between May 2007 and April 2015 or in Helsinki University Central Hospital (HYKS) between June 2009 and November 2013. All patients who underwent VLNT or VLNT with simultaneous breast reconstruction (BR) in the upper arm were included in this study, except for 2 who were excluded due to insufficient data. All patients suffered from lymphedema after breast cancer-related surgery.

We evaluated the results of 28 of 30 patients operated on in TYKS and 39 of 39 patients operated on in HYKS. Forty-six of 67 patients underwent the VLNT-BR, and 21 of 67 patients underwent the VLNT.

Our study group has previously published the results of some of the patients (28 of 67), but in this study, we have a different approach to the analyses of the results.[11,15-17]

Study Design

Our study design was approved by the Ethics Committee of Turku University Hospital. We gathered the study data with a permit from the local ethical community.

The following parameters were collected: the duration of lymphedema preoperatively, the number of cellulitis preoperatively and postoperatively, the need for prophylactic antibiotics, the use of compression garments (hours/day), and the extent of scar tissue in the axilla during the surgery. The extent of the scar tissue was a subjective evaluation by experienced surgeons. The following subjective parameters were also used (evaluated by the patient): the pain and function of the affected arm. The subjective parameters were categorized into either a negative or a positive outcome.

Patients underwent preoperative and postoperative measurements of arm circumference, and a subgroup of patients was also measured for volumetry of upper extremities and lymphoscintigraphy.

Surgical Method

VLNT begins with the search of the lower abdominal wall perforator vessels and the pedicle vessel in the inguinal area with a portable ultrasound device (Dopplex D900; Huntleigh Healthcare Ltd, United Kingdom). Preoperative computed tomography angiography was used in the VLNT-BR patients operated on in HYKS (25/39, 64%). The first operated patients underwent (20/67, 30%) visualization of the lymphatic vessels and lymph nodes using 0.5 ml of Patent Blue (Guerbet, Roissy CdG Cedex, France). Patent Blue was injected intradermally above the iliac crest.

The lymphatic flap was dissected from lateral to medial direction. This approach allows identification of the superficial circumflex iliac vessels or its perforators and the superficial inferior epigastric vessels. These vascular pedicles were later anastomosed to the thoracodorsal vessels, and lymph vessels were not anastomosed. Dissection of the flap was limited to the lateral border of the femoral vessels because most of the sentinel lymph nodes are located medial to the femoral artery.[18] If a simultaneous BR was performed, the flap was then continued to include the abdominal tissue flap, as specified below.

The BR was made using either the deep inferior epigastric perforator flap (21/46), the superficial inferior epigastric artery (4/46), or the muscle-sparing transverse rectus abdominis myocutaneous flap (21/46). The VLNT-BR was performed as has been previously described.[1,8,19] All possible scar constriction around the axillary vessels was released and excess scar tissue excised.

Lymphoscintigraphy

Thirty percent (20/67) of the patients underwent both preoperative and postoperative arm lymphoscintigraphy. We excluded the results from the patients without preoperative imaging to minimize bias. Both hands (between the first and second digit) were injected intradermally with 40 MBq of technetium-labeled sulfur nanocolloid (99mTc-Nanocoll; GE Healthcare Ltd, Italy) in the volume of 0.1–0.2 ml. The imaging was performed with Infinia Hawkeye single-photon emission computed tomography/computed tomography (General Electric Medical Systems, Milwaukee, Wis.) as previously explained.[9] We used the semiquantitative transport index (TI) of the operated arm in the analysis of the results. The TI value was calculated as previously described.[20] A TI value of over 10 was considered to be the borderline for pathological lymphatic function.

Volumetry and Circumference Measurements

The subgroup of 12 patients underwent upper extremity volumetry measurements. The arm circumference was measured at 4 cm intervals from the distal end of the ulna to proximal direction of both upper limbs on 12 different sites in these patients. The edema volume was calculated using Brorson's truncated cone model.[21] If volumetry was not performed, the arm circumference measurements were taken from fewer points: 12, 20, 28, 36, and 44 cm from the distal end of the ulna, and an average circumference difference was calculated. The contralateral arm of the patient was used as a control. Measurements were taken preoperatively and 6, 12, 24, and 36 months postoperatively, if possible. If the patient did not have both, a preoperative and a postoperative measurement, the result was excluded.

Postoperative Care and Follow-up

The perfusion of the VLNT flap was monitored for 3 postoperative days, using an axillary skin island for the patients operated on in HYKS or a tissue oxygen sensor (Licox; Integra, Germany) in TYKS. Postoperative care was carried out as previously reported.[11] All patients used

compression garments on the operated arm for at least 6 months after the operation, unless contraindicated due to patient-related reasons (3/67). Manual lymphatic drainage was started approximately 4 weeks after the surgery and continued on average 22 months after the surgery. The follow-up visits were 1, 3, 6, 12, 24, and 36 months after the surgery, if possible.

Statistical Analysis

Statistical analysis was done using GraphPad Prism 7 software. Students 2-tailed *t* test was used to compare differences between the groups for continuous variables, which follow a normal distribution. The postoperative results were correlated with the preoperative parameters and patient- and operation-related variables to identify factors predicting a good outcome of the surgery. Correlation analysis was done either with a Pearson or with a Spearman correlation coefficient, depending on the data normality. Kruskal–Wallis analysis of variance test followed by Dunn's multiple comparison test was performed to compare the preoperative measurements between the different compression garment usage groups. The *P* value of <0.05 was considered to be statistically significant. Results of statistically significant data are reported.

RESULTS

Patient Characteristics

Adequate data were available from 67 of the 69 operated patients. Patient characteristics are listed in Table 1.

The flap-related complications were reported in 24% (16/67) of the patients, which were hematoma (9%, 6/67), reanastomosis (7%, 5/67), and medial BR flap necrosis (16%, 11/67). Complications occurred either immediately, 1–2 days (28%, 19/67), or more than 1 week after the surgery (16%, 11/67). One patient lost the BR flap on the 12th postoperative day, but the VLNT flap was salvaged. No VLNT flaps were lost during the follow-up time. Twelve patients (18%, 12/67) had a postoperative complication in the donor site, including poor wound healing (15%, 10/67), infections (7%, 5/67), and loss of sensation in the upper thigh (3%, 2/67) (Table 2). Lymphedema of the donor limb was not detected during the follow-up. Ten patients (15%, 10/67) had seroma fluid drainage after the surgery, on average 2 ± 2 times.

Lymphoscintigraphy

Lymphoscintigraphy was performed preoperatively on the subgroup of 32 of 67 patients. On average, the patients had a preoperative TI value of 29.3 ± 14.4. The TI value decreased during 2 years of follow-up to 20.9 ± 14.2, reflecting a better lymphatic function. After 3 or more years of follow-up, the TI value slightly increased but still was at a lower level than preoperatively, 26.0 ± 14.2 (Fig. 1). The patients with the smaller preoperative TI values also had smaller postoperative TI values. This correlation was statistically significant ($r = 0.5497$; 95% confidence interval [CI], 0.1278–0.8031; $P = 0.0120$).

Table 1. Preoperative Patient Characteristics

Variable	Patients (n = 67)
Age, y	52 (±8)
BMI, kg/m²	26.5 (±3.3)
Diabetes	2 (3.0)
Smoking	0 (0.0)
Primary cancer surgery	
Breast lumpectomy	46 (68.7)
Mastectomy	21 (31.3)
Duration of preoperative lymphedema, mo	42 (±30)
Follow-up time, mo	70 (±17)

Data are presented as number of patients (percentages) or mean (±SD). BMI, body mass index.

Table 2. Patient Variables after VLNT Surgery

Variable	Patients (n = 67)
Postoperative complications	34 (50.7)
Immediate	17 (25.4)
Delayed (arm)	19 (28.4)
Delayed (groin)	16 (23.9)
Preoperative cellulitis	13 (19.4)
Postoperative cellulitis (n = 66)	7 (10.6)
Preoperative TI value (n = 20)	29.3 (±14.4)
Postoperative TI value (n = 20)	26.0 (±14.2)
Preoperative affected arm volume difference (n = 12), ml	416 (±432)
Postoperative affected arm volume difference 24 mo postoperatively (n = 12), ml	267 (±285)
Preoperative affected arm circumference difference (n = 20), cm	3.2 (±2.6)
Postoperative affected arm circumference difference (n = 20), cm	2.5 (±1.7)
Subjectively improved function of the affected arm	51 (76.1)
Able to discontinue the use of compression garment	28 (41.8)
Follow-up time, mo	70 (±17)

Data are presented as number of patients (percentages) or mean (±SD).

The VLNT patients had a greater reduction of TI values during the follow-up than the VLNT-BR patients. The comparison of the difference between the preoperative and postoperative TI values between these groups was statistically significant ($P = 0.03$). There was also a statistically significant correlation between the preoperative TI value and reduction of the TI value during the follow-up period ($r = 0.4636$; 95% CI, 0.02656–0.7519; $P = 0.0395$; Fig. 2).

Volumetry

In TYKS, a subgroup of 12 patients was measured for upper arm volumetry. Preoperatively the average volume difference between the contralateral arms was 416 ± 432 ml. After 2 years, the average volume difference still decreased (267 ± 285 ml) (Fig. 3). In our results, the smaller the volume difference was preoperatively, the smaller the volume difference was postoperatively. This correlation ($r = 0.6364$; 95% CI, 0.0792–0.8906; $P = 0.0299$) was statistically significant (Fig. 4). The change of upper arm volumetry during the follow-up was not statistically significant ($P = 0.452$).

Arm Circumference Difference

The average preoperative arm circumference difference of patients was 3.2 ± 2.6 cm. After 3 or more years of follow-up, the average arm circumference difference

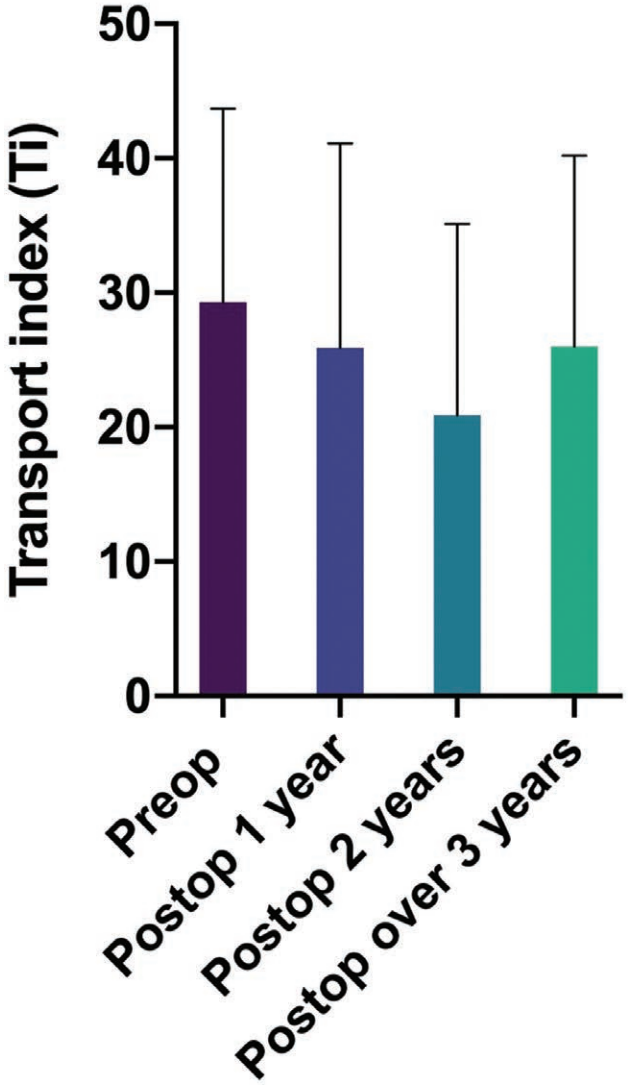

Fig. 1. TI value of the patients preoperatively and at 1, 2, and 3 years after the surgery reported as mean ± SD (n = 20).

decreased (2.5 ± 1.7 cm) below the preoperative level (Fig. 5). There was a positive correlation ($r = 0.6905$; 95% CI, 0.3448–0.8713; $P = 0.0008$) between the preoperative and postoperative circumference difference (Fig. 6). The change of arm circumference difference was not statistically significant during the follow-up ($P = 0.473$).

Compression Garment Therapy

All of our patients used preoperatively compression garments regularly. The patients were allowed to reduce the use of compression garments 6–24 months after the surgery, depending on the symptoms and the lymphoscintigraphy results. The need for the use of compression garments was evaluated using the following parameters: the arm circumference, pitting edema, incidence of postoperative cellulitis, and overall swelling of the arm. In our results, 30% of the patients (20/67) were able to discontinue the use of compression garments after 1 year of the surgery. After 3 years postoperatively, 42%

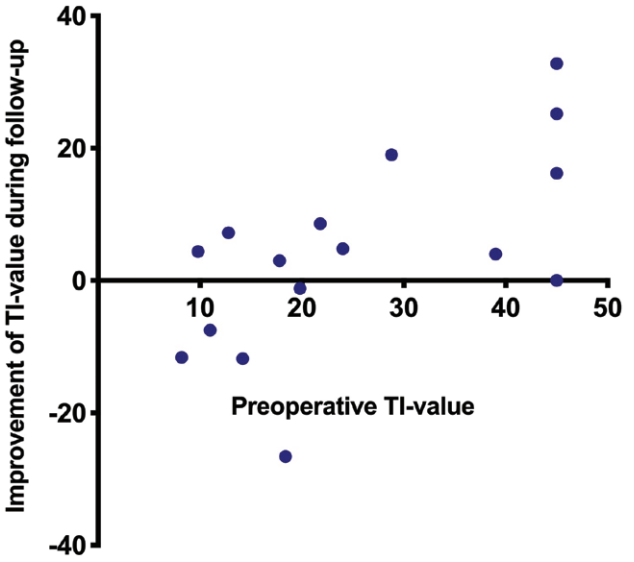

Fig. 2. Correlation of the preoperative TI value and the improvement of the TI value during the follow-up ($P = 0.0395$).

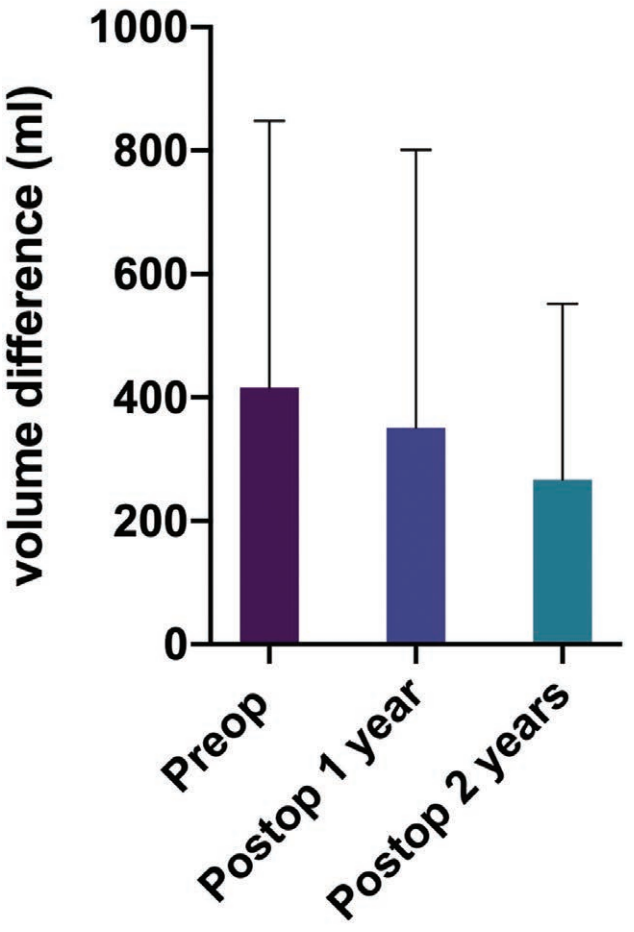

Fig. 3. The mean ± SD volume difference of the contralateral arms preoperatively and postoperatively 1 and 2 years after the surgery (n = 12).

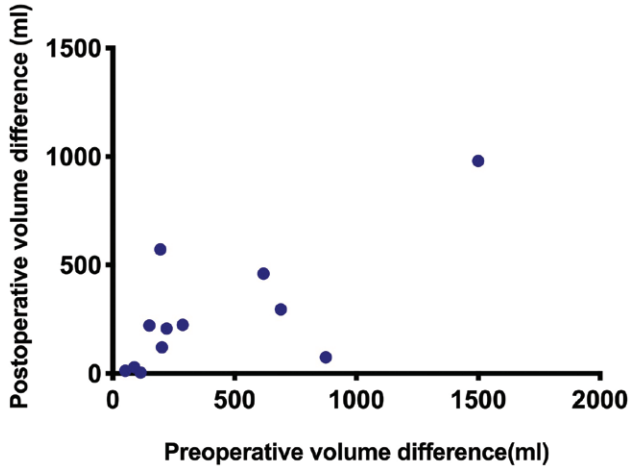

Fig. 4. The correlation of the preoperative and postoperative volume difference of the contralateral arms ($P = 0.0299$).

(28/67) of the patients were able to discontinue the use of compression garments (Fig. 7 and Table 2). The compression garments were discontinued on average 13 ± 12 months after the surgery. Eleven patients (16%, 11/67) were able to reduce the time of use of the compression garments between 2 and 12 h/d. There was a statistically significant difference in the incidence of preoperative cellulitis in different postoperative compression garment usage groups ($P = 0.0086$). The patients using compression garments 2–12 h/d and more than 12 h/d were more likely to suffer from preoperative cellulitis than the patients who were able to discontinue compression garment use ($P = 0.02$ and $P = 0.006$, respectively; Fig. 8). Other preoperative parameters did not have statistically significant correlation with the use of compression garments postoperatively.

Pain Symptoms, Cellulitis, and Day-to-day Function of the Arm

Sixteen patients (24%, 16/67) reported pain in the affected arm preoperatively, and 75% of them (12/16) indicated that their arms felt less painful after the surgery. In 76% of all the patients (51/67), the surgery helped subjectively the day-to-day functions of the affected arm. The day-to-day functions involved fine motor skills, the endurance of the arm, and the ease of finding suitable clothes (Table 1). The average follow-up time for the patients suffering from cellulitis was 74 ± 19 months.

The incidence of cellulitis was preoperatively 0.20 ± 0.55/y and reduced to 0.02 ± 0.08/y after the follow-up time (Fig. 9 and Table 2). Thirteen patients (19%, 13/67) had cellulitis before the operation. Seven (11%, 7/66) patients suffered from postoperative cellulitis, on average 10 ± 8 months after the surgery. Four (57%, 4/7) of these with postoperative cellulitis were patients who did not have cellulitis before the operation. Seven (10%, 7/67) patients used prophylactic antibiotics preoperatively because of recurrent cellulitis; 4 of them (57%, 4/7) were able to discontinue the use of prophylactic antibiotics postoperatively.

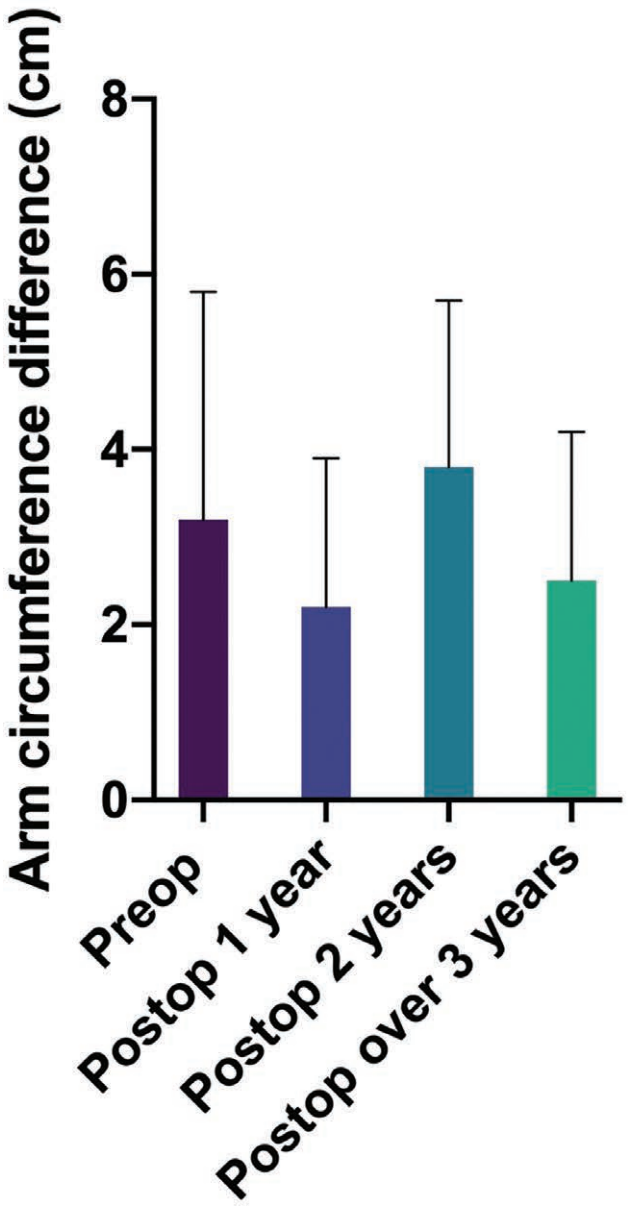

Fig. 5. The mean ± SD arm circumference difference of the contralateral arms preoperatively and during the follow-up at 1, 2, and over 3 years after the surgery (n = 20).

DISCUSSION

VLNT is gaining popularity; however, the reports on the effect of the surgery are heterogeneous and varying in results.[9] We report our long-term results of the VLNT in 67 patients. Our results show that after 3 years of follow-up, 42% of the patients were able to discontinue the use of compression garments. The subjective pain symptoms and the incidence of cellulitis were reduced after operation. The patients with preoperative cellulitis were more likely to continue the use of the compression garments. The smaller preoperative arm circumference, volume, and TI values correlated with smaller postoperative values. This suggests a linear correlation for preoperative factors and surgery outcome, thus a result of similar magnitude for

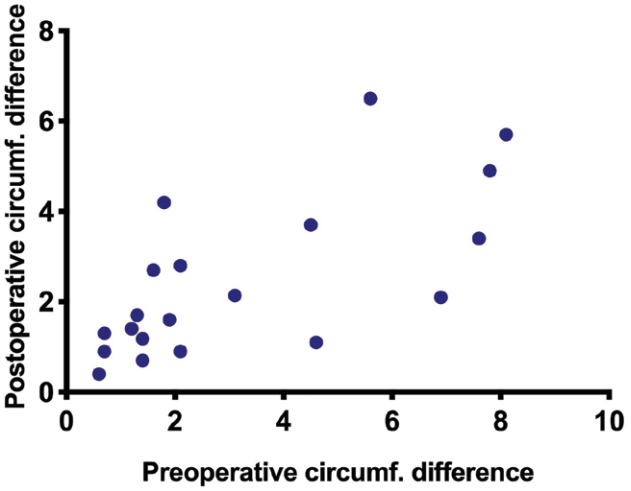

Fig. 6. The correlation of the preoperative and postoperative arm circumference difference ($P = 0.0008$).

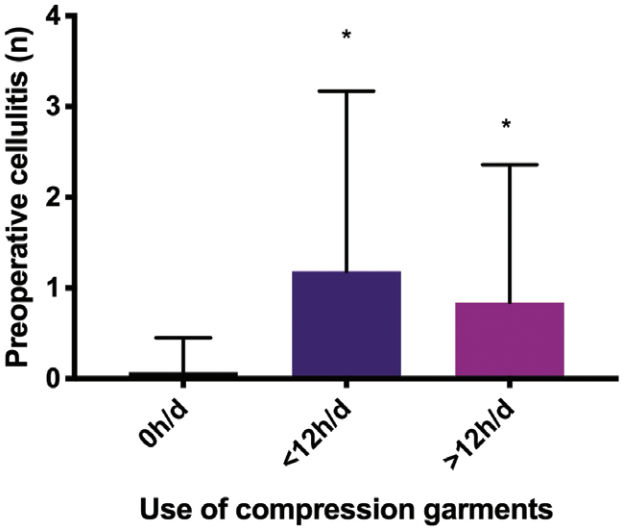

Fig. 8. The comparison of preoperative cellulitis and the use of compression garments postoperatively. $*P \leq 0.05$ compared to 0 h/d group.

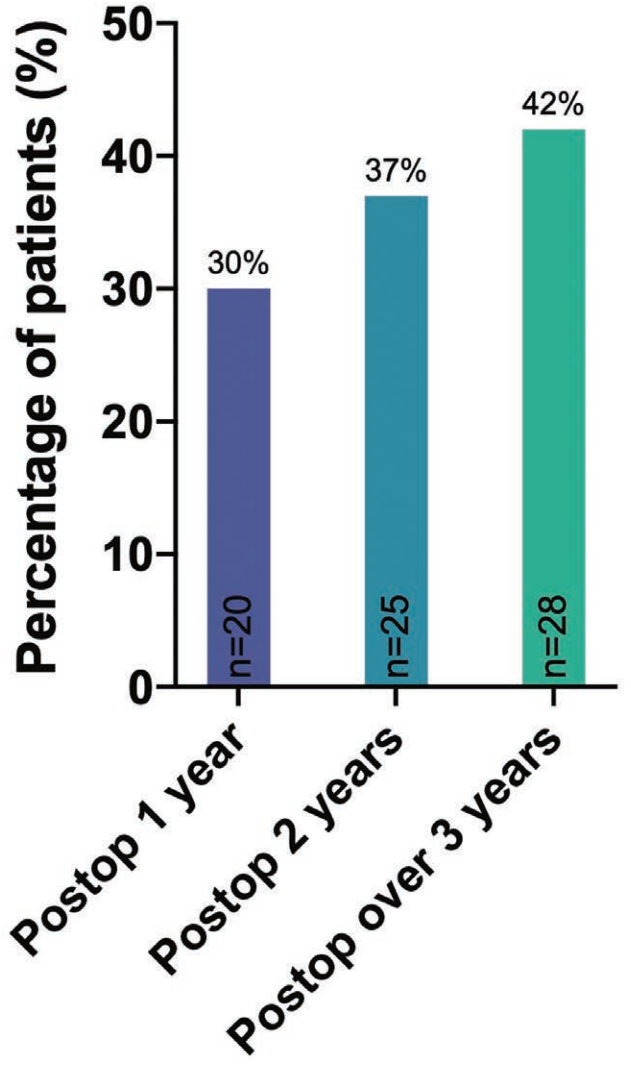

Fig. 7. The percentage of patients able to discontinue the use of compression garments at 1, 2, and 3 years after the surgery.

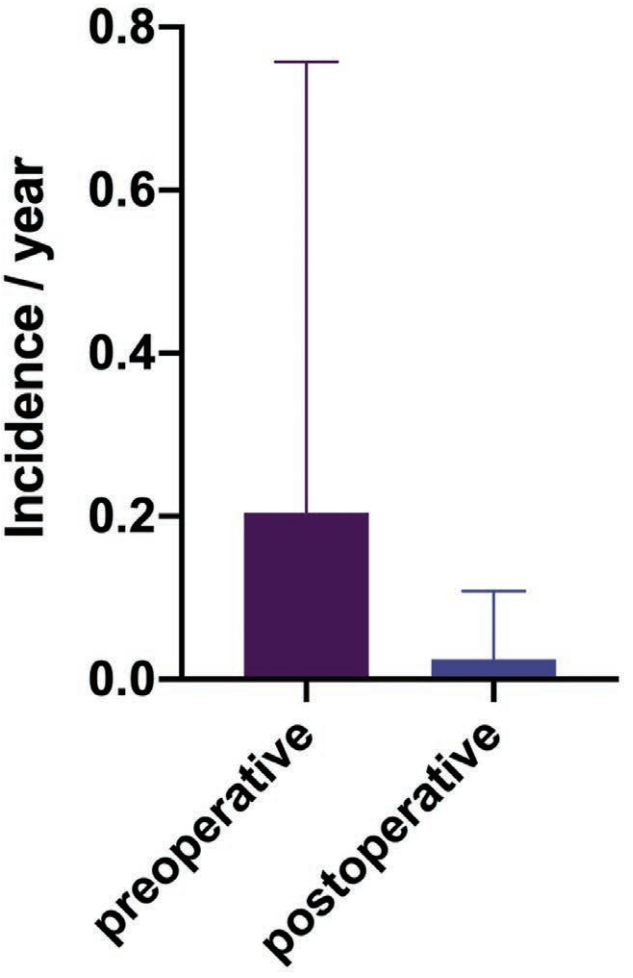

Fig. 9. The mean ± SD incidence of cellulitis/year preoperatively and postoperatively ($P = 0.0998$).

early- and late-stage patients can be expected. Donor-site lymphedema was not detected in any of our patients.

The use of compression garments affects everyday well-being and comfort of the patients.[22] In our study, 42% of the patients were able to discontinue the use of the compression garments after 3 years of follow-up. Also, 11 patients (16%) were able to reduce it to 2–12 h/d. This is in line with previous articles reporting the effects of VLNT, where 52% of patients were able to reduce the usage of compression garments.[23] However, the previous reports are varying in the length of follow-up times. Another factor that affects the well-being of the patients is pain due to lymphedema. Seventy-five percent of our patients reported a subjectively significant reduction of pain symptoms after the surgery. These results are likely to have a major impact on the quality of life of the patients and make everyday life easier.

Only a few studies have analyzed the results of VLNT after more than 1–2 years of follow-up[24–27]; our lymphoscintigraphy results show that although beneficial results are seen, the results are not consistent. It has been speculated previously that VLNT might be more effective at earlier stages of lymphedema.[27] Our study shows a linear correlation between preoperative and postoperative measures. Based on our results, it cannot be concluded that better results would be obtained only for early-stage patients as late-stage patients seem to benefit a comparable amount as well. If the patient is suffering from the late-stage fibrofatty lymphedema, a simultaneous liposuction is likely to improve the results as adipose tissue hypertrophy is an irreversible condition that cannot be cured with VLNT alone.[15]

Lymphedema causes an immune-deprived state in the arm and increases the risk of infection, such as cellulitis.[28] On the contrary, cellulitis can also induce the development of lymphedema and several reports have proven the role of immunological processes in the development of lymphedema.[14] One universal goal of VLNT has been minimizing the risk of cellulitis. Previous studies have shown varying reductions in incidence.[23] However, our study shows that the surgery does not eradicate the risk, although it seems to be greatly reduced. Over half (57%) of the postoperative cellulitis cases were in the patients who did not have any cellulitis preoperatively. The patients with preoperative cellulitis were more likely to continue the use of compression garments, which is a novel finding. This indicates that VLNT reduces the risk of cellulitis, but the results from the surgery may be poorer with patients suffering from preoperative cellulitis. It is worth discussing with patients that whenever cellulitis is present before the operation, the benefit of the operation regarding the usage of a compression garment might not be as good as in patients without preoperative cellulitis.

In our study, most of the patients (95%) had a significant amount of scar tissue in the axilla. It has been proven that scar formation is a key component in the development of lymphedema.[13] It has been thought that the scar removal and transfer of healthy tissue alone may improve the lymphatic function. Venous stasis is also a significant factor in the formation of the lymphedema.[29–31] The immediate reduction in the swelling of the arm postoperatively is most likely due to a reaction of released axillary vein in the scar.

In our study, short-term surgery-related complications were reported in many patients, including seroma, wound infections, and delayed wound healing. Long-term complications of groin lymph node transfer can include seroma, chronic pain, paresthesia, and worryingly donor-site lymphedema. In our results, 3% of patients reported loss of sensation in the upper thigh. Fortunately, none of the patients presented with donor-site lymphedema, likely because we have developed our surgical technique to avoid operation of the lymph nodes medial to the femoral vessels.[16]

The limitations of this study are its retrospective nature, the small total number of the patients, and the small subgroups. A major limitation in our study is that not all of the patients had results from the objective measurements. The subjective results are difficult to interpret, because of possible reporting bias. The results of the use of compression garments vary between the patients due to reporting bias.

CONCLUSIONS

Our study indicates that VLNT surgery can have beneficial effects for the patient, especially in the early stage of lymphedema. The risk of cellulitis is reduced, but the presence of preoperative cellulitis may significantly deteriorate the results of the surgery and should be discussed with patients beforehand. Right patient selection for the surgery reduces the risk of possible postoperative complications and may improve patient management.

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