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TREATMENT OF CHRONIC POSTMASTECTOMY LYMPHEDEMA WITH LOW LEVEL LASER THERAPY: A 2.5 YEAR FOLLOW-UP

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ABSTRACT

Ten women with unilateral arm lymphedema after axillary clearance (radical mastectomy) and radiotherapy for breast cancer received 16 treatment sessions with Low Level Laser Therapy (LLLT) over 10 weeks and seven patients were followed for 36 months. The effect of LLLT was monitored by arm circumference, plethysmography, tonometry, bioimpedance and a questionnaire dealing with subjective symptoms. After treatment, edema volume (both extracellular and intracellular) was decreased, the tissue (except for the upper arm) progressively softened or approached a normal texture, and the patients reported improvement in aches/pains, tightness, heaviness, cramps, pins/needles, and mobility of the arm. Skin integrity was also improved and the index for risk of infection decreased. Follow-up assessment at 1, 3, 6, and 30-36 months showed varying trends although at 30 -36 months most subjective parameters and bioimpedance derived data on ECF and ICF tended to return toward pre-treatment levels. Arm circumference continued to show overall improvement, however, with a volume reduction of the affected arm reaching 29%. Tonometry also showed maintenance of near normal values for the involved forearm and anterior and posterior chest; however, the upper arm showed progressive induration. The data suggest that laser treatment, at least initially, improved most objective and subjective parameters of arm lymphedema.

Operations and irradiation that involve radical destruction of lymph nodes and lymph vessels favor the development of peripheral edema. Initially, the tissue fluid load gradually exceeds the carrying capacity of lymph collectors and tissue fluid and lymph (containing plasma proteins) begins to accumulate in the perilymphatic tissue (1). As a result, there is subtle but gradual fibrosis of the lymphatic vascular wall and surrounding tissue through radial spreading (2), and lymph propulsion becomes progressively restricted. Radiotherapy also impairs the ability of lymphatics to regenerate (3). This phase, where changes in limb volume or soft tissue texture and circumference are still minimal (2,4) is termed the latent phase (1). With superimposed limb infection, trauma, or after strenuous exercise, however, the remaining lymphatic system becomes further deranged leading to overt limb swelling (4-6), which is termed clinically "lymphedema."

The incidence of peripheral lymphedema after radical treatment for cancer is estimated at 30% for the arms (9) and legs (10,11), although the statistics vary with the extent of dissection, radiotherapy (12), and the accuracy and discrimination of the measuring equipment. Lymphedema once established rarely resolves without treatment. Many current treatment protocols such as sleeves, bandaging, massage are time-consuming and relatively expensive to the patient and health care system. While effective (1,3), these non-operative treatments are not always available or feasible. In Australia, for example, only 33% of patients have private health insurance. With shrinking health care funds, there is a need for patients with non-lifethreatening chronic disorders to take greater responsibility for their care, whereas for health providers, there are equally complex decisions to make as, for example, whether to treat one patient intensively or to treat many patients less aggressively. Whereas laser therapy for lymphedema may not replace high-quality physiotherapy using appropriately fitted external garments and bandages, it may be of benefit or perhaps in combination with physiotherapy attain satisfactory patient outcome where funding is limited.

Studies of the efficacy of lymphedema treatment often focus solely on change in limb size. However, lymphedema is more than a disorder of size, encompassing also mobility restriction (13,14), anxiety, pain, heaviness, tension (4,5), and sensory deficit (9). Psychological morbidity and maladjustment are also common (15), which tend to improve as limb swelling regresses. Thus, treatment which improves the quality of life by reducing the organic and psychological complications while reducing the size of the limb for limited cost and effort would have a significant advantage over many other treatments currently advocated.

Experimental evidence suggests that Low Level Laser Therapy (LLLT) is effective for chronic lymphedema. The mode of action of LLLT on lymphedematous tissues is probably multifaceted resembling the actions of benzopyrones (16,17) and complex physical (lymphatic) therapy (33). Presumably, by increasing lymph flow (18), LLLT reduces both the amount of surplus tissue protein and fluid and thereby improves limb performance. Whereas the effect of LLLT on pain is still unclear because of a lack of double-blinded clinical trials, several reports describe subsidence of pain after LLLT (19-25). Whereas Gam et al (26) and Hall et al (27) have suggested LLLT is ineffective, these studies were conducted on patients with acute disease. To date, there have been no reports on the efficacy of laser treatment for chronic lymphedema.

MATERIALS AND METHODS

Eleven women entered the study; however, one was excluded after a severe bout of arm infection following an injury. One patient was excluded at the 6 month follow-up and two others failed to appear at 6 and 30 months.

Inclusion Criteria

Each patient underwent a unilateral standard or modified radical mastectomy with subsequent radiotherapy. Lymphedema arm volume was estimated between 130% and 160% greater than the normal contralateral arm. Patients had lymphedema for 3-10 years. Each showed notable fibrotic induration of the soft tissues (tonometry), and particularly of the anterior and posterior chest. Pretrial questioning disclosed each patient had arm complaints of varying degrees including aches, pains, tightness, heaviness, cramps, burning, pins and needles, and restricted arm mobility. Van Dam (9) and Husted et al (28) report the incidence of these complaints to be between 29-47%, which conforms to our group of patients.

Exclusion Criteria

Patients were excluded if metastasis was detected, the presence of other chronic inflammatory conditions, medication known to alter body fluid balance, ongoing massage or compression therapy (within the previous month), a past history or documented venous thrombosis, or continued radiotherapy. Patients were requested to contact us if any of these events occurred during the treatment or post-treatment period.

Apparatus

A Space Mid M3-UP Laser with a scanning head, comprising a 6.5 mW Helium Neon Laser emitting at a wavelength of 632.8 nm and two semiconductor diode infrared lasers (IR) emitting at a wavelength of 904 nm was used. The average power output at 904 nm was 14 mw. The 904 nM wavelength penetrates cutaneous and subcutaneous barriers without increasing the temperature and has an effect on tissues 5 cms below the surface. The 632.8 nm wavelength penetrates only to approximately 0.8 mm, and its power is 10 mw.

Assessment Schedule

Each patient acted as her own control while the contralateral arm was used as a baseline indicator for changes. Treatment was administered with the patient supine for 10 minutes each on the upper and forearm followed by 10 minutes to the axilla. Times varied slightly to ensure delivery of the appropriate level of energy to each site. There were 16 Laser treatment sessions. The dose range was 2-4 joules/cm^2 per treatment (29). There were 2 sessions in each of the first 6 weeks followed by a single session each week for a further 4 weeks. The total duration of therapy was 10 weeks.

Effect of Therapy

The following measurements were performed on the contralateral (control) arm and on the arm on the side of the mastectomy before the first laser treatment and thereafter at biweekly intervals until completion of treatment. The arms were again measured at 1, 3, 6, and 30-36 months after laser treatment.

a) Limb circumference at 10 cm intervals using a tape measure, at 7 anatomically based points on the arms including 10 and 20 cm proximal and distal to the antecubital fossa, at the wrist and mid-palm (1,5).

b) Volume determination using a plethysmographic tank with a standardized procedure (30).

c) Tissue tonometry (resistance of the tissues to compression) using three estimates at each of four sites—10 cm proximal and distal to the antecubital fossa and over the anterior and posterior chest at the mid-points of the respective "lymphotomes" (5,6).

d) Bioimpedance to determine extracellular and intracellular fluid volume (31,32). For this measurement, the first pair of electrodes were placed at the wrist and 10 cm proximal whereas the second pair were placed 10 cm and 20 cm proximal to the antecubital fossa.

e) Questionnaire. Each patient was interviewed and subjective comments regarding limb mobility, tightness, heaviness, aches/pain, cramps, pins/needles, circumference, and sensation of heat/burning were recorded using a 5 point Lichert scale. Skin integrity and infection risk were also assessed using a 5 point scale. Each fortnight, during the treatment period, each patient was questioned whether they noticed changes in the above parameters compared with the previous two weeks. If there was no change, then the previous score was unchanged; if greatly improved, the score was decreased by 1 and if it greatly worsened, it was increased by 1. If the patient reported slight improvement or slight worsening, then the score was altered by 0.5 accordingly. A similar rating system was applied to the post-treatment follow-up period. For verrucous changes of the skin, a "wart count" was made with the naked eye recognizing that small warts may be overlooked. With these three latter sets of data, there exists possible researcher bias because it was clear that all patients were treated and which arm was affected. It was also recognized that in the post-treatment period, the ability of the patient and of the researcher to rate on a comparative basis to a

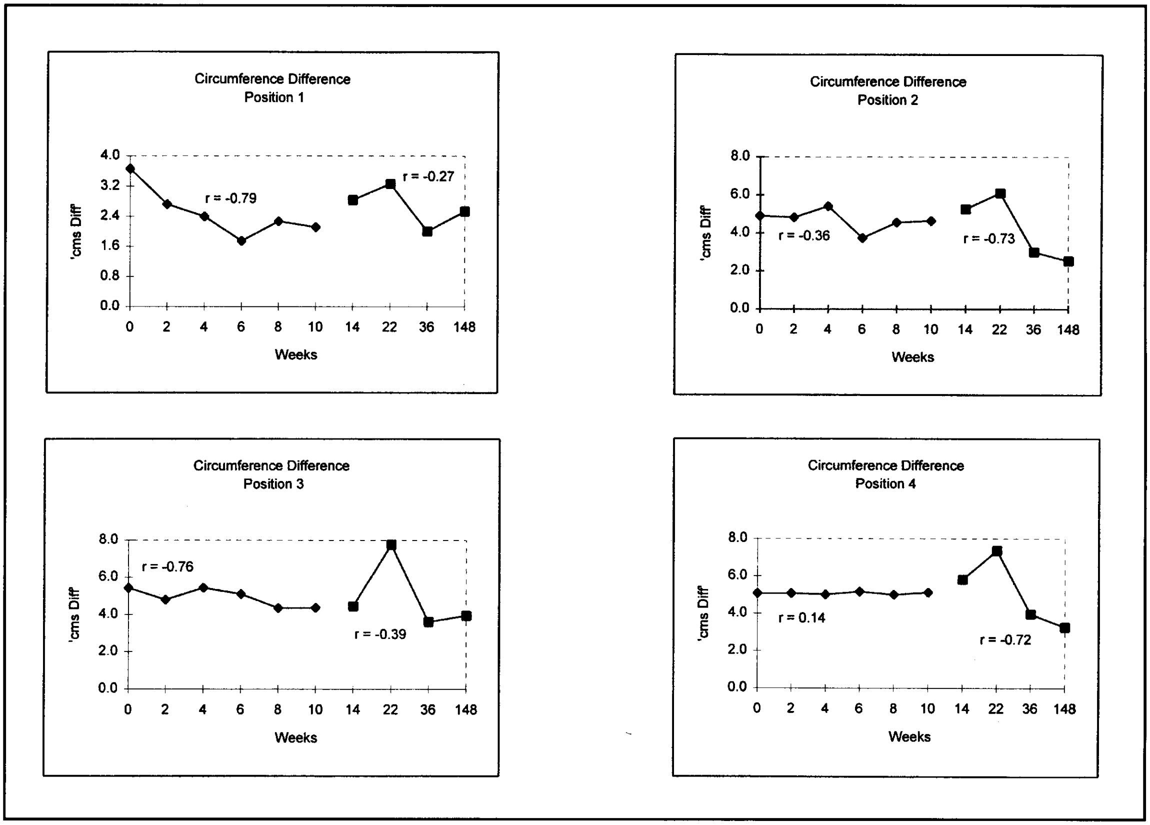

Fig. 1. Changes in circumference at indicated positions during treatment (◆) and post-treatment (■) periods. Position 1—upper arm (proximal); Position 2—upper arm (distal); Position 3—elbow; Position 4—upper forearm.

period 2.5 years earlier created uncertainty in the accuracy of the post-treatment subjective data.

Other than basic information about skin care and a list of "do's and don't's," patients did not receive other instruction on how to manage the arm lymphedema. On the other hand, patients may have obtained information from the news media and other patients over the 30 month trial period, and these may have contributed to better arm management. No attempt was made to determine the impact of these confounders with the exception of exclusion of those patients who had other significant accepted treatment directed at the lymphedema.

RESULTS

We have previously reported (49) preliminary changes after laser therapy for lymphedema although in a different format and with different exclusion criteria. The following results concentrate on the findings from the 30 month post-treatment period beginning 4 weeks after the end of treatment.

Circumference Changes

Position 1—upper arm (proximal) (Fig. 1a)

The greatest reduction in circumference was in week 6 of treatment (1.9 cm). There

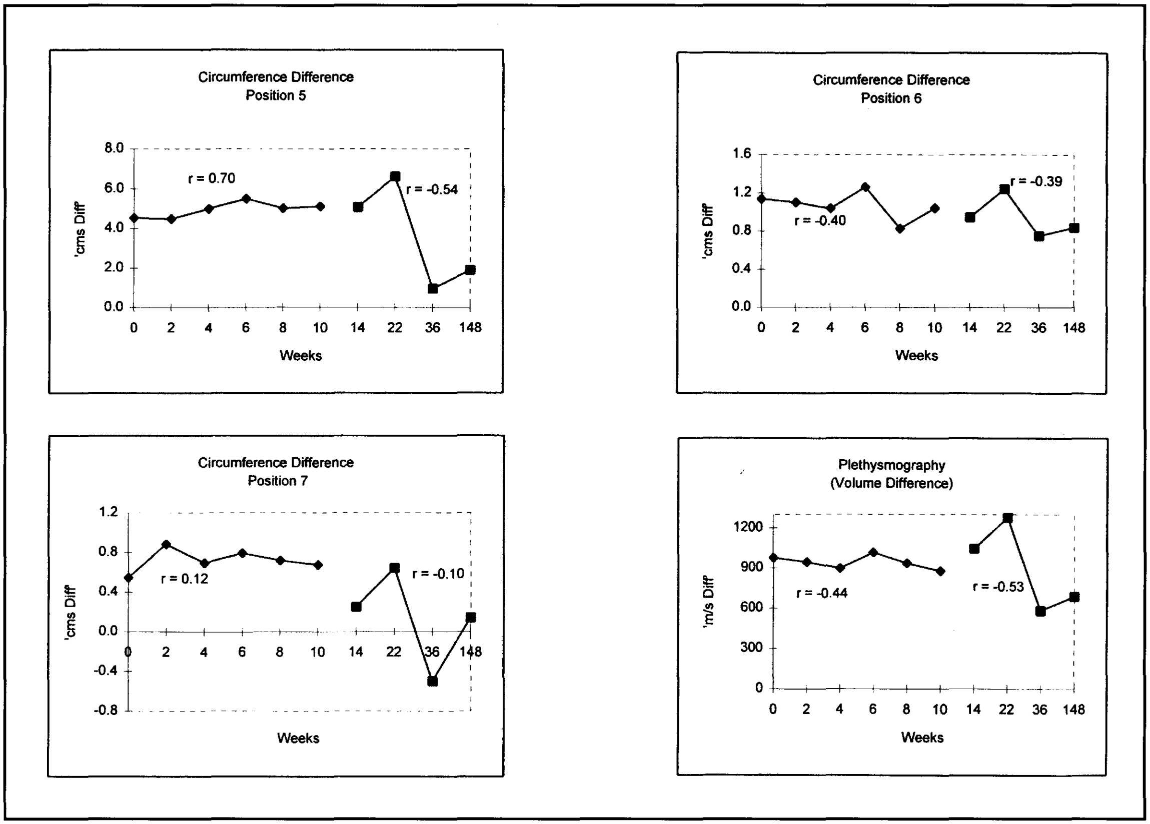

Fig. 2. Changes in circumference at indicated positions during treatment (◆) and post-treatment (■) periods and changes in volume difference (lower right) during treatment (◆) and post-treatment (■). Position 5—lower forearm; Position 6—wrist; Position 7—palm.

was a strong correlation between duration of treatment and reduction (r= -0.79) but by 1 month, the reduction decreased to 0.85 cm. At 3 months post-treatment, the reduction was 0.43 cm. This trend was reversed slightly at 6 and 36 months, so that there was a weak relationship between post-treatment time and arm circumference changes (r= 0.27). At 36 months, the average circumference difference was 1.1 cm. These trends were similar at most other measured arm sites.

Position 2—upper arm (distal) (Fig. 1b)

The greatest reduction in circumference was in week 6 of treatment (1.75 cm). Correlation was weak between duration of treatment and reduction of circumference (r= -0.36). For the first two observation periods post-treatment, arm circumference increased but thereafter showed a reduction to a maximum of 2.45 cm at 36 months. Overall, there was a continued reduction in arm circumference (r= -0.73).

Position 3—elbow (Fig. 1c)

The greatest reduction in circumference was 1.1 cm (treatment weeks 8 and 10). There was a good correlation (r= -0.76) between treatment duration and circumference reduction. At 3 month post-treatment, there

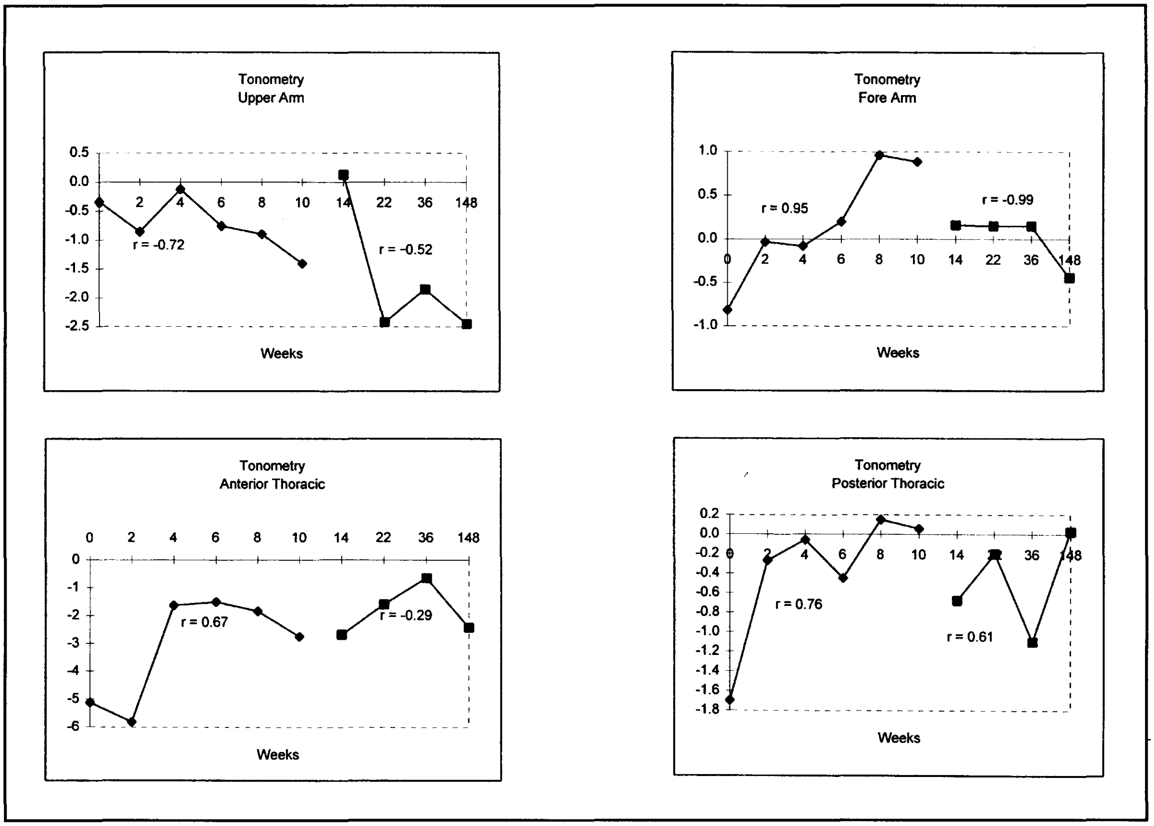

Fig. 3. Changes in tonometry of major anterior upper and lower arm lymphatic territories, and in anterior and posterior thoracic lymphatic territories during treatment (◆) and post-treatment (■) periods.

was an increase in circumference but at 6 and 36 months, arm circumference decreased with an overall weak correlation (r= -0.39).

Position 4 — upper forearm (Fig. 1d)

There was no notable change in circumference over the 10 week treatment period (r= 0.14). However, post-therapy showed reduction in arm circumference greatest at 36 months (1.8 cm) (r= -0.72).

Position 5 — lower forearm (Fig. 2a)

Circumference comparisons showed an increase over the treatment period (r= +0.70). However, as per position 4, there were post-therapy reductions in circumference with the greatest being 3.6 cm at 6 months with a relatively strong correlation (r= -0.54).

Position 6 — wrist (Fig. 2b)

Arm circumference showed considerable reduction over the treatment period with a maximum of 0.3 cm at 8 weeks (r= -0.4). The reduction continued post-treatment with the greatest reduction at 6 months (0.39 cm) (r= -0.39).

Position 7 — mid-palm (Fig. 2c)

There were initially slight increases in circumference most evident at 2 weeks (0.3 cm increase). However, subsequently there was a reduction to near pre-treatment

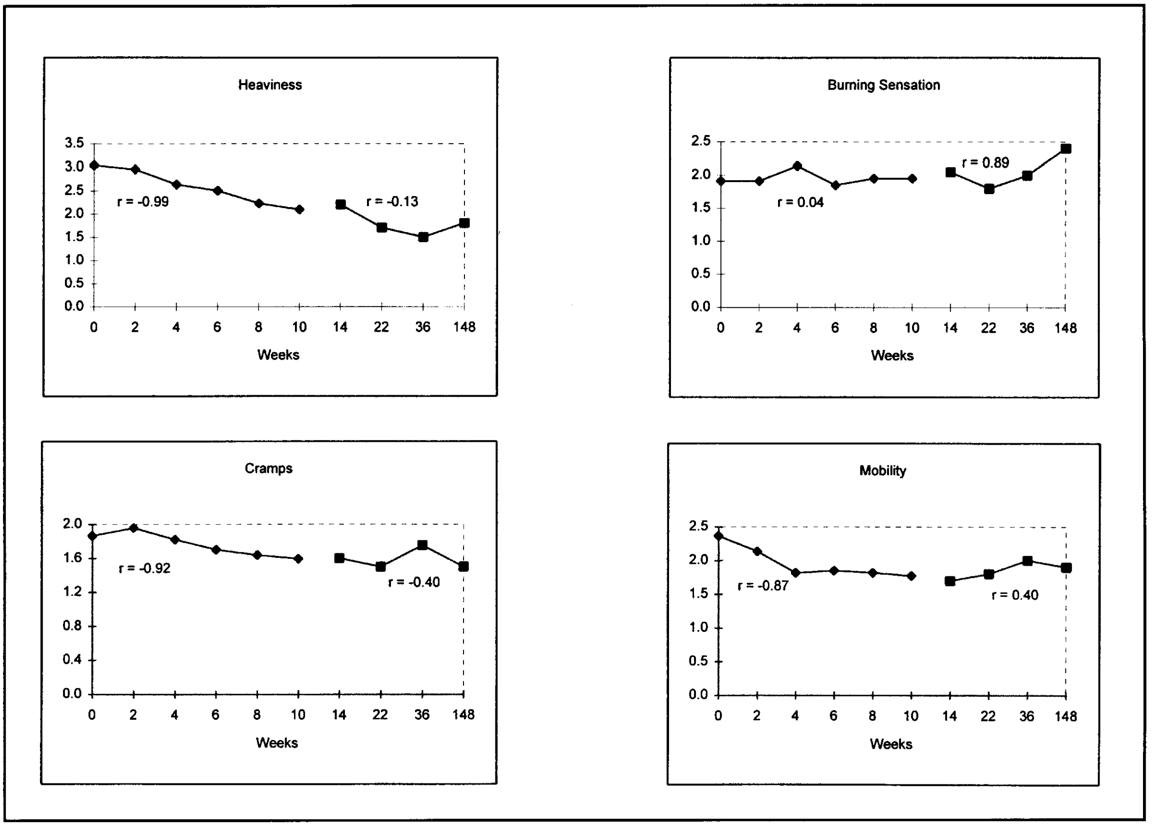

Fig. 5. Changes in indicated subjective parameters during treatment (◆) and post-treatment (■) periods.

values indicate less resistance to compression (i.e., softer tissue). Thus, with a large amount of mobile interstitial fluid, the tonometer depresses the tissue more readily displaying a higher value. For edema with fibrosis, depression of the plunger is less, thereby displaying a lower value. Details have been described by Clodius et al (34) and Clodius and Piller (1).

Tonometry of the upper arm (10 cm above the antecubital fossa) suggested increased fibrotic induration over the treatment period (r= -0.72). (This finding may relate to the reduction in circumference at this site with the underlying deep fascia closer to the skin surface, thereby creating a potential artifact.) This trend continued during the post-treatment period (r= -0.52).

Tonometry of the forearm (10 cm below the antecubital fossa) showed marked softening over the whole treatment period (r= 0.95). For most of the post-treatment period, there was no difference between the normal and lymphedematous arm. By 36 months, however, a tendency towards greater fibrosis was recorded, although again this may be an artifact created by ongoing volume and circumference reduction.

Tonometry of the anterior chest showed softening after an initial hardening phase of 2 weeks. However, by 10 weeks, there was a tendency towards increased fibrosis (r= 0.67). However, this finding was much less than the pre-treatment indicator of fibrotic induration. In the post-treatment phase, improvements were maintained although by 36 months, a

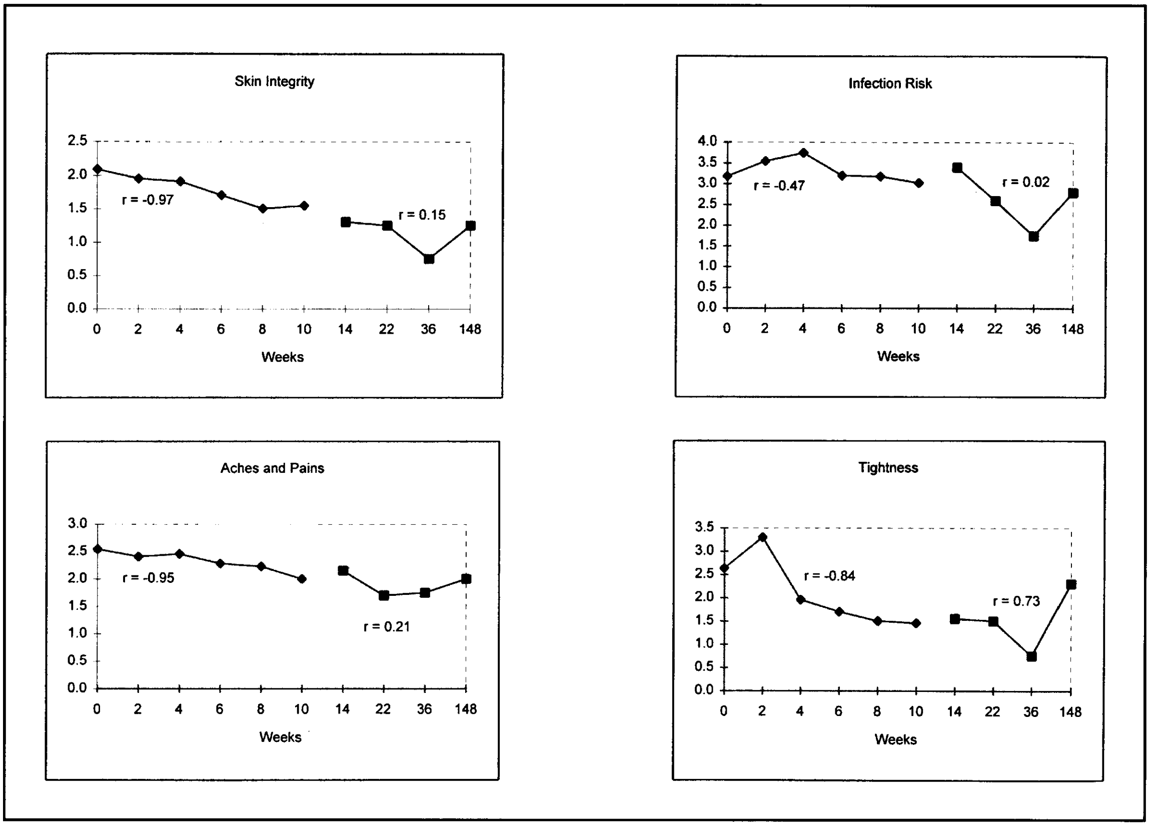

Fig. 6. Changes in indicated subjected parameters during treatment (◆) and post-treatment (■) periods.

tendency towards induration returned (r= 0.29). Tonometry of the posterior chest showed similar improvements to that of the anterior chest; however, here the improvements persisted and at 36 months, no tonometric difference was detected between the affected and contralateral chest (r= 0.76).

Bioimpedance (Fig. 4a-c)

Multifrequency bioelectrical impedance has recently been introduced to assess changes in fluid, fiber, and fat content of tissues (31,32). Over the 10 week treatment period, the calculated impedance values associated with the extracellular fluid (ECF) showed a significant reduction in volume (r= -0.82). During the post-treatment, a tendency to pre-treatment levels returned (r= 0.28). Intracellular fluid (ICF) compartment volumes also showed an initial reduction (r= -0.70), although again after treatment, a tendency to return to the above initial treatment level developed (r= 0.74).

Subjective perceptions (Fig. 5,6)

Skin integrity. Skin integrity improved significantly with treatment (r= -0.97). The trend continued post-treatment with the exception of the last observational period when it deteriorated. This latter finding made the association between time after treatment and skin integrity weak (r= 0.15). However, *end* point integrity was significantly better than *entry* point integrity (mean 1.25 vs. 2.09).

Infection risk (Index). This index was based on many factors including skin integrity, wounds, sores, solar keratoses, and disruption or disfigurement of the skin. The Index showed an increase over the first 4 weeks and a reduction thereafter. Overall, the improvement was moderate (r= -0.47). Post-treatment, the Index started at a higher point initially, then there was a rapid reduction over the ensuing 6 months but a return to near initial pre-treatment levels by 2.5 years (r= 0.02).

Aches and pain. A strong correlation existed between treatment duration and aches and pains (r= -0.95). The trend continued post-treatment but showed a reversal at the final observational period. The correlation overall was mildly positive (r= 0.21).

Tightness. At 2 weeks after the start of treatment, there was an increase in perception of tightness, but the general trend was for a continuing reduction (r= -0.84). This trend continued for the next 6 months, but the 2.5 year follow-up showed a significant reversal (r= 0.73).

Heaviness. There was a strong correlation between duration of treatment and a reduction in feelings of heaviness (r= -0.99), which continued into the post-treatment period but showed a reversal at 2.5 years (r= -0.13).

Burning sensation. This feeling of heat in the superficial or subcutaneous tissue may be "sharp" or "blunt" and no notable change occurred with treatment (r= 0.04). However, the perception worsened (r= 0.89) post-treatment and was most marked at 2.5 years.

Cramps. A strong correlation was found between the duration of treatment and reduction in cramps (r= -0.92); however, on a Lichert scale the changes were less than those of aches/pains, tightness, or heaviness. The trend continued post-treatment but with a reversal at 6 months the correlation was weak (r= -0.4).

Arm mobility. During treatment the perception of arm mobility improved (r= -0.87) despite an average change of approximately 0.6 units. Post-treatment, however, this trend was reversed with greater reduction in arm mobility (r= 0.4), although overall perception was that arm mobility was still better than at the start of treatment.

DISCUSSION

The efficacy of LLLT in treatment of swelling remains unclear primarily because of lack of control groups in conditions where spontaneous or natural repair is expected (e.g., sprains/strains) and where chronic conditions show fluctuating severity. There is also disagreement about the depth of penetration and scatter and reflection of the laser beam in the tissues (48). Because a chronic condition such as lymphedema is not likely to resolve spontaneously and the condition tends to be progressive, the importance of a non-treated control group is less problematic. Moreover, lymphedema is a disorder confined to the epifascial compartment (1); accordingly, issues related to scatter, reflection, and depth of the laser beam are less relevant.

LLLT is thought to increase lymph vessel diameter, contractibility, and facilitate lymphatic regeneration (collateralization) in untreated but otherwise damaged tissues (35). Low Level Laser is also reported to stimulate the phagocytic activity of neutrophils and monocytes (36), release agents from macrophages which stimulate or inhibit fibroblasts (37), activate the immune system (38), and improve neural function (39). Experimental studies have also suggested both microscopically and grossly that LLLT aids in resorption of edema fluid (23,40). Others have described that LLLT improves wound healing (24), favors lymphatic and blood vascular regeneration (42,43), and reduces scar adhesion to underlying tissues (35).

In lymphedema, enhanced activity of tissue phagocytes is thought crucial for reducing tissue swelling by proteolysis (2,4,16,17). This effect not only facilitates breakdown of tissue accumulated plasma proteins thereby allowing direct amino acid venous absorption and removal of osmotically obligatory-held interstitial fluid, but also favors collagen lysis over deposition with gradual regression of fibrosis (4,16,17,44). LLLT, therefore, should promote the removal of collagen fiber, protein and fluid from the tissues while its presumed immunostimulatory effect should also reduce the risk of skin infections, a major aggravating factor in peripheral lymphedema (45).

Our results suggest that LLLT has at least an initial favorable effect on secondary arm lymphedema. Thus, there was a 42% reduction in upper arm circumference with treatment and a 31% reduction post-treatment. For the mid-palm, there was a 92% reduction post-treatment. Other arm measurement sites showed a circumference reduction of 26-48%, with an average overall arm reduction of 45%. Edema volume of the lymphedematous arm decreased 10% with treatment and 29% post-treatment. Whereas the forearm softened (tonometry) during treatment, it regressed post-treatment. The upper arm, however, showed persistent hardening during and after treatment, a finding which remains puzzling. Bioimpedance showed a reduction of approximately 16% in ECF and 12% reduction in ICF with treatment although post-treatment the difference was minimal. Subjective parameters uniformly showed improvement with treatment and immediately post-treatment although a tendency to worsen developed after 36 months. The index of skin integrity, infection risks, and arm mobility also improved initially although with time the improvement abated. The feeling of arm tightness and heaviness was considerably eased.

This study also demonstrates that lymphedema is more than mere tissue swelling and includes a wide range of objective and subjective signs and symptoms. Whereas the findings can be explained in terms of the putative modes of action of LLLT, the clinical benefits generally lasted for only 6 months. Perhaps if LLLT is used in conjunction with combined physiotherapy, the benefits may be accelerated while reducing the need for labor-intensive bandage wrapping particularly in patients who already demonstrate tissue induration from fibrosis.

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