

INTERMITTENT PNEUMATIC COMPRESSION : IT'S EFFECT ON BACTERIAL SKIN LOAD AND T CELL MARKERS IN INDIAN LYMPHEDEMA PATIENTS

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Abstract

Background: Filarial Lymphedema develops from damage to lymphatics by adult parasite, leading to impaired lymph drainage. Management of filarial lymph edema is largely conservative. We present our experience of using intermittent pneumatic compression in stage 2, 3, 4 of filarial lymphedema. The patients with stage 2 lymphedema had significant reduction in the limb girth at all the levels in the limb except above knee following intermittent sequential pneumatic compression, which was not seen in subsequent stages. Significant reduction in the limb girth in early stage of the disease clearly reflects and supports the view that the pneumatic compression should be employed early to achieve maximum benefit. Use of intermittent pneumatic compression in the patients with filarial lymphedema patients leads to decrease frequency and severity of the attacks of Dermatolymphangioadenitis (DLA), favourable changes in cutaneous micro flora besides the change in the limb girth.

INTRODUCTION

Lymphoedema results from accumulation of tissue fluid in the interstitial space due to obliteration of the cutaneous Lymphatics (Segal et al. 1976). In India most common cause of lymphedema is Lymphatic Filariasis. (Ramaiah et al., 2000)

Problem is once acquired it remains for the life as there are no curative measure, so more emphasis is now being shown for prophylaxis and on the conservative measures. (Azhar et al. 2020)

There are several conservative methods for managing lymphedema of which most common are pressure garments and intermittent pneumatic compression (IPC). A lot has been said about the pressure garments and their gradual pressure gradient, but not much is said about IPC.

Problem statement

India is responsible for around 40% of global burden. Patients with chronic filariasis lose around 29 days of work every year due to complications of infection. Depressive illnesses are very common among the patient subgroup. (Ramaiah et al., 2000 ; Babu et al., 2006; Ton et al., 2015).

Aim of study

1. To see the effect of Intermittent Pneumatic Compression (IPC) on the limb girth at different pre-fixed levels of lymphedematous extremity in stage II, III, and IV lymphedema. [SEP]

2. To document the presence of various microbial organisms on the extremity skin of the patients with filarial lymphedema and see the effect of IPC. [SEP]
3. To see the presence of CD 4+ and CD 34+ T cells in the skin before and after IPC. [SEP]

Brief Review of literature

Acute manifestations of chronic filariasis are thought to be caused by bacterial infection of damaged skin (Dreyer et al., 1999). A history of local trauma and/or entry lesions, especially in the interdigital area, is common (McPherson et al., 2006), and recurrent episodes have been associated with progression of lymphedema.

Acute manifestations of filariasis often present with sudden onset of fever and painful lymphadenopathy. They may involve genitalia. Inguinal lymph nodes and lower extremities are commonly involved sites. Usually, it resolves after four to seven days. Recurrences typically occur one to four times a year; the number of recurrent events increases with increasing severity of lymphedema (Pani et al., 1995).

Immune response

Early in infection, filarial antigens provoke Th2-type immune responses. But later on, immune responses to parasite antigens are down-modulated with suppression of T lymphocyte proliferation and impaired Th1 and Th2 cytokine production, likely

contributing to the chronicity of infection (Nutman et al., 2011).

MATERIALS AND METHODS

The cross-sectional study was carried out in 214 patients attending the out-patient Department of Plastic Surgery. This study was approved by the Institute Ethical Committee.

Inclusion Criteria

The patient with secondary lymphedema of filarial origin with or without positive *Filaria* antigen test, at least 10 years of age.

Patients with cellulitis/ulcer or venous disease were not included. Also the patients with Genital Filariasis, edema with underlying systemic disease were excluded.

IPC was done using sequential circulator device, which has multi-compartmental inflatable sleeve that applies a sequential pattern of compression. Pressure gradient was kept from 60 to 90 mm of Hg. The duration of IPC was 60 minutes per day for 6 consecutive days a week for 6 months. Compressive garment was applied in-between compression therapy.

Punch biopsy/incisional biopsy was taken from the site of maximum enlargement of the affected limb before IPC and after 6 months of therapy and was sent for immunohistochemical analysis. Controls were taken from the normal tissue from the skin specimens of normal limbs undergoing plastic surgery procedures other than for lymphedema. Immunohistochemistry (IHC) was done for CD-4+ T cells, and CD-34+ T cells.

Pre and Post IPC measurement of the limb girth was done by specific measuring tape at fixed points at 1. Foot: dorsum of mid foot, 2. Ankle: just above the malleoli, 3. Mid-calf: 20 cm from medial malleolus 4. 5cm below knee joints, at the level of tibial tuberosity and 5. Above knee: 20 cm from medial femoral condyle.

The microbial samples were collected in swabs, from the crevices of the maximum enlargement site and from the second web space of foot by rubbing over the skin. Skin tissue scraped from the affected site for fungal culture. Drying of collected swabs was prevented and samples were processed as early as possible.

The pre and 6 months post pneumatic compression data of limb girth, irrespective of the stage of the disease, were compared at the different levels in a limb, and also in stage wise distribution. The limb circumference was measured in centimeter and expressed as mean \pm SD.

A double tail Student t-test was applied with significance at < 0.05 level using SPSS software version.^[16]

RESULTS

Limb girth

There was definite reduction of limb girth in all the patients with significant results in Stage II. (Fig 2,3,4)

Bacteriological Evaluation

The gram staining of skin surface swabs from 214 limbs before starting IPC revealed Gram-positive organisms in 102(48.5%) samples and only 14 (6.5%) were found to be gram negative. The remaining 96 samples (45%) did not reveal any microorganism. Many of them later were discovered to be commensals.

On culture, Blood Agar and MacConkey's agar plates, it resulted in positive culture in 58 (27.1%) and remaining 156(72.9%) were sterile. *Staphylococcus aureus*, *Bacillus cereus*, *staph saprophyticus* were the most predominant microorganisms isolated followed by *Micrococcus* spp. However, *Klebsiella pneumonia* isolated from the second interdigital web of the affected foot in two persons.

Fungus was found on culture in 10 limbs (4.3%), all from Stage IV lymphedema, 08 from the second interdigital space and two from the crevices of deep skin fold. Out of the fungal isolates obtained some were yeasts and filamentous fungi. There were two cases of *candida albicans*.

Immunohistochemical Evaluation

CD4+ T cells were positive in 52 (78.7%) and CD-34+ T cells were positive in 14 (21.2%). At the end of 6 months of IPC, CD4+ T cells were seen in only 12 (18.1%) and CD 34+ T cells in 36 (54.5%) patients.

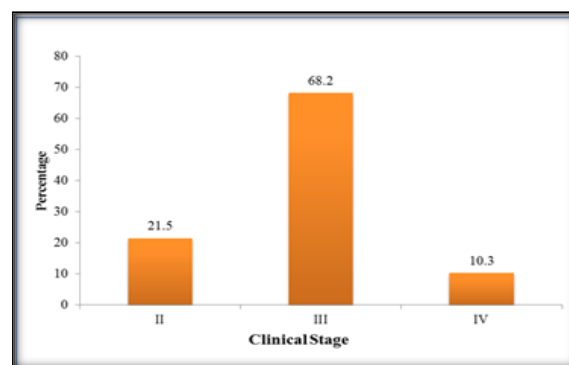


Figure 1: Total distribution of lymphedema patients in our study

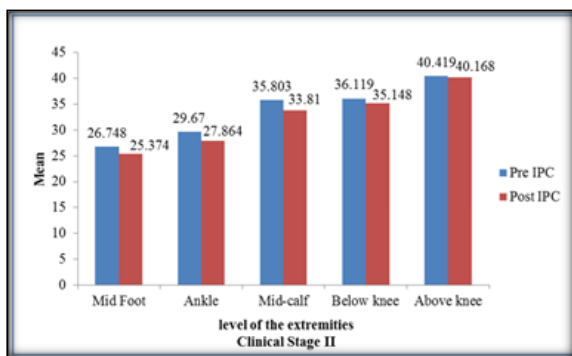


Figure 2: Reduction following pneumatic compression in all the regions of the affected lower extremity from mid-foot to below knee

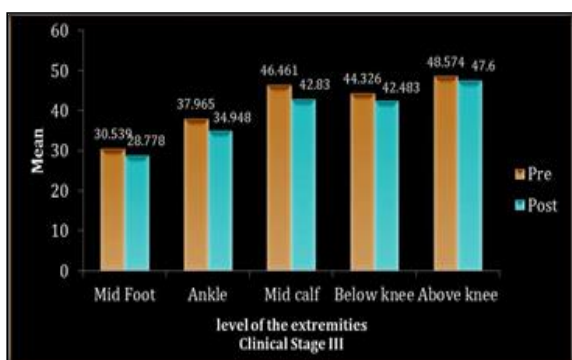


Figure 3: Stage III lymphedema with more solid component, significant reduction in the limb girth at the level of mid-foot, ankle, and mid-calf level, insignificant reduction below and above knee in lymphedematous limbs

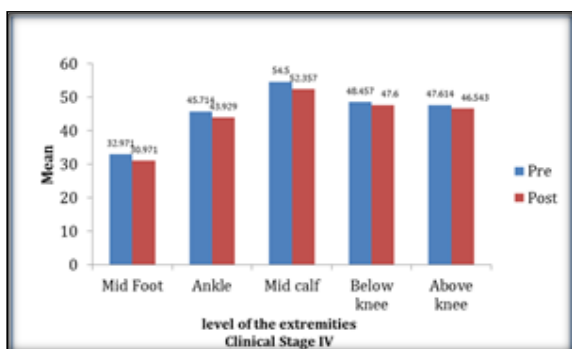


Figure 4: Stage IV lymphedematous limb did not significantly yield to intermittent pneumatic compression at any level from mid foot to above knee

DISCUSSION

The longer duration of the disease in our patients also resulted into an overwhelming majority of them suffering from attacks of Dermatolymphangitis (DLA) (88.8%) with over 40% experiencing it more than twice in a year. But about 10% of them (all of the Stage 4 patients) had more than 4 bouts of DLA in a year. Panicker et al. (1990) estimated the number of attacks of DLA per year in a study carried out in the lymphedema patients in Pondicherry and Sherthallai in South India and found that there were an average of 4.47 attacks of DLA per year lasting for 4 days on an average. However, these

attacks tended to be more prolonged and frequent in the presence of persistent lesion such as eczema, paronychia, or severe fungal infection. Jamal et al. (2005) also reported the incidence of DLA in 99% of their patients with history of on an average 5 attacks of DLA (range 1-24) in a year at the time of presentation. The repeated attacks of DLA are indirect evidence of improper care of the edematous extremity and the necessity of employing conservative measures more regularly and efficiently.

Shenoy et al. (1995, 1998, 1999) postulated that presence of moisture in the web spaces of the closely apposed swollen toes promotes fungal infections damaging the skin, which in turn favour the entry of infecting organisms.

However, we could establish fungal infection in only 4.3% of the patients and two patients had it in the second interdigital web skin of the affected extremity and two in the crevices of thick skin fold in the lower leg, all in stage 4.

Jamal et al. (2005) isolated Gram+cocci, Spore forming bacilli, and Corynebacterium from the skin surface of the affected extremities. 60% of the Gm+cocci were Micrococci, 20% were coagulase-negative Staph, and 20% were Aerococci. Joseph et al. (2004) proposed Streptococci to be responsible for the attacks of DLA as they found elevated titres of anti-streptococcal antibodies in 84% of the attacks recorded.

We found Staphylococcus aureus, Bacillus cereus, Staph saprophyticus were the most predominant microorganisms isolated followed by Micrococcus spp. Two patients, both stage IV lymphedema with severe involvement of foot, revealed Klebsiella pneumonia.

Other authors reported presence of not only some commensal bacteria (eg, Staphylococcus epidermidis and coagulase-negative strains, S aureus, and Corynebacterium) but also other pathogenic microbes emanating from the perineal region (eg, Enterococcus, Enterobacter, Acinetobacter, Proteus, Escherichia coli, and Pseudomonas). These authors believed that these commensals, on getting entry into the tissue, proliferate and become pathogenic, (Olszewski, 1996; Karonidis & Chen, 2010). Olszewski, (1996) and Celestin et al. (2007) believed that as the host immune response decreased, its inability to neutralize and eradicate the microorganisms penetrating the skin made these organisms to persist in the host tissue and cause attacks of delay from time to time. Olszewski (2018) in another study found that the cocci isolated from the skin surface of lymphedematous limbs were primarily staphylococci and other coagulase negative strains in 60-90% of the isolates. He also found E.coli, Citrobacter, and Bacillus cereus but less frequently. An important observation made by him was that although these organisms were susceptible to most of the antibiotics but has low susceptibility to Penicillin. Despite this fact he found long acting penicillin to be efficient in preventing the attacks of

DLA. Our experience in this region of the country was also the same since Penidure Prophylaxis (Benzathine Penicillin 12 lakh IU every three weeks) prevented such attacks of DLA in our patients. We kept our patients on long acting Penicillin therapy administered every three weeks as long as they underwent pneumatic compression. Some authors believed that infections in some patients might lead to secondary lymphedema by causing lymphatic dysfunction, (Soo et al., 2008; Valente et al., 2000). This concept was supported by Jones et al. (2018). We feel that lymphedema in initial stages is due to irritation by the filarial worm leading to recurrent lymphangitis, and its further progression was due to superadded bacterial invasion through minor cracks in skin due to poor skin care and hygiene as the adult worm dies after 5-6 years. Thus, proper care of skin hygiene by using various measures as discussed earlier and by avoiding bare foot walking are important pillars of conservative care.

We measured the limb circumference of our patients and not the limb volume as an outcome of IPC because the total changes in the limb volume do not reflect the alteration in the limb volume at different levels from mid-foot to thigh. Zaleska et al. (2014) also felt that the girth measurement was a better index than the limb volume for understanding the mechanics of fluid translocation under IPC.

Significantly greater reduction in the limb circumference in earlier stage of the disease like in stage 2 and also to some extent in stage 3 as compared to stage 4 in our patients was perhaps due to greater fluid component responsible for edema and increased girth. However the progression of the disease from stage 1 to 4, and repeated attacks of DLA cause more and more dermal fibrosis and deposition of fat in the subcutaneous tissue. Thus, in advanced stage of the disease, fat deposition and fibrosis contribute much more to the increased limb girth than the fluid may do.

Tashiro et al. (2017) analysed the adipose tissue taken from the healthy limbs and from lymphedematous lower limbs and noted significant differences between the two. They found that the fat from lymphedematous limbs had larger lobules, surrounded by thicker collagen matrix and lymph fluid than that from the healthy limbs. They further observed that the adipocytes from the unaffected limbs were uniform in size and were unruptured as compared to adipocytes from the affected limbs which were varying in size and were hypertrophic. We also observed the large chunks of fatty tissue in the subcutaneous region of the affected limb intra-operatively in those patients who underwent limb reduction surgery as well as in histologic sections.

Rabe et al. (2020) reported skin irritation, discomfort and pain as the most common adverse events in the patients undergoing compression therapy. However, none of our patients reported any of such events following the use of IPC

Some improvement in the limb circumference in our stage 4 lymphedema patients, though insignificant,

could be explained from the fact that some fluid channels might have been formed in the subcutaneous tissue region as also reported by Zaleska et al. (2015). Using the advantage of the sophisticated technology, they demonstrated formation of such channels on Lymphoscintigraphy, and such channels were spared from the brunt of fibrosis.

Wilson et al. (2004), however, dealing with filarial lymphedema patients demonstrated about 50% reduction in the perivascular infiltrate and other histologic features at the end of one year only with conservative measures such as hygiene, skin care, elevation, and lower limb movement. We also achieved significant improvement in the various histologic features such as Lymphovascular changes, Perivascular lymphocytic infiltrate, Hyperkeratosis and Acanthosis, elongation of rete pegs, and collagen deposition in the dermis but with IPC and other conservative measures much earlier only in 6 months. This perhaps could be attributed to use of greater pressure and sequential circular technique used in inflation of sleeve in our patients.

Olszewski et al. (2009), and Zaleska et al. (2013) recommended to use the IPC for long period of time at high pressure with a specially designed pneumatic pump which prevented fluid backflow and was more efficient in formation of tissue channels. There are many researchers (Belgrado et al., 2007; Pilch et al., 2009; Rockson, 2010) who have found the IPC to be beneficial in the management of lymphedema but all those subjects had lymphedema of non-filarial in origin

The inflammatory changes in lymphedema have been characterized by CD 4+ T cells. Avraham et al. (2013) found the number of such cells to correlate with the severity of disease. Other authors have also concluded that the activation of CD 4+ cells is essential for development of lymphedema, (Nores et al., 2018; Ly et al., 2019). Nores et al. (2018) are of the opinion that after reaching the skin, CD4+ T cells promote impaired lymphangiogenesis, fibrosis, and increased inducible nitric oxide synthase (iNOS) expression all of which were helpful in producing lymphedema.

We could carry immunohistochemical study in 66 patients with CD 4+ T cells dominating in the majority (52), and CD 34+ T cells in 14 patients. We found CD 4+ cells in all the patients with stage 4 and in few cases of stage 3 with long standing lymphedema of more than 10 years. However, olszewski et al. (1993) found CD68+ cells (macrophages) to be the most common cells in the lymphocytic infiltrates in the tissue from lymphedematous extremities. They observed that the skin specimens of non-filarial patients revealed increased numbers of CD1+ epidermal Langerhans cells, and moderate pericapillary infiltrates of CD68+, CD4+ and CD8+ cells.

Conflict of interest

There is no conflict of interest.

CONCLUSION

We found Intermittent pneumatic compression to be an effective conservative modality for treating lymphedema of extremity, and can propose without hesitation that it needs to be used regularly for sufficient length of time or even for life long to decrease the morbidity and improve the quality of life. It can be used in any stage of the disease as long as the limb can be accommodated in the pneumatic sleeve and is free of ulcers or weeping lesions.

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