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Recent advances in management of lymphedema

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ABSTRACT

There has been a paradigm shift in the management of lymphedema with a better understanding of the functioning of lymphatics with the introduction of "lymphosome concept" and with the recent advances in super-microsurgical techniques. The most frequently used intraoperative imaging modality now is indo cyanine green lymphangiography. In endemic countries, any patient with lymphedema without prior history of trauma or, oncosurgical or radiotherapy interventions must undergo Alere filariasis test strip. Patients in early stages of disease can benefit from complex decongestive therapy and physiologic surgical procedures such as lymphovenous anastomosis or vascularized lymph node transfers. However, in advanced disease, excisions or debulking through radical reduction with preservation of perforators will be required. The localized adipose tissue deposits in lymphedema can be removed by liposuction. At present, there is still no cure for lymphedema, but emerging research in tissue engineering, lymphangiogenic growth factors, and immunomodulatory therapy may provide better management options for lymphedema in future.

Keywords: Lipedema, Liposuction, Lymphatic vessels, Lymphatico-venous anastomoses, Lymphedema, Vascularized lymph node transfer

INTRODUCTION

There has been a paradigm shift in the management of lymphedema recently, with a better understanding of the physiology of lymphatic system and with the recent advances in super-microsurgical techniques.

Lymphedema management starts with conservative management, followed by surgery and maintaining the surgical results during the entire lifetime of the patients.[1] For lymphedema treatment to be effective, it has to be initiated early in the disease and demands a continued compliance from the patient. Recent advances in management of lymphedema are mostly focused on a thorough understanding of the microscopic anatomy of lymphatics (please refer to the section of the symposium on pathogenesis) and provision of alternate physiologic pathways to redirect lymph flow to prevent secondary changes in the tissues such as cellulitis, fibrosis, adipose tissue deposition, and functional loss.[2]

Lymphedema is divided into stages 0-5 using indo cyanine green (ICG) lymphography, based on the patency of lymphatic vessels, dermal backflow, and lymphatic vessel contractility.[3] The International Society of Lymphology (ISL) staging charts the progress and reversibility of lymphedematous changes from subclinical disease in stage 0 to irreversible lymphostatic elephantiasis in stage 3 [Figure 1].[3,4] With the progression of the disease, the microvascular networks that nourish the collecting lymphatic vessels are lost; the lymphatic

vessel lumen is dilated with an increase in endolymphatic pressure in the ectasis type, whereas in contraction and the sclerosis types, an increase in smooth muscles and collagen fibers make the lymphatics more thickened and prominent.[5]

Patients in early stages of disease will benefit from conservative multi-modality management and physiologic surgical procedures such as lymphovenous anastomosis (LVA) or vascularized lymph node transfers (VLNT). However, for patients in late stages of lymphedema with fibrotic limbs and warty skin changes, we have to complement conservative therapy with debulking procedures such as Charles graft replacement, Homans soft-tissue debulking, radical reduction with preservation of perforators or liposuction, alone or in combination with the physiologic procedure, VLNT. These procedures are used to excise the excess diseased tissue above the plane of deep fascia. The localized adipose tissue deposits in lymphedema can also be removed by liposuction.

CURRENT DIAGNOSTIC MODALITIES FOR SURGICAL PLANNING

The diagnosis of lymphedema is clinical and involves a detailed history and physical examination of the patient. The most frequently used intraoperative imaging modality now is ICG lymphangiography. It has an advantage of providing real time images of dye uptake and flow pattern, which help in planning skin incisions for LVA. However, it does not visualize deep lymphatics which can be seen with lymphoscintigraphy. Magnetic resonance imaging lymphangiography is also used with a sensitivity of 60%–70%.[6-8]

In endemic countries, any patient with lymphedema without prior history of trauma or oncosurgical or radiotherapy interventions must undergo Alere filariasis test strip.[9] It is a rapid diagnostic test recommended for mapping, monitoring, and transmission assessment surveys for the qualitative detection of *Wuchereria bancrofti* antigen in human blood samples. It is an immunochromatographic test used to detect circulating filarial antigen. It is now integrated into the global program for eradication of lymphatic filariasis protocols for mapping lymphatic filariasis endemicity, stopping mass drug administration(MDA), and post-MDA surveillance.

NON-SURGICAL TREATMENT OF LYMPHEDEMA

Initial management with complex decongestive therapy (CDT) for up to 2 years is recommended before undertaking surgical management.[10,11]

MANUAL LYMPHATIC DRAINAGE (MLD)

It involves low pressure graded sequential pressure application by trained therapist or nurse practitioners for superficial skin stretching.[11] MLD sessions of 60 minutes duration are repeated thrice a week for at least 4 weeks in conjunction with the compression garments.

Multi-chambered sequential graded pneumatic compression devices can be used in extremities to propel lymph from distal to proximal direction [Figure 2].[12,13] Daily session lasting 1–2 hours can be operated by the patient at home, followed by compression garments. Although several other non-surgical treatment modalities have been described including ultrasound, deep oscillation, electrostimulation, low level LASER, acupuncture, and kinesiology tapes, most have only anecdotal evidence.[14]

RECENT ADVANCES IN SURGICAL MANAGEMENT OF LYMPHEDEMA

Success of surgical management of lymphedema is dependent on the severity of the disease. In tropical countries, where endemic filariasis is the predominant etiology, patients tend

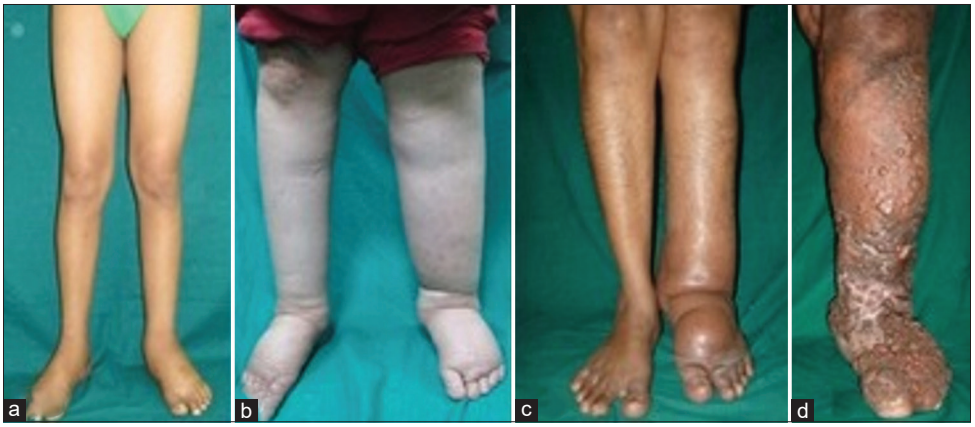

Figure 1: International society of lymphedema classification (a) Stage 0: subclinical lymphedema; (b) Stage 1: Pitting edema; (c) Stage 2: tissue fibrosis; (d) Stage 3: Skin changes.

to seek treatment only in late fibrotic stages with severe functional impairment of the affected limbs, where only radical excision and resurfacing surgeries will be the only possible option.[1] Ramachandran *et al.* have proposed an algorithm for lymphedema management based on the ISL stages.[15] In the last decade, with an increasing interest in the early management of post-mastectomy lymphedema, focus is shifting towards more physiologic surgical procedures to promote lymphatic drainage.[16] This parallels the advent of "super-microsurgery" as well as new imaging techniques such as ICG fluorescence and magnetic resonance lymphangiography to visualize the lymphatics and veins.[17,18]

Super-microsurgery is the technique by which vascular channels such as lymphatics of <1 mm diameter can be anastomosed.[19,20] Lymphatics are very small, transparent, thin walled and easily collapsible. Their identification, dissection and suturing demand considerable technical expertise and a thorough understanding of lymphatic anatomy and physiology of our body.[21] Patients in early stages of disease will benefit from procedures like LVA whereby lymphatic vessels are connected to the veins or by VLNT where lymph nodes from one donor lymph node basin are transferred to the affected area to reestablish the lymphatic drainage.[1]

LVA bypass surgery

By this surgery, subdermal lymphatic vessels <0.8 mm are anastomosed to subdermal venules under ×20 or ×30 magnification using 12-0 sutures.[1,21] Prior localization of lymphatics can be done with ICG mapping and lymphatics visualized intraoperatively by distal injection of isosulphan blue dye. Either end-to-end anastomosis or less commonly lymphatic side to end of vein allowing bidirectional flow of lymph is done [Figure 3]. Chen *et al.* described an "octopus technique" whereby multiple small lymphatic channels are anastomosed to a single vein to overcome the intravenous back pressure.[22] Similar technique of "multiple in one" was described by Yamamoto *et al.*[23] In "lymphatic microsurgical preventive healing approach" prophylactic lymphovenous bypass at the time of axillary lymph node dissection is advised to prevent post mastectomy lymphedema.[24] Several studies have shown objective reduction in circumference measurement, subjective symptom relief as well as reduction in the episodes of cellulitis post-LVA surgeries.[1,25-28]

VLNT

This surgery involves the transfer of functional lymph nodes with their blood vessels to a diseased area where native nodes have been removed and restoring their blood supply through microvascular anastomosis to recipient site blood vessels[29] [Figures 4a and b, and 5a-d]. It can be done in lymphedema

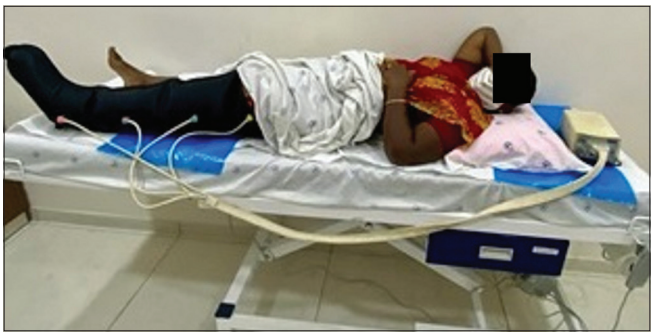

Figure 2: Intermittent pneumatic compression therapy for lymphedema of lower limbs

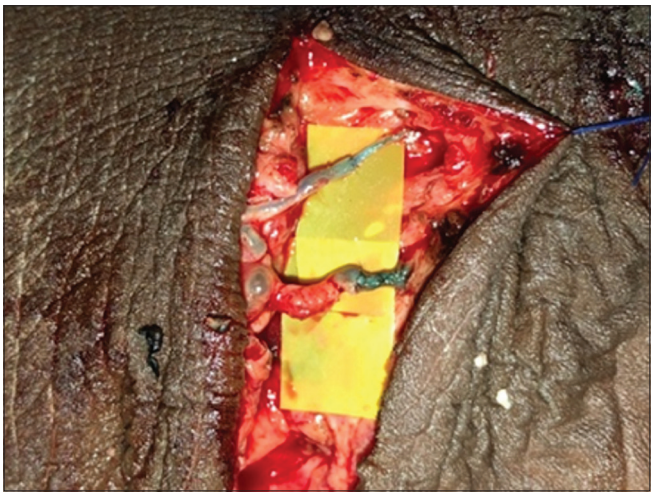

Figure 3: Intraoperative view of lymphatico-venous bypass under magnification

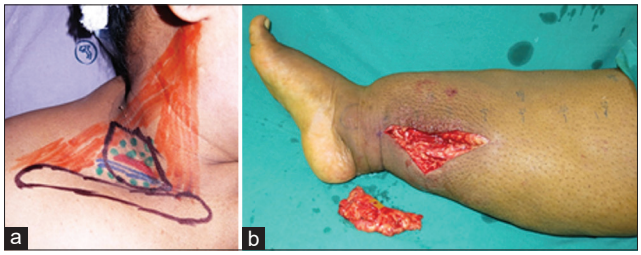

Figure 4: (a) Vascularized lymph node transfer from supraclavicular region; (b) vascularized lymph node transfer to the ankle.

with sclerotic changes and in combination with LVA or deep inferior epigastric perforator or other flap surgeries for breast reconstruction.[30] VLNT is postulated to work by growth factor induced neo-lymphangiogenesis. By this, collateral pathways to connect with adjacent lymph nodes are created, that restore outflow tracts.[31,32] Honokien *et al.* proposed that the VLNT act as a "lymphatic wick" to aid in lymphatic drainage.[33] The lymphatic flow is driven by a perfusion gradient between the newly restored arterial inflow and venous outflow in the VLNT. The transferred nodes can be

placed orthotopically (proximally) or heterotopically (distally) in the lymphedematous limb. While orthotopic proximal placement helps in concealment of scar, distal placements offer a gravitational advantage for lymphatic flow.[34]

Most frequently used technique is the groin VLNT that transfers superficial inguinal lymph nodes based on superficial circumflex iliac artery and vein.[35] Supraclavicular flap, submental flap, and lateral thoracic flaps are also being used less frequently.[36-40] Gastroepiploic-greater omental flap and jejunal mesenteric flap VLNT are modifications of pedicled omental flap and entero-mesenteric bridge procedures, which can be harvested through laparoscopic or even robotic surgery, thereby reducing patient morbidity.[41,42] Becker *et al.* demonstrated 40%–50% resolution of lymphedema by VLNT in post-mastectomy patients.[43] Keeley *et al.* have shown significant patient satisfaction on disease specific lymphedema quality of assessment following VLNT surgeries.[44] Donor site distal lymphedema is a dreaded complication of VLNT and is avoided by reverse lymphatic mapping and avoiding harvest of sentinel lymph nodes, draining the limb.[45]

Role of liposuction in lymphedema

In later stages of lymphedema, excessive subcutaneous deposits of adipose tissue are noticed due to slow or absent lymph flow. The presence of fat results in persistent non-pitting edema in extremities even after CDT. Liposuction has shown good results in non-pitting arm lymphedema and primary lower limb edema with complete reduction with 6 months of post-operative continued compression therapy.[46,47] The liposuction procedure has been shown unlikely to injure epifascial lymphatics.[48]

Surgical debulking of lymphedema

Despite the recent innovations, surgical debulking continues to be the mainstay of management in advanced class 3 lymphedema (with fibrosis and warty or ulcerous skin changes), filarial lymphedema and when microvascular facilities are unavailable.[3] Several modifications of the original Charles procedure of supra-fascial excisions and skin grafting have been described. Van der Walt *et al.* applied negative pressure wound therapy on the wound bed to improve skin graft take.[49,50] Modifications of Charles procedure (combining with VLNT and preservation of superficial veins) have helped to reduce worsening of distal edema and to prevent recurrent cellulitis.[51] Staged subcutaneous excisions beneath skin flaps are still required in advanced lymphedematous limbs with skin excess, but the raised skin flaps frequently have poor vascularity.[52] With the knowledge of anatomy of the perforators in the limbs, flaps with better vascularity can now be raised, while radical excision of the excess tissue gives esthetically and functionally better limbs [Figure 6a-d].[53,54]

CONCLUSION

Lymphedema has no cure, but more recently, the prospects of preventing progression and improving the quality of life are promising [Table 1].[55] Success of lymphedema management depends on the stage of the disease, availability of diagnostic and therapeutic options and the patient compliance. Recent advances such as ICG lymphangiography and micro-lymphatic surgery are showing promising results in early stages of the disease. However, if the patient presents in

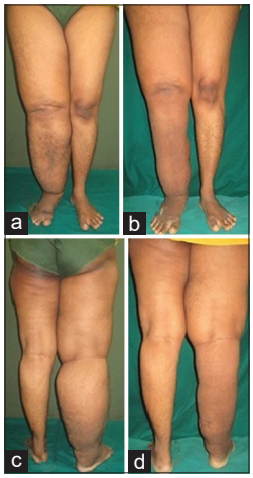

Figure 5: (a) Image before vascularized lymph node transfer from the supraclavicular region to the ankle; (b) image after vascularized lymph node transfer from the supraclavicular region to the ankle; (c) image before vascularized lymph node transfer from the supraclavicular region to the ankle; (d) post-operative image of (c).

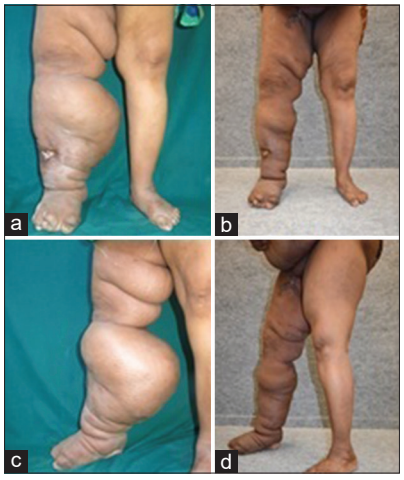

Figure 6: (a) Before debulking of post-filariasis lymphedema; (b) after debulking of postfilariasis lymphedema; (c) image before debulking of post filariasis lymphedema; (d) after debulking of post filariasis lymphedema.

Table 1: Do's and don'ts for lymphedema patients.

What you should do in lymphedema	What you should not do in lymphedema
• Refer patients with lymphedema to an expert clinic for inter (multi)-disciplinary analysis if lymphedema is present in one or more limbs and no obvious other explanation is present, especially if a child with lymphedema has other congenital anomalies or disorders • Every family with one or more children or adults with primary lymphedema should be referred for genetic counseling. Gene testing should be performed only in the context of evaluation by an inter (multi) disciplinary clinic, in which a clinical geneticist participates • The expert centers should organize a network of care and work with the local healthcare provider and have an open door policy. Ensure patient cooperation for treatment and do regular follow-up. Monitoring of the patient's weight and volume/circumference, with measurement charts and photographs should be done • After confirming the diagnosis of lymphedema, an interdisciplinary treatment protocol should be created for the individual patient with initial and maintenance treatment phases monitored by the lymphedema therapists • Measure the affected limb to provide "made to measure" garments, which should be frequently changed. Various compression technologies individualized to the patient should be used and the patient should be taught how to use them • Do exercise to reduce weight to maintain weight and prevent muscle wasting. Wear light compression garments during exercise if tolerated • Be aware of the daily recommended physical activity level for adults (10,000–15,000 steps a day). Have a normal healthy diet • The patient and care givers should pay attention to skin care, toenail problems and be vigilant for signs of cellulitis, interdigital fungal infections (Athletes foot) and eczema • Take preventive measures such as good hygiene following injury or insect bite, clean with soap and water and disinfect using topical antiseptic cream. Give prompt treatment of cellulitis/erysipelas • Be aware of medications that can increase swelling and consider the risks and benefits while prescribing them (calcium channel blockers, corticosteroids, NSAIDs, sex hormones, and related compounds, pregabalin, docetaxel, zoledronic acid, and sirolimus) • While caring for lymphedema patient with traumatic injuries consider extra compression to the swelling of the limb, monitor the swelling and be aware of the increased risk of cellulitis and consider antibiotic prophylaxis • Avoid the use of lymphedematous limb for blood blood pressure	• Do not perform routine genetic testing, lymphoscintigraphy, and blood examinations without dedicated lymphovascular expertise • Do not wait and see without follow-up • Do not do surgery for lymphedema without an interdisciplinary team approach • Do not operate in primary lymphedema before 18 years of age unless indicated • Do not fail to follow-up the patient • Compression therapy and MLD should be not done by untrained persons • Firm massages and hot fomentations over lymphedematous areas should be avoided • Do not ignore a worsening of the fit of the compression garment • Do not refrain from physical activity because of lymphedema or allow obesity to develop (BMI>29) • Do not sleep with lymphedematous limbs dependent • Do not overdo physical activities that may harm the skin without proper protection or cause muscle fatigue • Do not take antibiotics without clear signs of cellulitis/erysipelas • Do not withdraw compression without proper monitoring • Do not use diuretics to treat the lymphedema • Do not forget the routine lymphedema treatment (e.g., compression garments) while managing trauma • Precautions should be considered especially when an operation is performed on a lymphedematous limb, even for conditions which are not directly related to the lymphedema (e.g., varicose veins, and hydrocele) and routine lymphedema management should not be discontinued

MLD: Manual lymphatic drainage; BMI: Body mass index

end stage disease, combination of radical excisional surgery and VLNT may be the feasible option. It needs to be seen whether the emerging research in tissue engineering, lymphangiogenic vascular endothelial growth factor treatment and immunomodulatory therapy may provide better management options for lymphedema.[56-58]

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Image courtesy - Ganga Hospital, Coimbatore.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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