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Surgical Treatment of Advanced Lymphatic Filariasis of Lower Extremity Combining Vascularized Lymph Node Transfer and Excisional Procedures

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Abstract

Background: Lymphatic filariasis (LF) in advanced stage is a clinically challenging disability resulting in poor quality of life. In advanced stage of filariasis, medical management is seldom effective and few surgical procedures are beneficial. In this study, we assessed clinical efficacy of a surgical technique combining vascularized lymph node transfer (VLNT) and serial excision for patients affected by advanced LF.
Patients and Methods: A total of 17 patients with grades 2 and 3 lower limb lymphedema after three consecutive humanitarian missions in India between 2014 and 2018 underwent excision of excessive soft tissue of leg and supraclavicular lymph node flap transferred to dorsum of foot. Recipient vessels were prepared and microanastomosis was performed. Lymphedema was assessed by measuring leg circumferences at different levels, episodes of infectious lymphangitis, and lymphoscintigraphy.
Results: A significant decrease of lower limb circumference measurements at all levels was noted postoperatively. Postoperative lymphoscintigraphy revealed reduced lymph stasis. One patient suffered of a seroma on donor site. Six patients had partial loss of skin graft over the flap at recipient site and it was managed by regrafting. Data analysis observed statistically significant reduction in feeling of heaviness ($p < 0.005$) and episodes of acute lymphangitis after surgery.
Conclusion: Advanced LF of leg is difficult to manage using traditional medical treatment. The combination of VLNT and surgical excision provided a safe and reliable approach to treat this debilitating disease.

Keywords: filariasis, lymphedema, elephantiasis, lymph node transfer, excisional procedure, supraclavicular flap

Introduction

LYMPHATIC FILARIASIS (LF) of extremity is a progressive disfiguring disorder of lymphatic system caused by filarial parasite infestation. Dysfunction of the lymphatic system results in the development of lymphedema of the legs that progresses to elephantiasis, which may be a irreversible and devastating condition. LF is a tropical parasitic disease that affects almost 120 million people worldwide.[1] It has been estimated that ~15 million people have lymphedema and elephantiasis of the extremities due to filarial parasitic infestation.[2] It commonly affects the unilateral or rarely bilateral lower extremity, causing obstruction in the lymphatic system of leg. Sometimes upper limbs, male genitalia, and female breast may also get affected.

Patients usually show gradually increasing of swelling, heaviness, and tightness. As the disease advances, the leg becomes grossly enlarged, heavy, and painful. In some cases,

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nodule formation, ulceration, and lymphorrhea become evident. Stagnation of lymph encourages growth of bacteria invading the region. Any interference to the skin integrity of the affected region such as injuries, fungal or bacterial infections, fissuring of the skin, and paronychia or eczema favors entry of pathogenic bacteria into the tissues.[3–5] These bacteria, mainly streptococci and occasionally other pathogens, are responsible for acute attacks of dermatolymphangioadenitis (DLA) commonly seen in filarial limbs. Local pain, embarrassment, and limited physical activities are the main distressing aspects of LF that reduces quality of life and causes sociopsychological trauma to patients and their families.[2] Reduced productivity experienced by LF patients results in hundreds of millions of dollars in economic losses each year.[6–9]

Medical management and supportive care are the conventional therapeutic options in early and later stages of LF. However, the effect of these therapeutic modalities is short lasting. Diethylcarbamazine (easily made in endemic countries) and albendazole (Glaxo-SmithKline) are the drugs of choice when there is an active infection from *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*. However, this does not seem to reverse the lymphatic damage.[10] It has been reported that once LF has been established, the lymphatic pathology is irreversible even after treatment or elimination of the filarial parasite. Therefore, further progression of the disease will occur.[11]

Various surgical procedures for advanced lymphedema have been described in the literature. Charles, Sistrunk, Homans, Macey, Auchincloss, and Thompson demonstrated excisional procedures,[12–17] which reported potential complications such as recurrence of the lymphedema, skin graft loss, infections, hyperkeratosis, lymphorrhea, functional impairment, sensitive deficit, and poor cosmetic results.[16] Other techniques such as omentoplasty, lymphaticovenous, and lymphnodovenous shunts have been introduced with inconsistent results.[18–20]

With the advancement of microsurgical techniques, vascularized lymph node transfer (VLNT) showed promising early results as well as long-term postoperative activity of the transplanted nodes, but there is still a paucity of scientific literature related to the surgical management for advanced filarial lymphedema.[21–25]

Over the past 3 years, we have treated patients affected by LF by combining VLNT and excisional procedures. We advocate the combination of both a debulking procedure to reduce tissue load and a physiologic reconstructive procedure (VLNT) to restore lymphatic network, prevent infections, and lymphorrhea reducing complications. In this report, we present our surgical experience for patients with advanced stage of LF and investigate its clinical benefits among these patients.

Patients and Methods

From September 2014 to March 2018, after three consecutive humanitarian missions in India, 17 patients with advanced stage of LF (late grade 2 and grade 3) underwent VLNT along with excisional procedure.[26] The average age of the patients was 43 years (±15, range 17–67). Table 1 gives different parameters of study participants. Lower limb lymphedema was right sided in seven (41.2%) patients, left sided in eight (47%) patients, and bilateral in two (11.8%) patients. Out of 17 patients, 9 (52.9%) were male and 8 (47.1%) were female, 5 (29.4%) were of grade 2 lymphedema and 12 (70.6%) were of grade 3 lymphedema.

Patients' inclusion criteria were advanced stage LF of the lower limb (late grade 2 and grade 3 International Society of Lymphology).[27] Patients were diagnosed focusing on the clinical history of evolution of the disease and clinical examination of the affected limb. Preoperative routine tests such as night blood examination to detect microfilariae, immunochromatographic card test to test filarial antigenemia, and ultrasonography to locate the adult worms were performed in all patients.

Data related to patient age, gender, grade of lymphedema, type of surgery, recipient area, leg circumference measurements at different levels of leg before and after the surgery, and complications (episodes of lymphangitis before and after operative procedure) were collected in a predesigned proforma.

The Declaration of Helsinki protocol was followed, and preoperatively all patients gave informed consent for surgery. A local ethics committee approved the study as well as data analysis. Data storage was performed in consistence with good clinical practice guidelines.

Patient evaluation

Preoperative assessment included photography and serial measurements of limb circumference at 15 cm above and below the midpoint of patella at knee level. Measurements around the ankle were recorded 10 cm above and below the most prominent point of lateral malleolus and are given in Table 2. All clinical measurements were taken preoperatively, 3, and 6 months postoperatively by the same assistant. Photography was used to compare preoperative and postoperative clinical assessment.

Doppler study (arterial and venous) and routine investigations were performed to obtain fitness for surgery. Lymphoscintigraphy with technetium 99m was obtained preoperatively and at 6 months postoperatively to evaluate interruption of the lymphatic system, lymphatic drainage, and VLNT activity. Two physicians interpreted the lymphoscintigrams independently.

Table 1. Patients Data

	Cases	*Gender*	*Age distribution*	*Lower limb involved*	*Lymphedema staging*[a]
	n: 17	M: 9 (52.9%) F: 8 (47.1%)	<40 years: 8 (47%) >40 years: 9 (53%)	Left: 10 (58.8%) Right: 7 (41.2%)	Grade 2: 5 (29.4%) Grade 3: 12 (70.6%)
Total	17		43 ± 15[b] (17–67)		

[a]International Society of Lymphology.
[b]Average, SD, range.
SD, standard deviation.

Table 2. Preoperative and Postoperative Results

	Measurements of lower limbs before and after operation										
	Above knee		Below knee		Above ankle		Below ankle				
	Preoperation	Postoperation	Preoperation	Postoperation	Preoperation	Postoperation	Preoperation	Postoperation	Compare heaviness and tightness preoperation/postoperation[a]	Compare self confidence preoperation/postoperation[a]	Compare acute lymph angitis episodes preoperation/postoperation[a]
Mean ± SD	58.9 ± 8.7	48.3 ± 4.6	49.3 ± 6.8	40.5 ± 4	45.6 ± 8	40.5 ± 4	34.3 ± 9.6	28.2 ± 5			
t	8.9		8.05		3.6		2.25				
df	16		16		16		16				
Z									−3.663[b]	−3.654[b]	−3.541[b]
p	0.000		0.000		0.002		0.039		0.000	0.000	0.000

[a]Wilcoxon signed ranks test.
[b]Based on positive ranks.

Patient satisfaction (heaviness, level of self-confidence) at follow-up was classified as poor, fair, good, or excellent, using a standardized questionnaire. Measurements were presented as the mean, standard deviation, and range. Differences were assessed using the Student's *t*-test to compare means Wilcoxon signed ranks test used for ordinal data; $p < 0.050$ was considered significant. All calculations were done using SPSS (Statistical Package for Social Sciences) 16.0 version.

Surgical technique

Surgical markings were planned in standing position, the markings were vertical along the thigh, leg, and foot on medial or lateral aspect depending on excessive soft tissue swelling (Fig. 1). Patients were admitted 7–10 hours before the surgery. They were advised bed rest, leg elevation, massage, and compression garment application. It improved the softness of swelling with some reduction, which helped for final planning of the surgical excision at the time of surgery.

Patients were placed in supine position under cervical and lumbar epidural anesthesia. Regional anesthesia was offered by the expert anesthesiologists' team and agreed by all patients. Tourniquet was applied to thigh, and excision of excessive soft tissue of thigh, leg, and foot was planned as per the markings shown in Figure 1B. The soft tissue was excised till the supra fascial region with careful hemostasis. The approximation of edges tried to reassess the sufficiency of excision. In the foot incision, long saphenous vein and dorsalis pedis vascular pedicle were isolated to use them as recipient vascular pedicle for supraclavicular lymph node flap. Tourniquet was deflated and hemostasis achieved. The leg incision closed in layers keeping tube drain in subcutaneous plane.

Right supraclavicular incision was planned parallel and 2 cm above the clavicle.[28] Figure 1A shows the anatomy and markings for preparation of supraclavicular flap. Incision was extended from lateral border of sternocleidomastoid muscle to anterior border of trapezius muscle. Incision was deepened through skin and platysma muscle to identify and isolate external jugular vein. Inferior belly of omohyoid muscle was identified and isolated to expose transverse cervical vascular pedicle, which was usually found just deep to omohyoid muscle on the medial aspect. Dissection was also performed on the anterior border of trapezius muscle to identify the transverse cervical vascular pedicle.

Once these landmarks were identified, flap dissection was started from inferior and medial aspect deep to the transverse cervical vascular pedicle. The external jugular vein was included in the flap and transverse cervical pedicle was ligated on medial aspect. The dissection was continued toward the anterior border of trapezius muscle to identify and ligate transverse cervical pedicle anterior to the muscle. Hemostasis was achieved and incision sutured in layers keeping tube drain in the wound. After this, the lymph node flap was transferred to the dorsum of the foot for anastomosis with the vessels already prepared. The transverse cervical artery was anastomosed to the dorsalis pedis artery as end to side manner, the accompanying vein was anastomosed to the concomitant vein of dorsalis pedis pedicle as end to end manner.[29] The external jugular vein was anastomosed to the great saphenous vein as

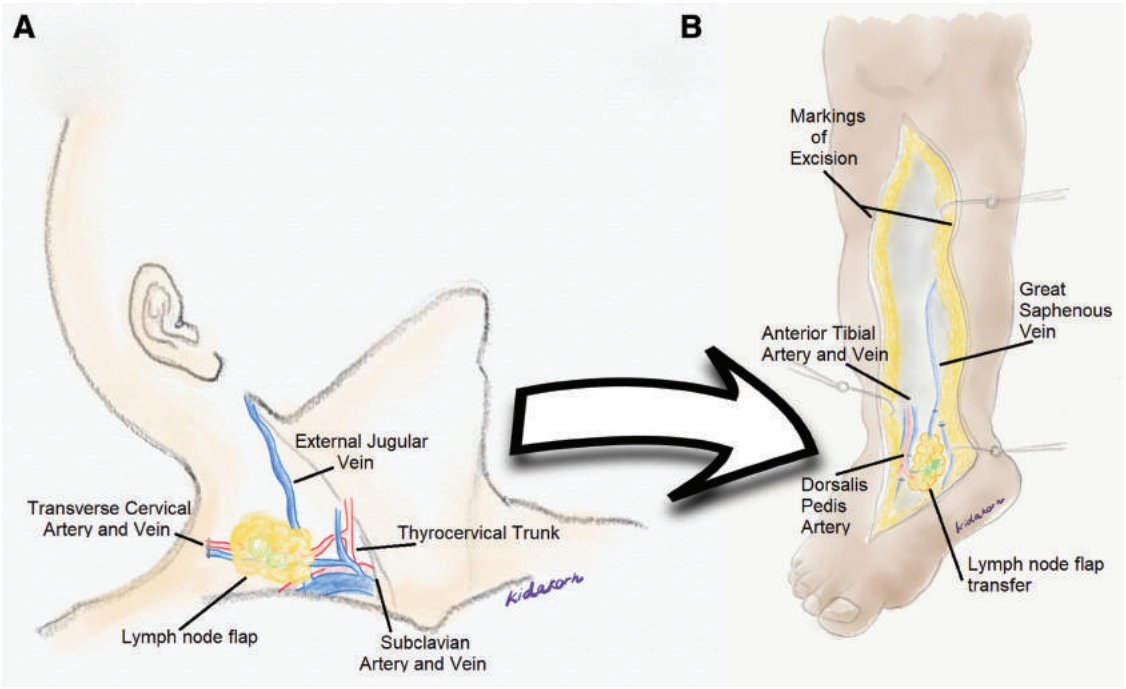

FIG. 1. Diagram of lymph node transfer and excisional procedures. Markings of donor site from the right supraclavicular region **(A)** and recipient site of the lower limb **(B)**. Color images are available online.

end to end manner. The microanastomosis was performed using 10-0 Nylon suture under microscopic magnification. The flap was anchored with the surrounding soft tissue; however, direct closure of surrounding skin over the flap was avoided to prevent direct pressure and flap monitoring purpose. The exposed flap was covered with split thickness skin graft. It was meshed for monitoring and drainage of any collection. The flap area was covered with single piece of nonadherent gauze to avoid pressure. Drain in the leg as well as right supraclavicular area was removed once it was <30 cc. Patients were discharged on the next 7–10 days. The limb elevation, massage, and pressure garment application should be followed to help as adjunct to the surgery.

Results

Seventeen patients suffering from advanced stage of LF underwent lymph node transplantation and excisional procedure. The results are evident by comparing pictures of lymphedematous limb before and after the surgery as shown in Figures 2 and 3. There was significant reduction in circumference of legs after surgery. Leg circumference measurement the day before surgery and 3 months after surgery was compared to evaluate the results. All the lymph node flaps survived well. Lymphoscintigraphy also clearly demonstrated improvement in lymph drainage as evident on images taken before and 6 months after the surgery. Lymphatic

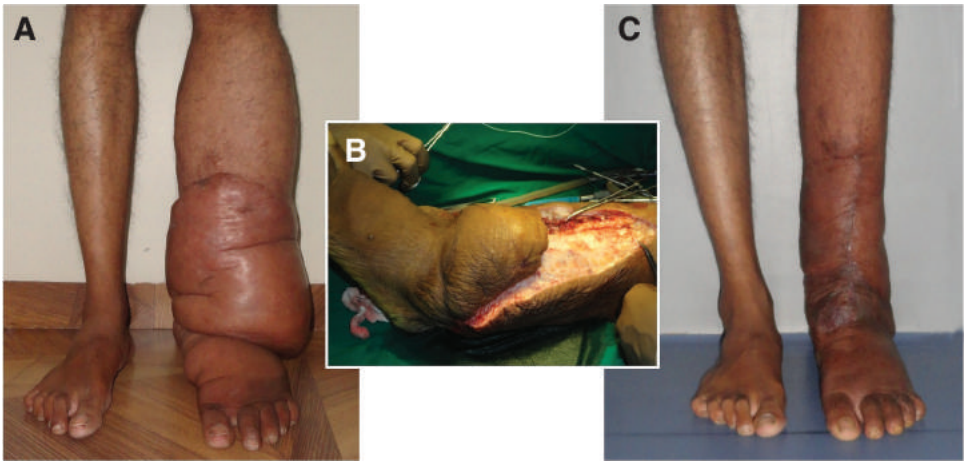

FIG. 2. Case 1: **(A)** Preoperative picture of a 26-year-old patient with advanced left lower limb lymphatic filariasis, **(B)** intraoperative picture showing debulking and preparation of recipient vessels **(C)** postoperative result at 1 year follow-up. Color images are available online.

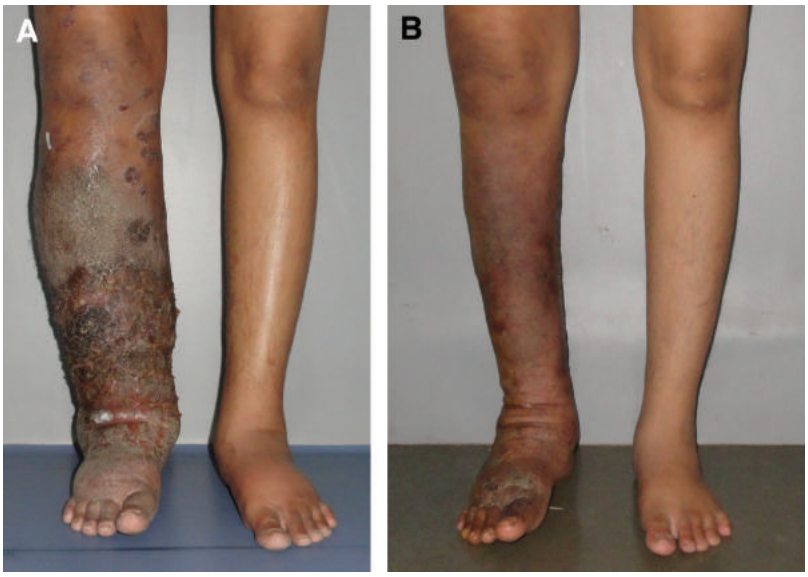

FIG. 3. Case 2: A 40-year-old man underwent supraclavicular lymph node transfer and excisional procedure of the right leg. Preoperative frontal view **(A)** showing the burdened leg with hyperkeratosis and warts. At 6 months follow-up **(B)**, the patient had shown good contour of the lower limb, no complications such as infection or lymphangitis. Color images are available online.

drainage was improved (Fig. 4) and dermal backflow became cleared in even delayed images of the lymphoscintigraphy as given in Table 2. There was significant reduction in leg circumference at all four sites ($p < 0.005$) summarized in Figure 5. There was a statistically significant reduction in feeling of heaviness ($p < 0.005$) and episodes of acute lymphangitis after surgery. Also, there was significant increase in level of self-confidence after surgery. All patients who underwent the procedures were satisfied with the improvement in limb size and functional outcome. All the patients followed physiotherapy, and were able to return to their normal daily activity within the first 2 months after the operation.

No major complications of the lymph node flap donor site were reported. Donor site seroma was present only in one case and was managed by aspiration and pressure dressing was changed every 2 days. This was resolved after 7 days. In

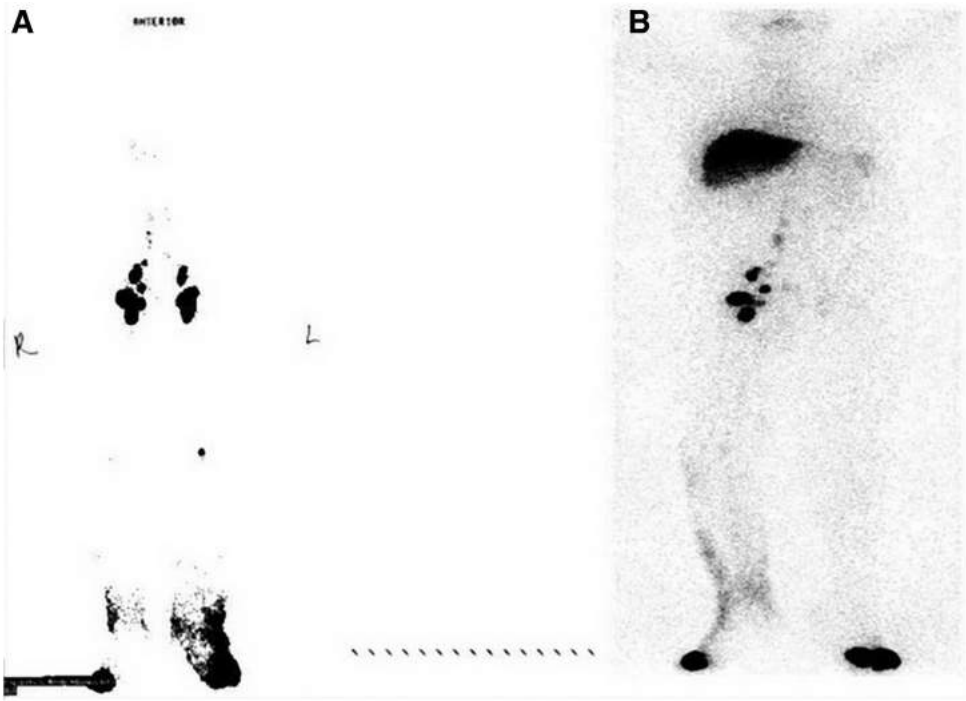

FIG. 4. Preoperative **(A)** and postoperative **(B)** lymphoscintigraphy of a patient with left lower limb lymphedema showing significant improvement of the dermal back flow and impaired lymphatic function on the left side.

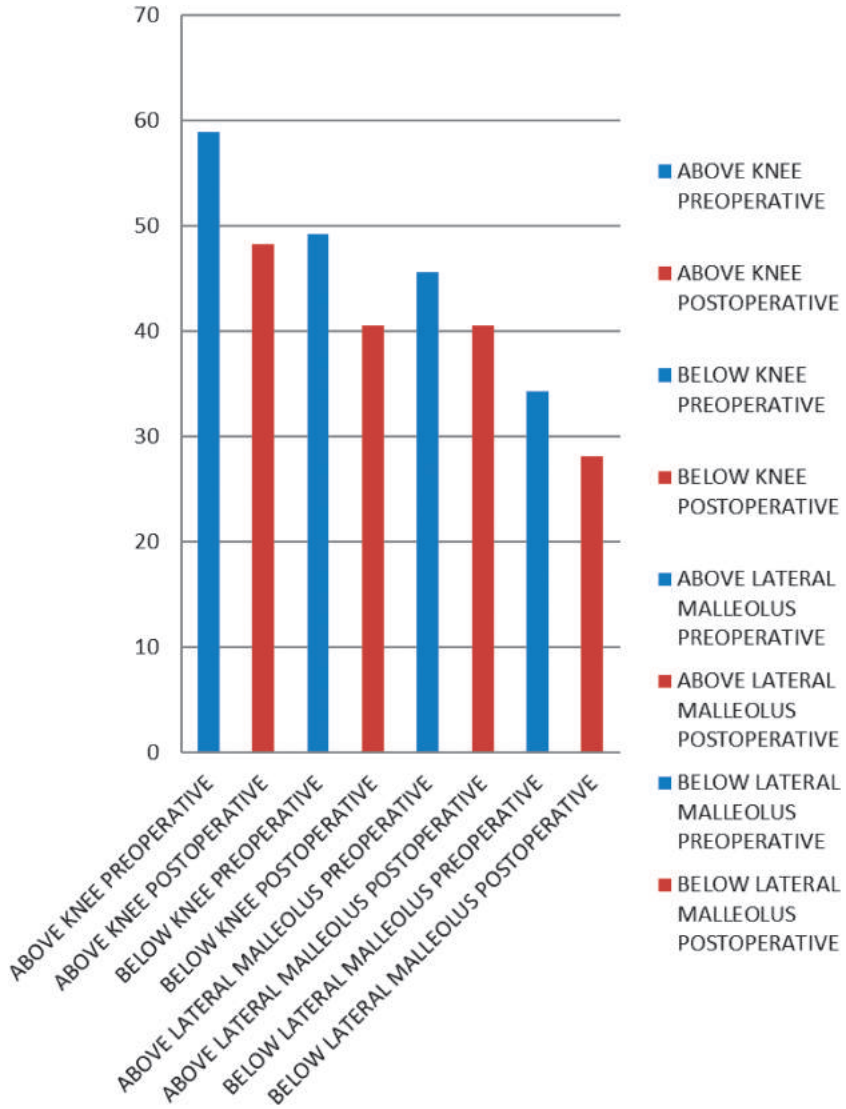

FIG. 5. Diagram showing differences in lower limb circumference measurements at various levels before and after operations. Color images are available online.

six patients, the skin graft on flap site was partially lost due to lack of pressure applied during the initial few days of the dressing; however, hydrocolloid dressings were applied and no infections were registered in the recipient leg site. A regrafting of the area was performed after 1 month. The crepe bandage application was started from seventh day of surgery with minimal pressure on the flap recipient site. All patients were encouraged to begin wearing compression elastic bandage 1 month after the operation, when the skin graft or secondary graft was completely healed, for a period of 3–4 months.

The mean follow-up was 12 months (range 3–16 months). During this period, no recurrence or worsening of lymphedema was observed. None of the patients experienced severe infection or DLA.

Discussion

LF is a vector-borne neglected tropical disease recently targeted by WHO for elimination as a public health problem.[30] Lymphedema and elephantiasis are the chronic disabling consequences of the damage produced by infections of the lymphatic vessels caused mainly by three types of filarial parasites: *W. bancrofti*, *B. Malayi*, and *B. timori*.[1–6] Early infections are often subclinical and mainly acquired during childhood, leading to a lifetime of an impaired lymphatic system and increased risk of debilitating episodes of DLA, including lymphangitis, lymphadenitis, cellulitis, or abscess formation.[30–32] The disease affects physical, psychological, and economical status of the patients.[4–10]

Various surgical methods are described in the literature for treating advanced stage of LF of the extremities using excisional procedures, or physiologic procedures such as nodovenous shunt and lymphaticovenous anastomosis.[12–23] However, the mentioned methods never became popular as standard care for advanced disease due to inconsistent results and variable recurrences.[18] In recent years, VLNT is becoming popular to treat lymphedema of extremities secondary to cancer with increasingly promising outcomes.[21–25,30–35] Nevertheless, there is a lack of knowledge of the LF surgical treatment. So, in this

study, we translated our previous clinical experience to evaluate the efficacy of a combined treatment for advanced stage filariasis of extremities using excisional method as modified Charles procedure and microsurgical techniques as VLNT.[29] It is now well known that the earliest structural change in LF is the dilation of lymph vessels where the adult worms live.[32] Once the lymphatic damage progresses, stasis of lymph tends to occur in the dilated vessels due to incompetence of the unidirectional valves in them.[30–32] This damage is aggravated by recurrent bacterial infections of the extremities, prolonged standing, or strenuous exertion.[36,37] The transient lymphoparalysis that sets in during acute bacterial infections also worsens the lymph stasis.[38] Such repetitive attacks later perpetuate and worsen the lymphedema, leading to elephantiasis. Advanced stages of lymphedema are characterized by increasing dilation and tortuosity of the lymphatics, endothelial proliferation, formation of new lymph channels, and obstructive changes and dermatosclerosis with nodular and warty changes.[31,32,37] The excisional procedure helped to reduce the bulkiness of the tissue from leg and VLNT promoted the lymphatic drainage adding an extra load of immune defenses. Efficacy and mechanism of functioning of VLNT have been extensively discussed in the literature in cases of postmalignancy lymphedema.

Clodius et al.,[39] in 1982, first time used the VLNT procedure in the management of lower leg lymphedema in the clinical setting, but nowadays it is commonly performed to treat breast cancer-related lymphedema of upper limbs.[40] Becker et al.[35] reported improved lymphatic function in 31% of the patients and significant reductions in episodes of infections of lymphedema arm that underwent autologous microsurgical VLNT.

In our study, the combined approach of excision and VLNT was effective with consistently reproducible and favorable results. Several donor site options are available to harvest the VLNT. These include flaps harvested from within the axillary, inguinal, or cervical lymph node basins, including the groin (superficial inguinal lymph nodes), supraclavicular (cervical level Vb lymph nodes), and submental (cervical level Ia/Ib lymph nodes) flaps.[40] In all patients, we transferred the supraclavicular lymph node flaps harvested from the right side to avoid potential injury of the main lymphatic duct on the contralateral side. The opposite groin lymph node as donor flap was avoided as there is risk of opposite leg filariasis as patients were usually from filarial endemic areas. There were also reports of risk of donor site lymphedema after lymph node transfer further constraining selection of opposite leg as donor site.[41–43]

In addition, the supraclavicular region offers several advantages, the skin incision in right supraclavicular area heals with barely noticeable scar, and usually this area is covered with clothing. The anatomy in this area is consistent and flap harvest can be performed in supine position, avoiding change of position of patient during the surgery. Right side supraclavicular flap is not bulky that helps in proper inset and avoids bulge on dorsum of foot in long term. In this study, supraclavicular flap was harvested without skin paddle as it is not reproducible in every case. The flap inset was performed on dorsum of foot as pedicle is easily accessible. Skin graft was preferred over buried closure as it gives less pressure on the flap as well as flap monitoring is possible through the skin graft. Skin grafts were usually well accepted when combined with VLNT. To the best of our knowledge, this study is the first to use VLNT in combination with excisional procedures for the treatment of lower extremity LF, offering an effective and comprehensive surgical treatment for patients affected by this debilitating disease.

Sapountzis et al.[29] used a combined excisional procedure (Charles) and VLNT in 24 cases of advanced lower extremity lymphedema secondary to cancer treatment. In this study, they modified Charles method[12] by preserving superficial venous system of dorsum of foot including greater and lesser saphenous veins and using it as recipient vein of the transferred lymph node flap. During our procedure, we have also tried to spare the main veins of the superficial system. Using this technique, maximum reduction was observed that increased the lymph backflow without any major postoperative complication and recurrence. Lymphoscintigraphy also showed significant improvement of tracer uptake in delayed images with absence of dermal backflow.

The cervical and lumbar epidural anesthesia was considered as the first method of choice to induce anesthesia over general anesthesia. That is because our specialists felt extremely confident adopting such kind of regional anesthesia for these surgeries and as they routinely perform it. Moreover, by avoiding general anesthesia, postoperative monitoring was definitely easier with reduced costs for the service. Then, it is possible to maintain *in situ* the epidural catheter in the lumbar region for 1 or 2 days to supply analgesic and in case of urgent re-exploration.

VLNT resulted in a safe reliable promising procedure for patients with late stage II and stage III lymphedema. Various mechanisms about improvement of lymphatic function by VLNT have been proposed in the literature by several researchers.[19–25] Transfer of lymph nodes induces local anti-inflammatory and antifibrotic response in the flap recipient site.[44,45] This phenomenon was studied by comparing concentration of inflammatory markers such as interleukin (IL) 10, IL-4, IL-14, and tumor growth factor beta in preoperative and postoperative period in cases with lymphedema.[46,47] New lymphatic collateral pathways between adjacent lymph nodes are formed to re-establish outflow, promoted by lymphatic growth factor secretion of the transplanted lymph nodes, especially by vascular endothelial growth factors C and D (VEGF-C and VEGF-D).[46] The neo-lymphangiogenesis is established by new lymphaticovenous drainage within the transplanted lymph nodes, with the ''pumping'' mechanism driven by perfusion gradients between arterial inflow and venous outflow.[48–52]

An additional postulated positive effect is the introduction of the lymph node flap as an immune system organ.[49] Lymphatic channels from the affected limb connect with the lymphatics of the lymph node flap and present antigens to the lymph nodes that can then mount an immune response and minimize the risk of infection for the lymphedematous limb.[48–51,53] That was also observed in our patients wherein we found a significant reduction of recurrent bouts of cellulitis, infections, and DLA in the lymphedematous limb postoperatively (Table 2).

The novel idea in this report is combining surgical techniques of excision and microsurgery to treat and make patients able to lead an independent life. Although postoperatively, the study found a remarkable reduction in limb

volume and a decrease in infection rate. There are limitations to this study, such as a small sample size and a lack of a control group. Therefore, the net effect of the lymph node transplanted could not be evaluated from this study. Unfortunately, the study did not have access to advanced technology due to limited resources and poor facilities. Further studies may use advanced technology and high-quality imaging to enhance the credibility of these results.[50–54]

In future, more refinements in techniques and improvement in overall management of such patients will make this complex problem treatable with consistent outcomes.[55,56]

Conclusion

We present a consecutive series of patients treated with excisional procedures and VLNT for advanced stage of LF of the lower limb. Our preliminary results are very promising. We found that both components of the procedure, VLNT and modified Charles procedure, are safe and reliable, improving the lymphedema burden. The strategy to combine these two methods to improve outcomes offers an ideal option for the treatment of patients who suffer from advanced stage of LF. So, this will be a ray of hope in the management of LF in late stage when medical conservative management has limited role. These patients will be followed up further, and long-term outcomes will be reported.

Acknowledgments

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Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Author Disclosure Statement

Dr. Fabio Nicoli and Dr. Ram M. Chilgar are founders and coordinators of Give me 5 Foundation,[26] a No Profit international organization focusing to restore and rehabilitate patients affected by pathologies of the extremities. All donations collected through the organization were spent to provide treatments free of charge for all patients.

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