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The Long-Term Effects of Low Level Laser Therapy (LLLT) Combined with Complex Decongestive Therapy (CDT) in the Treatment of Breast Cancer Lymphedema: A Double-Blind, Randomized, Placebo-Controlled Study

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The Long-term Effects of Low Level Laser Therapy (LLLT) combined with Complex Decongestive Therapy (CDT) in the treatment of Breast Cancer Lymphedema: A Double-Blind, Randomized, Placebo-Controlled Study

By

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A capstone project submitted to the Graduate Faculty in Physical Therapy in partial fulfillment of the requirements for the degree of Doctor of Physical Therapy, The City University of New York

2014

This manuscript has been read and accepted for the Graduate Faculty in Physical Therapy in satisfaction of the capstone project requirement for the degree of DPT

Date: Dr. Susan Pivko, PT, Cert. MDT, Adv. CIECP, Cert. FDM

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Executive Officer

THE CITY UNIVERSITY OF NEW YORK

Abstract

The Long-term Effects of Low Level Laser Therapy (LLLT) combined with Complex Decongestive Therapy (CDT) in the treatment of Breast Cancer Lymphedema: A Double-Blind, Randomized, Placebo-Controlled Study.

By

Olivia Bramlett
Igor Daysudov
Toshi Odaira
Bethany Rodriguez

Adviser: Professor Susan Pivko PT, Cert. MDT, Adv. CIECP, Cert. FDM

Complex Decongestive Therapy (CDT), the gold standard for lymphedema treatment, fails to demonstrate long-term efficacy. The purpose of this study was to determine the long-term efficacy of low level laser therapy (LLLT) in reducing post-mastectomy lymphedema when used with CDT. The experimental group received LLLT and CDT (n = 7) while control group received sham laser and CDT (n = 7), twice a week for 4 to 8 weeks. Percent arm circumference difference between affected and unaffected limbs was collected over 18 months. Results revealed no statistical difference between both groups at all time periods: 1 (p = 0.902), 2 (p = 0.535), 3 (p = 0.445), 6 (p = 0.095), 12 (p = 0.537) and 18 months (p = 0.4). Further study with a larger sample size may prove more significant for long-term efficacy of LLLT.

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Introduction

Cancer is a major public health issue in the United States and the rest of the world. Currently, cancer accounts for 25% of all mortality in the United States (Siegel, Ward, Brawley, & Jemal, 2011). Among women, the cancers of the lung, bronchi, colorectal and breast are leading causes of cancer deaths. Breast cancer is the second leading cause of cancer death among women, with approximately 232,600 new cases expected for 2011 and an estimated 39,500 deaths (Siegel et al., 2011). Although there has been a decline in incidence of breast cancer reports since 1998, the decline in rate since 2003 has become stagnant (Siegel et al., 2011).

Treatment for breast cancer is complex. It entails a high risk of causing the onset of lymphedema, which is considered the most dreaded, secondary pathology related to breast cancer treatment (Fu, Ridner, & Armer, 2009). Lymphedema is swelling and chronic inflammation that develops in the limb as a result of abnormal accumulation of tissue proteins and interstitial fluid (Brennan, DePompolo, & Garden, 1996). Abnormal accumulation of lymph fluid mostly occurs in the interstitial spaces of the arm, shoulder, neck, breast or the thorax, which can lead to physical discomfort, pain, impaired function and emotional distress (Fu et al., 2009). Of the approximately three to five million patients in United States who suffer from lymphedema, a significant proportion have developed lymphedema as a result of breast cancer treatment (Lawenda, Mondry, & Johnstone, 2009).

The lymphatic system plays a critical role in maintaining homeostasis in the body. It is a system that is responsible for ridding tissues of metabolic waste, foreign debris and excess materials by carrying them away from the tissues to the lymph nodes

via circulation of lymph fluid (Mortimer, 1998). The lymphatic system is composed of deep and superficial lymph vessels, as well as lymph nodes, which are filled with lymph fluid (Cohen, Payne, & Tunke, 2001). Lymph fluid consists primarily of protein, water, fatty acids, salts, white blood cells, micro-organisms and foreign debris (Lawenda et al., 2009). Excess protein, interstitial fluid or toxic foreign debris present in the skin and subcutaneous tissues are absorbed into lymph fluid and collected through the superficial lymphatic system (Lawenda et al., 2009). The deep system is responsible for collecting lymph fluid in the deeper tissues (Lawenda et al., 2009). Once waste and excess metabolic substances are collected, lymph fluid flows from lymph capillaries into the lymph nodes in the axillary and inguinal regions. Lymph nodes then transport the fluid to lymphatic trunks, which will then drain lymph directly into the venous system for either disposal of waste or reabsorption of proteins (Lawenda et al., 2009).

The lymphatic system also plays a major role in reduction and prevention of infection. In addition to collecting excess interstitial water and proteins, the system can pick up bacteria and other foreign antigens and transport them to lymphocytes in the lymph node for processing (Cohen et al., 2001). In a normal physiological state, the lymphatic system maintains a transport capacity that exceeds the volume of lymph fluid needed for transportation. Lymphedema can be triggered due to either overload of lymphatic fluid or dysfunction of the lymphatic vessels that decrease the transport capacity (Lawenda et al., 2009).

Lymphedema can be classified into primary and secondary lymphedema. Primary lymphedema refers to congenital impairment of the lymphatic system (Fu et al., 2009; Brennan et al., 1996). Secondary lymphedema can result from trauma such as cancer,

cancer treatment, infection, inflammation, chronic venous insufficiency, immobility, radiation or surgery (Fu et al., 2009; Brennan et al., 1996; Lawenda et al., 2009). Lymphedema triggered by breast cancer treatment is classified as secondary lymphedema.

First described as a side effect of mastectomy operations by William Halstead in 1921, secondary lymphedema related to breast cancer can be caused directly by the tumor on the lymphatic vessels or more recently from indirect side effects of anti-cancer therapies (Mortimer, 1998; Brennan et al., 1996). Significant impairment of lymphatic function can occur when lymphatic structures are injured and replaced with fibrotic tissue as a result of resection of nodes and radiation therapy that are conducted as part of cancer treatment (Brennan et al., 1996). Lymphedema occurs more frequently in breast cancer patients who receive *both* resection of lymph nodes and radiation therapy. The incidence can be up to 23% for patients receiving a combination of sentinel lymph node biopsy (SLNB) and radiation therapy, and up to 48% for patients receiving axillary lymph node dissection (ALND) and radiation therapy (Lawenda et al., 2009).

Lymphedema can be classified into four stages according to skin condition and degree of swelling (Fu et al., 2009). Stage 0 is latent or sub-clinical lymphedema, with no visible edema but with possible, minor heaviness in the limb. Stage 1 is considered reversible but exhibits visible edema, while stage 2 is considered non-reversible and displays visible edema with added characteristics of pitting and fibrosis of the skin. Stage 3 exhibits pitting edema in a largely affected area of the limb, as well as fibrosis and leakage of lymph through damaged skin (Fu et al., 2009). Stage 3 is considered severe but rare in upper extremity lymphedema (Fu et al., 2009).

The signs and symptoms of lymphedema are readily visible, significantly altering not only the physique but also the self-perceived image of one's physical presentation. Lymphedema can have significant negative effects on wellness and on one's ability to perform activities of daily living. Range of motion of the wrist, hand and arm are affected by the inability of muscles and joints to move freely as a result of progressive stiffening of swollen superficial and deep tissues (Casley-Smith, Boris, Weindorf, & Lasinski, 1998). Lymphedema can be accompanied by other distressing symptoms such as pain, fatigue, decreased physical activity, loss of sensation of the limb, diminished body image and other psychological distress associated with physical disfigurement caused by this substantial swelling (Fu et al., 2009; Lawenda et al., 2009; Cohen et al., 2001). Often individuals socially isolate themselves secondary to physical presentation of edema and bandaging. Currently there is no cure for lymphedema, but intervention is essential to delay onset and to eliminate further progression of the symptoms (Lawenda et al., 2009).

Physical therapy has been traditionally used for intervention of lymphedema since the techniques of "lymphatic massage" were first introduced in the 1930s (Casley-Smith et al., 1998). Currently the gold standard for treatment of lymphedema is Complex Decongestive Therapy (CDT). In one study, 35 patients with post-mastectomy lymphedema who underwent CDT reported a 25% decrease in percent excess volume in the affected limb when compared to the unaffected limb (Randheer, Kadambari, Srinivasan, Bhuyaneswari, Bhanumathy, & Salaja, 2011). This study recruited subjects following the completion of breast cancer treatment with a 4-month onset of lymphedema. Inclusion criteria required patients to have a difference in limb volume

between the two arms greater than 200 ml and a difference in one point of circumference of the two arms greater than 2 cm. In addition, participants must have been free from reoccurring carcinoma, metastasis, cellulitis or from edema resulting from other medical causes (Randheer et al., 2011). Parameters of interest were baseline circumference measurements of the upper limbs and water displacement volumetry (Randheer et al., 2011). Following the initial measurement, patients underwent CDT comprised of a 45 minute session of manual lymphatic drainage and multi-layered compression bandaging for the duration of four times a weeks for 2 weeks**.** Patients were also instructed to conduct massages on their affected limbs twice a day, apply compression bandages throughout the day and to elevate the limb at night. After the 2 week CDT phase, patients were followed up once a month for three months for assessment of limb volume changes (Randheer et al., 2011). Effectiveness of CDT was calculated as the change in absolute limb volume of the treated limb before and after the two-week phase and at each month of follow up. The volume was also measured by calculating the difference in limb volume between the affected and unaffected limb and expressing it in percentage reduction of edema (Randheer et al., 2011).

CDT is comprised of the following components:

Manual Lymphatic Drainage (MLD):

Manual Lymphatic Drainage is a technique that mobilizes excess lymph fluid in the extremities back into the body's central lymph system to be removed. It can be effective in decreasing edema, increasing range of motion of the limb, improving texture, increasing circulation and diminishing the risk of cellulitis (Casley-Smith et al., 1998).

Compression:

Compression garments:

Based on individual needs, participants will receive a compression sleeve and gauntlet/glove that are to be worn in the daytime during the self-management phase in order to maintain the improvements made during intensive intervention (Casley-Smith et al., 1998).

Multilayer Bandaging (MLB):

Multiple layers of short stretch elastic bandages are applied to the lymphedematous limb. The tension of the bandages facilitates muscle pumping in order to push the accumulated lymph fluid back into the body's central lymphatic system. As with MLD, MLB has been proven to improve the range of motion of the limb, soften tissue texture, increase circulation and decrease risk of cellulitis (Casley-Smith et al., 1998).

Vasopneumatic compression:

This may be used as an adjunct to treatment including MLD, MLB, and therapeutic exercise. The compression device provides an automated sequence of gradient compression to the limb with lymphedema. When compression is applied, it exerts gentle, external pressure on the affected extremity in order to rid edema by mechanically pumping the excess lymph fluid back into the center of the body (Casley-Smith et al., 1998).

Exercise:

Therapeutic exercises prescribed by the physical therapist promote active participation by the patient, in order to enhance muscle pump action to decrease the edema in the limb (Casley-Smith et al., 1998).

Education:

Physical therapists educate the patients on posture, body mechanics, skin care and lymphedema precautions, such as avoiding venupuncture and vital readings (blood pressure) on the affected side. Education is crucial in order to optimize activities of daily living and minimize risk of infection and exacerbation of lymphedema (Casley-Smith et al., 1998).

Self-management:

When maximum improvements in girth measurement reduction and tissue softening have been achieved, the patient is provided with a self-managed plan of care upon discharge. This may include a combination of compression garments, MLD (self-administered), MLB (self-administered), exercise, and a vasopneumatic compression device (Casley-Smith et al., 1998).

Despite the empirical support of CDT, there are numerous contraindications associated with CDT. Complex decongestive therapy can increase venous blood volume in patients with hypertension and increase risk of injury or infection in diabetic patients with decreased tactile sensation (Fu et al., 1996). Some absolute contraindications for CDT are acute infections, congestive heart failure, and deep vein thrombosis. The compression involved in CDT may exacerbate infections, increase central venous blood volume in individuals with heart failure, and release clots in the blood vessel (Lawenda et

al., 2009). Use of CDT for patients with these afflictions is contraindicated. For such patients not suitable to be treated with CDT, it is necessary to develop an alternative mode of intervention.

Low-level laser therapy (LLLT) is a physical modality with potential for a wide application of clinical use. It has been used to relieve common symptoms ranging from stiffness and pain related to Achilles tendonitis, low back pain, orofacial pain, tendonitis, neck pain, temporomandibular pain, chronic periodontis and subacromial impingement syndrome (Yeldan, Cetin, & Ozdincler, 2009; Carcia, Martin, Houck, & Wukich, 2010; Djavid, Mehrdad, Ghasemi, Hasan-Zadeh, Sotoodeh-Manesh, & Pouryghoub, 2007). Low-level laser therapy has also been studied for its efficacy in reducing swelling and pain related to surgical removal of the third molar, commonly referred to as "wisdom tooth" (Ferrante et al., 2012).

Historically both *in vitro* and *in vivo* studies have been conducted that aimed to study the efficacy and the mechanism of low-level laser (LLL). The focus of many *in vitro* studies using the LLL has been on the effect of laser irradiation on the growth and repairing capacity of cells involved in wound healing and decreased formation of scarring (Posten et al., 2005; Omar, Ebid, & Morsy, 2011). Most of such studies have focused on fibroblast growth, locomotion, and production of collagen, as fibroblasts play a significant role during the proliferative and remodeling phases of wound healing (Posten et al., 2005). In addition, effects of LLL on monocytes and endothelial cells have also been studied. The overarching result of these studies has shown that LLL enhances deposition of collagen and proliferation of fibroblasts and monocytes (Posten et al., 2005).

Effect of LLL on wound healing has also been investigated with *in vivo* experiments using rodents as an animal model. One earlier study used a Helium-Neon (HeNe) laser at 632.8 nm at a dose between 4 to 20 J/cm^2 on surgical wound sites created in rat models to observe wound healing differences between different doses (Kana, Hutschenreiter, Jaina, & Waidelich, 1981). The authors observed wound healing at a much more significant rate with application of 4 J/cm^2 and also found that the lasers increased formation of granulation tissue and deposition of collagen (Kana et al., 1981).

In addition to fibroblast activity during wound healing, many past animal studies have also investigated the effect of LLL on tissue tensile strength, vascularization around fractured bones, and wound healing around nerves (Posten et al., 2005). Low-level laser therapy continues to stimulate the immune system by increasing prostaglandin levels, reducing edema, improving lymphatic drainage motility by vasodilatation and inhibition of platelet aggregation, and improving cellular growth for wound healing in human subjects (Omar et al., 2011).

Historically, the therapeutic use of LLL can be traced back to a series of human studies conducted by Mester et al. beginning in 1971, that exhibited improvement in wound healing in chronic ulcers and neuropathic foot ulcers with application of low energy (1 J/cm^3) laser (Mester, Spiry, Szende, & Tota, 1971). Studies on the role of LLLT in wound healing were eventually applied to and used in treating secondary lymphedema. The U.S. Food and Drug Administration (FDA) recommended that the dose for lymphedema treatment with laser was indicated to be 650 – 1000 nm in 2013 (Ridner, Poage-Hooper, Kanar, Doersam, Bond, & Dietrich, 2013).

Currently, LLL has also been focused as an effective intervention in the treatment of post-mastectomy lymphedema (Carati, Anderson, Gannon, & Piller, 2003). Approved by the FDA in November 2006, LLLT is a relatively new form of lymphedema treatment that utilizes light to stimulate healing response (Anderson, Pillar, Gannon, Carati & Angel, 2008). It has been suggested that LLL enhances lymphangiogenesis (the growth of lymphathic vessels) and stimulates macrophage cells and breaks down fibrous tissue (Tammela, & Alitalo, 2010; Carati et al., 2003).

One double-blind controlled trial was conducted that investigated the effect of LLL on post-mastectomy lymphedema in 11 women with unilateral lymphedema (Kaviani, Fateh, Nooraie, Alinagi-zadeh, & Ataie-Fashtami, 2006). Th**e** subjects were randomly assigned to either the sham laser or laser treatment group and received laser application in the affected arm and axillary area three times a week for 3 weeks, followed by an 8 week interval. Laser application was repeated for three more weeks after the 8 week interval, for a total of 18 treatment sessions. The laser used was a low-energy gallium arsenide laser at 890nm for a dose of 1.5J/cm^2 (Kaviani et al., 2006). The baseline assessment of limb circumference, range of motion, pain score and heaviness of the affected limb were compared between the two groups during the treatment period at 3, 8, 12, 18 and 22 weeks. Data were collected regarding the difference in circumference of the affected and unaffected limb and was measured using a non-elastic tape measure at 6 specific anatomical points. The circumference difference of the two limbs was compared to the circumference difference at pre-treatment sessions in order to calculate the total reduction in circumference (Kaviani et al., 2006). The total reduction in circumference and the reduction in fluid as measured with the L-Dex scores of

bioimpedence in the treatment group was significantly more than in the sham group in all sessions (p <0.001) (Kaviani et al., 2006). In addition, pain significantly decreased in the treatment group in all sessions compared to the sham group with the exception of week 3 and 9 (p <0.001) (Kaviani et al., 2006). There was no significant difference in range of motion and in heaviness score between the treatment and sham groups. The study does not depict the components of the heaviness and pain score, nor does it explain at which joints range of motion was studied.

Another study on human subjects conducted a similar double-blind, placebo controlled trial to investigate the effect of LLL on limb volume, shoulder mobility and handgrip strength in women with post-mastectomy lymphedema (Omar, Ebid & Morsy, 2011). The study recruited 50 participants, all with unilateral lymphedema who qualified under the protocol and were assigned to either sham laser group or active laser group. Low-energy gallium arsenide laser at 904nm, power of 5mW and spot size of 0.2cm^2, at a final dose of 1.5J/cm^2 was applied over the arm and axilla three times a week for 12 weeks (Omar et. al., 2011). Total reduction of circumference, shoulder mobility measured as shoulder range of motion in flexion, abduction and external rotation; grip strength measured using a hand dynamometer were assessed at baseline prior to treatment (week 0) and at every 4 weeks during the 12 week treatment period (week 4, 8, 12) (Kaviani et al., 2006). The total reduction in limb circumference was significantly greater in the treatment group than in the sham group at all assessed sessions (Kaviani et al., 2006). Shoulder flexion and abduction significantly increased during week 8 and 12 in the treatment group, but there was no significant difference in external rotation between the two groups during any session (Kaviani et al., 2006). Grip strength

improved in both groups, but the laser group exhibited significant percentage of improvement at week 12 compared with the sham group (Kaviani et al., 2006).

Need for Study

Several double blind, placebo-controlled studies have been conducted to investigate the efficacy of LLL on treating post-mastectomy lymphedema. However, most studies follow up on the efficacy of LLL application for less than a year. The interest of this research was to investigate the long lasting effect of LLL application in preventing recurrence of lymphedema, if any, by following subjects over time after active treatments have ceased. In addition, most studies do not assess LLL in conjunction with the use of CDT. For patients already receiving CDT, it is worthwhile to know if the further addition of LLL intervention would have any positive impact on treatment outcome.

LLL has several parameters that must be defined clearly in each study, at times complicating meaningful comparisons of results between studies. Low-level laser has 5 defining factors: power, wavelength, pulse rate, pulse duration, total irradiation time, intensity and dose (Posten et al, 2005). Low-level laser is defined to have a power with a range between 10^{-3} and 10^{-1} W, wavelength with a range between 300 and 10,600nm, pulse rate with a range between 0 and 5,000 Hz, pulse duration with a range between 1 to 500 milliseconds, total irradiation time between 10 to 3,000 sec, intensity between 10^{-2} to 10^{0} W/cm^2, and a dose between 10^{-3} to 10^{2} J/cm^2 (Posten et al, 2005). Although the overall effects of LLL seem to be positive, there is no agreement on the most optimal physiological and physical parameters of the use of LLL that yield the best clinical

outcome (Kaviani et al., 2006). Further studies are necessary to help define the exact parameter of LLL that is most optimal for clinical use in treating lymphedema.

Longitudinal data supporting CDT efficacy is limited and lends to poor carry over when compared to more conservative treatment like compression stockings. One recent study revealed no significant difference between percent arm reduction volume at all time period: 3, 6, 12, and 24 weeks between a control group which donned a compression sleeve 12 waking hours for 4 weeks and an experimental group which received CDT and MLD for 1 hr by a specialist 5 days per week for 4 weeks (Dayes, Whelan, Julian, Parpia, Pritchard, D'Souza, Kligman, Reise, LeBlanc, McNeely, Manchul, Wiernikowski, & Levine, 2013). Each session followed with compression bandaging performed by a specialist to be worn for 23 hrs and each subject was taught self-bandaging to be used over the weekend. After 4 weeks of the active phase was over, subjects of the experimental group received compression sleeves similar to that of the control group (Dayes et al., 2013). Although still statistically insignificant, greater arm reduction was seen in subjects receiving CDT for the sub group with a shorter duration of onset (Dayes et al., 2013). Greater duration (> 1 year versus < 1 year) may explain an increased risk of tissue fibrosis in a lymphedematous arm. Manual Lymphatic Drainage in addition to compression stockings, may be effective. Greatest arm volume reduction may occur over the first several weeks (approximately 3) (Dayes et al., 2013). If there is no benefit to costly CDT, when compared to economical compression sleeves, conservative therapy may be indicated. Complex Decongestive Therapy depends heavily on patient compliance and incorporates MLD, daily bandaging, exercise, and skin care. During the maintenance phase (long-term post treatment phase), the individual is responsible for

compression bandaging, exercise and skin care. Subjects in both sham and active laser group may have had low rates of compliance, except for the benefits of LLLT outweighing any decrease in efficacy due to decreased individual compliance (Javid & Anderson, 2013).

Purpose

The purpose of this study is to determine if LLLT in conjunction with CDT can have a long-term effect in reducing post-mastectomy lymphedema in breast cancer survivors. The implementation of LLL is quick, easy to administer, and non-invasive; while CDT is time consuming for patients and clinicians. Efficacy of MLD and bandaging are also dependent on the skill level of the Clinical Lymphedema Specialist as well as the compliance and skill level of the patients. In addition, proper technique of bandaging with the non-dominant upper extremity can be difficult when the lymphedatemous arm is the dominant hand. If LLLT is effective, it allows for non-specialized clinicians to be involved in the care of people with secondary lymphedema and is simpler to don for those whose dominant arm is affected (Ridner, Poage-Hooper, Kanar, Doersam, Bond, & Dietrich, 2013).

Omar et al (2011) showed that there was significant improvement in reduction of limb volume in the lymphadematous arm up to 12 weeks post LLLT treatment, compared to a sham laser group in a double blind, randomized study. Subjects in both groups received skin care, therapeutic exercises, compression bandaging but NOT MLD. This study shows that rather than just a hypothesized in-direct effect of LLLT on MLD, LLLT alone does have good efficacy (Omar et. al., 2011).

One double-blind, placebo-controlled study revealed no significant correlation between the duration of lymphedema (2 – 336 months) and reduction of arm volume. However, at three months, after two treatment bouts of LLLT (8 week rest period between two rounds of laser treatments), mean affected limb volume was significantly lower than that of placebo group or group receiving one bout of LLLT (8 week rest period between placebo and one round of laser treatment) (Carati, Anderson, Gannon, & Piller, 2003). Research shows subjects who developed lymphedema in the leg post surgery for gynecological cancer showed the effectiveness of CDT reached the greatest reduction in Percentage Excess Volume (PEV) 3 and 6 months post CDT, but reduction became insignificant as edema returned to pre-CDT level (2 months and 24 months) (Kim, Hwang, Kim, Chang and Lee, 2012). Percent average limb reduction had been noted until 6 months, but did return to pre-trial level during assessment time period at long-term defined as 12 months and 18 months (Kim et al, 2012). Moreover, one study where subjects were divided into 2 groups –PEV $< 20\%$ (group 1) and PEV $\geq 20\%$ (group 2) and received 2 weeks of CDT treatment followed by maintenance phase (self-care) and data collected at 3, 6, 12 and 24 months; PEV in group 2 was significantly lower than baseline at all time periods, while PEV in group 1 began to increase at 6, 12, and 24 months (Hwang, Hwang, Kim, Lee, Chang & Chu, 2013). Complex decongestive therapy has been shown to be less effective long-term with initial PEV $< 20\%$ (Hwang et. al., 2013).

With regard to possible development of fibrosis as one of the complications of lymphedema, fibrotic tissue inhibits efficient MLD and fluid drainage. Another study noted the tissue indentation resistance (TIR) by calculating the amount of force required

to indent tissue to a certain depth (Mayrovitz & Davey, 2011). The LLL implemented by this research was produced by RianCorp LTU 904H – pulsed 904 nm, with an average output of 5 mw from head size $0.2cm^2$. In addition, use of tonometry revealed significant reduction in indentation forces with 5 minutes of LLLT as compared to pre LLLT forces (Mayrovitz & Davey, 2011). A study by Ramos et al. recruited 69 subjects and showed that rather than the timing of initiation of treatment, the biggest factor for efficacy appeared to be PEV at baseline (Ramos, O'Donnell, & Knight, 1999).

When compared to LLLT, CDT has been criticized partly for high cost over a long-term period and for time consumption. Complex Decongestive Therapy incorporates an average of 60 minutes of MLD, as well as highly involved individual participation during the maintenance phase that can yield decreased compliance (Lasinski, Thrift, Squire, Austin, Smith, Wanchai, Green, Stewart, Cormier, & Armer, 2012). Empirical research suggests the implementation of conservative treatment of a compression sleeve, pneumatic pump or LLL could be recommended (Haghighat, Lotfi-Tokaldany, Maboudi, Bahadori, & Weiss, 2013; Dayes, et al., 2013).

Currently no study examines the relationship between the use of LLLT and the possible recurrence of, or increased risk of, metastasis (Lima, Lima, Figueiredo, Carvalho de Andrade, & Bergman, 2012). One i*n vitro* study showed a down regulation of protein expression responsible for cell adhesion, which can be related to metastasis (Leeuwen, Dekker, Byers, Vermeer and Grevelink, 1996).

In consideration of the importance of promoting public health and wellness, obesity (BMI > 30kg/m2) is a risk factor at reportedly three times greater risk for

developing lymphedema (Helyer, Varnic, Le, Leong, & McCready, 2010). Although lymphedema risk is associated with numerous factors such as stage of cancer, age, type of surgery, adjunct treatment, BMI is an important predictor for development of lymphedema (Helyer et, al., 2010).

Educating breast cancer patients to the importance of detection of lymphedema well into post-ALND is paramount since the average onset of post surgical lymphedema is 36 months and some research notes onset up to 2 years later (ALND = 20% vs. SLNB = 5.6%) (Liao, Li, Huang, Chen, Kuo, Chen, & Wei, 2013; Javid & Anderson, 2013). Teaching individuals to detect early onset of mild lymphedema is crucial as research shows approximately 20% of mild lymphedema progresses into more severe lymphedema in one year (Bar, Cheville, Solin, Dutta, Both, & Harris, 2010). In addition, increase risk in lymphedema is associated with post-operative infection or delayed wound healing and LLLT may be implicated for management of infection control and wound management as 17-25% of breast cancer survivors are at risk for secondary lymphedema (Lima et. al., 2012).

Hypothesis

The implementation of low level laser therapy (LLLT), in conjunction with standard lymphedema intervention (CDT), can potentially decrease risk of infection, decrease arm girth measurement, reduce tissue fibrosis, and enhance tissue texture in the involved upper extremity yielding longer advantageous effects than standard CDT intervention.

Methods

Design

This study is a double-blind, randomized, control trial of breast cancer survivors with post-mastectomy lymphedema all receiving CDT. Participants were randomized into a placebo group that received sham LLL application and a treatment group that received active LLL application.

Subjects

The venue of this study is Rusk Institute of Rehabilitation Medicine and NYU Clinical Cancer Center in New York, NY. A total of 16 subjects were recruited, 7 of which were assigned to the placebo group, the other 7 assigned to the active laser group, and 2 who dropped out after the intensive phase. Participants were recruited through informational flyers that were circulated at Rusk Institute of Rehabilitation Medicine, NYU Clinical Cancer Center and local community organizations (i.e. SHARE, Gilda's Club) throughout the 5 boroughs of New York City. Breast cancer survivors already receiving outpatient physical therapy for post-mastectomy lymphedema were invited for initial screening as a potential participant. Patients interested in participating in the study proceeded through a referring physician or a nurse practitioner. Signed hard copies of agreement of the participant's inclusion into the study were obtained from both the participant and the referring physician prior to the participant's inclusion. All participants signed the consent form to participate in the study. The NYU School of Medicine/NYU Langone Medical Center Institutional Review Board (IRB) and Human Research Protection Program (HRPP) committee and the Hunter College (HRPP)-IRB committee approved this research.

The following criteria were required for participant inclusion to the study: female of 21 years of age or older; affected by unilateral breast cancer which was treated by unilateral mastectomy (no prophylactic mastectomy); lymph node dissection surgery [sentinel lymph node biopsy (SLNB) and/or axillary lymph node dissection (ALND)]; affected with unilateral upper limb lymphedema; involved upper extremity fluid volume that is greater than or equal to 200 mL and/or a circumferential girth measurement of the affected limb at any 4 cm segment with a difference of 2 cm or greater in comparison to the unaffected contralateral upper extremity; stage I or stage II lymphedema; cognitively intact; and able to make the time commitment to participate in all treatment sessions. Interpreters were assigned to all non-English speaking or limited English proficiency participants who met all inclusion criteria during each treatment session for the length of the study.

Potential participants were excluded from the study based on the following: BMI > 40; active or metastatic cancer; currently or later undergoing adjuvant radiation or chemotherapy therapy; restrictive active range of motion interfering with the purposes of treatment; history of severe surgical disruption of arm; presence of primary or secondary lymphedema in the contralateral upper extremity; active renal failure; arterial insufficiency; congestive heart failure; chronic inflammatory conditions; use of a pacemaker; a past medical history of deep vein thrombosis (upper extremity); past use of CDT and/or LL; use of medication which alters fluid balance (i.e. diuretic, certain chemotherapy); pregnancy.

Materials

The following materials were used to capture the data analyzed in this study:

- The LTU-904 infrared laser manufactured by RianCorp (Marleston, South Australia) was used in this study at a wavelength of 904nm.
- Perometer Type 350 S manufactured by Pero-System Messgeraete GmbH (Wuppertal, Germany) was used to calculate total limb volume.
- A bio-impedance analyzer, the L-Dex XCA U400 manufactured by ImpediMed (Brisbane, Australia) was used to measure the extracellular fluid volume of affected and unaffected limbs.
- The DF-50 BIA manufactured by ImpediMed and the InBody 230 Body Composition Analyzer manufactured by BioSpace (Seoul, Korea) were used to measure and calculate percent body fat and BMI of each participant.
- The Lymphedema and Breast Cancer Symptom Experience Index was used to monitor changes in overall experience pertaining to lymphedema in each participant as adapted from the Lymphedema and Breast Cancer Questionnaire (LBCQ) (Armer, Radina, Porock & Culberston, 2003; Fu et al., 2008). Participants were asked to self-assess the following lymphedema symptoms: swelling, heaviness, breast swelling, firmness/tightness, numbness, tenderness, aching, stiffness, impaired limb mobility, seroma formation, and arm weakness. Presence of each symptom is expressed as either “yes” or “no” whether they currently or recently had experienced the symptoms. Severity of each symptom is expressed in a scale of 1 (a little) to 4 (severe). The type of symptom distress is expressed as temporal, situational/functional, or attributive.
- The Short-Form Health Survey version 2 (SF-36v2) was used to assess physical and mental health outcomes in each participant by monitoring changes in disease

burden associated with lymphedema. The SF-36v2 was developed by John E. Ware Jr., PhD, and co-licensed by Medical Outcomes Trust (Dartmouth, NH), Health Assessment Lab (Boston, MA), and QualityMetric Incorporated (Lincoln, RI). It consists of 36 questions, each with five different magnitudes of responses. An 8-scale profile is gathered with measures of functional health and well being, physical and mental health that is a psychometric summary and a health utility index that is based on various preferences. A median reliability coefficient of greater than or equal to 0.8 was used to establish reliability and validity for each of the 8 scales (Hormes, Bryan, Lytle, Gross, Ahmed, Troxel & Schmitz, 2010; Ahmed, Prizmet, Lazovich, Schmidtz, & Folsom, 2008).

Procedures

Participants were recruited as described above. All principle investigators except for Annika Ginsberg, unaffiliated Research Coordinator, and Dr. Tamara Bushnik, unaffiliated Reasearch Director, both at Rusk Institute of Rehabilitation Medicine, were blinded to the subject's randomization and whether a participant was in a sham laser or an active laser group.

A total of four low level lasers, two active and two placebos were prepared, each pre-calibrated before use. The laser discrimination for sham and active laser were known only to two unaffiliated personnel: the Research Coordinator and the Director of Research of Rehabilitation Medicine at Rusk Institute. Recruited participants were randomly designated to the next available slot in either Group 1 that received sham laser application and CDT or Group 2 that received active laser application and CDT. Each participant received an individual identifier number for use in all documentation, as well

as a laser number. Each of the four low level lasers were designated a number of 1 through 4.

The laser treatments were administered by one of the two co-principal investigators who were trained in using the LLL distributed along a fabric grid. Each participant in both groups had a personalized grid to be consistently used throughout the study. The grid was placed over the axillary region and medial-lateral chest wall of the involved upper quadrant implementing pre-determined anatomical landmarks to ensure consistency from treatment to treatment. This grid was used to ensure consistent application of the LLL among treatments and in order to treat the entire area equally. The grids were pre-cut with 40 punctured holes. The holes were color coded into 4 groups: red, blue, green and black. The holes alternated in color spaced $\geq$ 2 cm between consecutive same-colored holes. The laser treatment followed a set of color-coded holes rotating each treatment on a four-week cycle. Systematic treatment of the involved area was provided by alternating the color-coded holes as follows:

- LLL treatment 1, 5, 9, 13 (red holes)
- LLL treatment 2, 6, 10, 14 (blue holes)
- LLL treatment 3, 7, 11, 15 (green holes)
- LLL treatment 4, 8, 12, 16 (black holes)

In each treatment session, LLL was applied for 1 minute each at 10 locations in the axillary region of the lymphadematous arm as designated through the use of the standardized grid application. Laser treatment sessions were scheduled twice a week for 4 to 8 weeks, as part of the Intensive Phase, for a total of 8 to 16 treatment sessions. The

duration of total weeks of treatment period was dependent on a timeline required to achieve clinical goals. Each laser treatment session was followed by a CDT session.

The effects of sham and active laser treatment in combination with CDT on the lymphadematous arm were investigated by conducting a time course measurement of the following parameters: limb circumference, total limb volume, total extra-cellular fluid volume in limb, tissue texture, percent body fat, BMI, pain intensity, symptom experience of lymphedema, perceived health outcome, photography of limbs and demographics/ medical information (2nd visit only). Measurement of each parameter was taken at the 1st treatment session (baseline reading), at the 8th treatment session and at the final treatment session. Following the last treatment, measurements were recorded at 3, 6, 12 and 18-month intervals, as part of the Maintenance Phase. See Appendix for description on parameters.

Results

This research used Average Percent Difference of Circumferences between affected and unaffected upper extremity (UE) as the main outcome measure. Circumference measure is the most relevant outcome measure for comparison to other research. It is easy to measure and is the most relevant measure to those affected with lymphedema. Landmarks for circumference measurements were the index finger, thumb, MCP joint, CMC joint, and wrist. Distance from wrist was calculated as 4 cm + 4*i*, where *i* is equal to the next 4cm interval number, for a total of 9 intervals; with longer limbs, 2 more intervals were added.

Data Reduction

1. Percent difference of each landmark – an affected UE is compared to unaffected

    - Let R be circumference of a landmark on the right UE
    - Let L be circumference of a landmark on the left UE
    - If right UE is affected: (R-L)/L x 100%
    - If left UE is affected: (L-R)/R x 100%

2. Average percent difference across landmarks of a participant for a given visit in time – an average of percent differences of landmarks in #1 above

3. Average percent difference of all landmarks for all participants in a sham or an active laser group for a given follow-up visit - #2 averaged across all participants for a given visit in time in a given participant group.

Table 1

Average % difference of all landmarks for all participants in a sham or an active laser group for a given follow-up visit (n = 14)

Visit number	Month	Active (%)	Sham (%)	Sham laser subjects (n)	Active laser subjects (n)
1	1	10.86	7.85	7	7
2	2	8.42	7.17	7	7
3	3	9.06	6.38	6	7
4	6	9.82	2.52	5	5
5	12	9.38	6.79	5	6
6	18	4.73	8.81	3	3

Figure 1

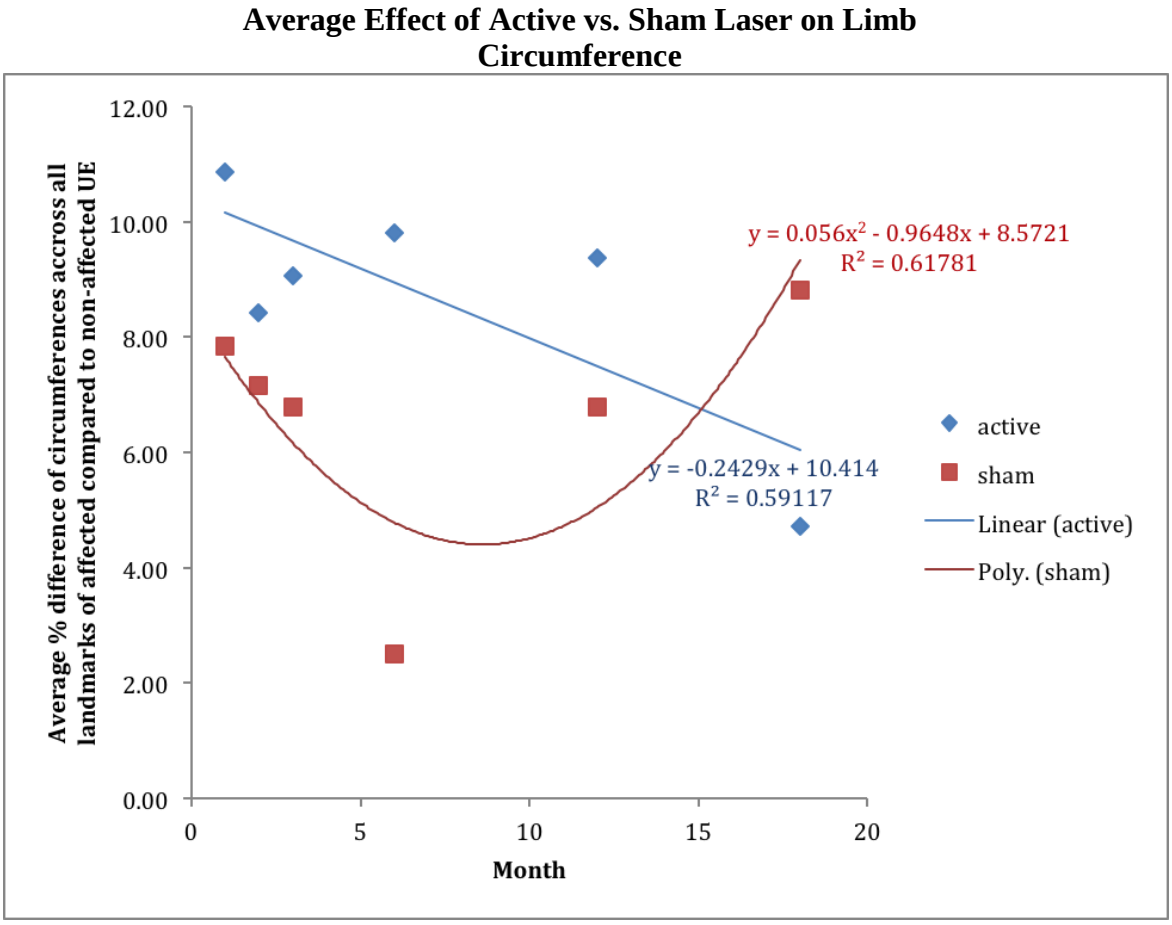

Average Effect of Active vs. Sham Laser on Limb Circumference
Average % difference of circumferences accross all landmarks of affected compared to non-affected UE
12.00
10.00
8.00
6.00
4.00
2.00
0.00
0
5
10
15
20
Month
y = 0.056x² - 0.9648x + 8.5721
R² = 0.61781
y = -0.2429x + 10.414
R² = 0.59117
active
sham
Linear (active)
Poly. (sham)

Table 2

Results of Mann-Whitney U Test to determine significance of data distribution between laser vs. sham groups at each time period.

Null Hypothesis	Significance	Decision
The distribution of Month 1 is the same across categories of Group.	0.902	Retain the null hypothesis.
The distribution of Month 2 is the same across categories of Group.	0.535	Retain the null hypothesis.
The distribution of Month 3is the same across categories of Group.	0.445	Retain the null hypothesis.
The distribution of Month 6 is the same across categories of Group.	0.095	Retain the null hypothesis.
The distribution of Month 12 is the same across categories of Group.	0.537	Retain the null hypothesis.
The distribution of Month 18 is the same across categories of Group.	0.400	Retain the null hypothesis.

According to Table 2, low significance in p-values suggests the results might have happened at random and that there is no significant difference between the two groups of participants. However, using a regression analysis a better understanding of possible differences between the two groups of participants could be revealed. Due to low significance values regression models are used for every group of participants and scatter plots gauge any trends in data. No attempt to extrapolate any data points was made.

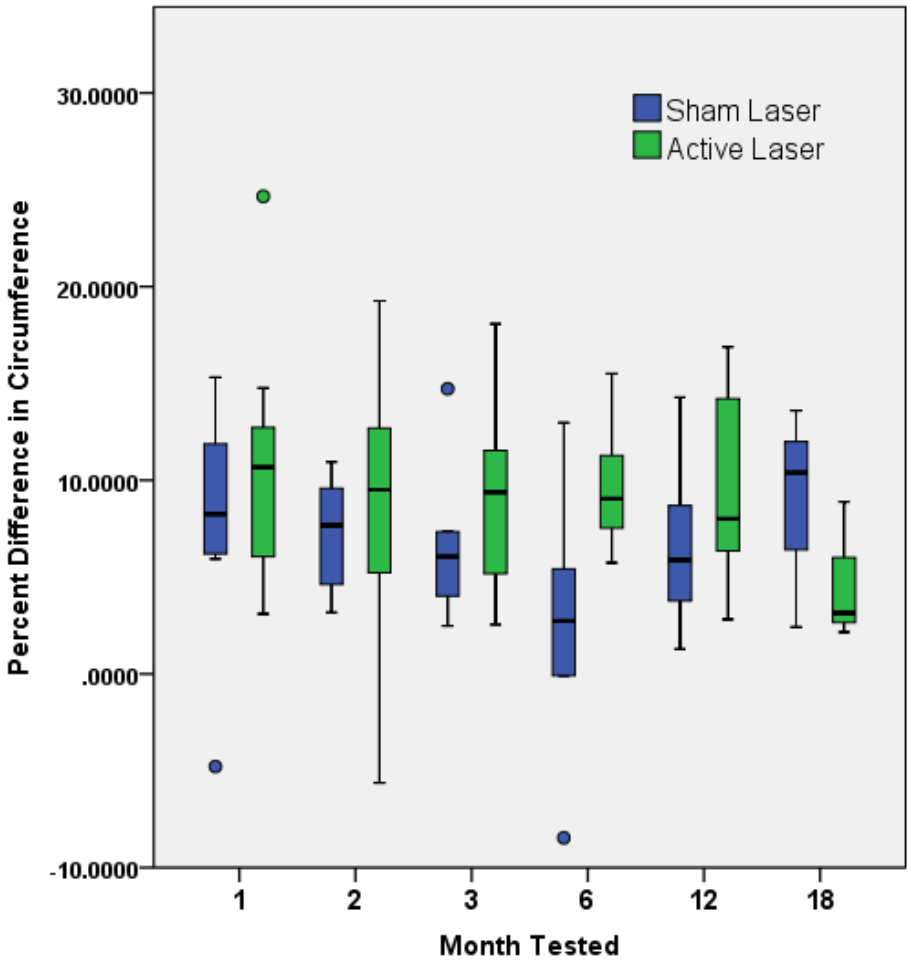
Data in Figure 1 indicates that there seemed to be a downward trend in the difference of average percent circumference between affected and unaffected UE over an 18-month period for the participants who received an active laser treatment. For this participant group linear regression model was used and revealed a reasonable data-trend representation with $R^2 = 0.5912$. This may suggest that lymphedema had a decreasing trend over the 18-month period for this participant group.

However, data for a sham laser group fit into a parabolic regression model also having a reasonable data-trend representation with $R^2 = 0.6178$. Although statistically

insignificant, a decrease in average percent circumference was observed until 6 months, followed by an increase in average percent circumference for 12 and 18 months, as demonstrated by this parabolic trend. This may suggest that initially participants in this group experienced a decreasing trend in lymphedema until about 6 months but then lymphedema continues to increase over the long term.

Figure 2

Effect of active vs. sham laser on limb circumference using raw measurements (extrapolated from the Mann-Whitney U Test)



Although statistically insignificant, greatest percent average limb circumference difference in interquartile range and median were observed at 6 and 18 months between the sham and active laser treatment group (figure 2).

Discussion

The purpose of this study was to determine the long-term efficacy of LLLT in conjunction with CDT in reducing post-mastectomy lymphedema in breast cancer survivors. Post-mastectomy lymphedema is a common complication, affecting 17 – 25% of patients who have undergone axillary lymph node dissection (Javid & Anderson, 2013; Lima et al., 2012). Ever since "lymphatic massage" was first established in the 1930s, CDT has been the preferred treatment method for lymphedema (Casley-Smith et al., 1998; Randheer et al., 2011). However, Javid and Anderson (2013) reported that recent randomized trials have failed to confirm the efficacy of CDT over standard compression therapy. The study by Dayes, Whelan, Julian, Parpia, Pritchard, D'Souza, Kligman, Reise, LeBlanc, McNeely, Manchul, Wiernikowski and Levine (2013) demonstrated that CDT had a poor long-term effect in reducing lymphedema. In their study, control groups wore compression sleeves for 12 waking hours for 4 weeks, while the experimental group received MLD for 1 hour by a clinical lymphedema specialist for 5 days a week for 4 weeks (Dayes et al., 2013). Both groups received patient education on skin care, therapeutic exercise and body weight management during the follow up period. Results indicated no significant difference between percent arm volume reduction, quality of life measures and arm function measures at all periods of 3, 6, 12 and 24 weeks (Dayes et al., 2013). Many authors agree that the greatest reduction in arm volume after the use of CDT peaks in the first several weeks (Javid & Anderson, 2013).

Another purpose of this study was to examine the general efficacy of LLLT in reducing lymphedema post-mastectomy. Efficacy of LLLT alone will facilitate clinical professionals who are not licensed to carry out MLD to be involved in lymphedema care. Opportunity exists for advanced practice nurse practitioners operating the low level lasers in areas with shortage of clinical lymphedema specialists (Ridner, Poage-Hopper, Kanar, Doersam, Bond, & Dietrich, 2013). However, this research aimed to determine if LLLT, in conjunction with CDT, is still needed for long-term efficacy.

The results of this study demonstrate a general trend toward a decrease in percent limb circumference difference over an 18 month period between the affected and unaffected limbs in the active laser group. Despite the statistically insignificant difference between the two groups, the decreasing trend of percent limb circumference difference may indicate support for the alternative hypothesis that the use of LLLT in conjunction with CDT will decrease arm girth measurement in the involved upper extremity at 12 months when compared to sham LLLT with CDT. The indirect effect of decrease in tissue fibrosis and direct effect of laser application may explain the arm volume reduction in the lymphadematous arm. Work by Rufina, Lau and Cheing (2013) demonstrated that 4 weeks of LLLT on the axillary region decreased tissue fibrosis in the lymphadematous arm by 33%. In the likelihood that our subjects had fibrotic tissue compositions in their lymphedematous arm, LLLT may have helped soften the fibrotic tissue to facilitate effectiveness of LLLT. A study by Carati et al. (2003) demonstrated the efficacy of LLLT in a double-blind, placebo-controlled study. The study had three groups; a control group receiving only placebo laser treatment, an experimental group receiving one dose of LLLT, and another experimental group receiving two doses of

LLLT with an 8-week rest period in between the doses. The results indicated no immediate reduction of arm volume after the laser treatment, but the experimental group receiving two doses of LLLT demonstrated significantly lower arm volume in the affected limb than the control or the other experimental group at the 3-month period.

The results of our study also demonstrated an increasing trend in percent circumference difference over an 18-month period between the affected and unaffected limbs in the sham laser group receiving placebo laser treatment and conventional CDT. The rather surprising result demonstrating the inefficacy of CDT over the 18-month period may be explained by several factors.

The total number of 17 subjects may have been too low to delineate any meaningful statistical significance to validate the finding of this study. It is possible that use of CDT might have reduced the percent circumference difference between the affected and unaffected limb if the subject numbers were higher.

Previous research has shown that the efficacy of CDT does not carry over past the 6 month follow up period, causing the arm volume to return toward the baseline level. It examined the percent excess volume (PEV) in affected limb compared to the unaffected limb in subjects who developed lymphedema in the lower extremity after surgical treatment for gynecological cancer (Kim, Hwang, Kim, Change & Lee, 2012). It was found that the effectiveness of CDT reached the greatest reduction in PEV at 3 and 6-month post CDT, but lymphedema returned to pre-trial level at 12 and 24 months. Our study findings were in congruence with findings by Kim et al. (2012) with average limb reduction observed until 6 months before returning to pre-trial level at 12 and 18 months.

Previous research has also demonstrated that CDT has decreased long-term effectiveness if initial PEV of subjects is less than 20%. A study by Hwang et al. (2013) divided the treatment group into two sub groups; Group 1 composed of subjects with initial PEV less than 20% and Group 2 composed of subjects with PEV greater than 20%. Both groups received 2 weeks of CDT followed by a maintenance phase, during which difference in PEV was monitored over 24 months. Their study revealed that PEV in Group 2 was significantly lower than baseline at all time periods, while PEV in Group 1 began to increase at 6, 12, and 24 months. Our findings were in congruence with findings by Hwang et al. (2013), as the initial PEV for our subjects was recorded as 10.86%.

Possible development of fibrosis as one of the complications of lymphedema could have inhibited effectiveness of MLD in our study and subsequent fluid drainage. Previous studies have demonstrated that 5 minutes of LLLT significantly reduced indentation forces in the lymphedematous arm, indicating possible effect of LLLT in decreasing soft tissue fibrosis (Mayrovitz & Davey, 2011). To calculate fibrosis in skin, many authors use the tonometry method or measure the tissue indentation resistance by calculating the amount of force required to indent tissue to a certain depth (Mayrovitz & Davey, 2011). Tissue texture assessment by palpation, tonometry, or calculation of tissue indentation force in future studies may reveal any presence of fibrosis in our subjects as well as any decrease in fibrosis when LLLT in conjunction with CDT are utilized.

Future Studies

Future studies could incorporate greater use of functional outcome measures as well as a focus on effect of lymphedema severity using LLLT as opposed to the use of standard compression sleeves. Such studies could facilitate physical therapists and other clinicians in formulating rehabilitation goals and potentials for patients, knowing when to make appropriate referrals to other clinical disciplines dependent on lymphedema severity and having viable treatment alternatives for lymphedema patients inaccessible to LLLT due to financial or geographical reasons.

Future studies could include functional outcome measures such as the Disability of the Arm, Shoulder and Hand (DASH) outcome measure to allow assessment of activities of daily living (ADL) affected by changes in physical function and symptoms caused by lymphedema. In addition, future studies could measure combined upper extremity range of motion (ROM) of shoulder flexion, abduction, and external rotation to assess reaching tasks and self-care activities such as washing ones hair, as well as shoulder extension and internal rotation required for donning of undergarments. Along with goniometric measurements of functional ROM, measurements of grip strength by hand dynamometry in functional positions may also assist physical therapists in monitoring patient progress and formulating treatment plans (Omar et al., 2011).

Efficacy of LLLT against use of standard compression sleeves could be examined to assess if LLLT and compression sleeves are comparable in their efficacy in reducing lymphedema. One criticism of CDT is its high cost, which often requires 60 minutes of MLD conducted by a certified lymphedema specialist (Lasinski et al., 2012). If LLLT and compression sleeves demonstrate comparable efficacy, LLLT presents as another

viable treatment alternative for cost reduction and for patients with low compliance with which CDT would not be appropriate.

Efficacy of LLLT on varying lymphedema severity and stages could be examined to explore if LLLT would be a good alternative over a CDT treatment strategy for patients with a greater PEV. A study by Ramos, O'Donnell and Knight (1999) demonstrated that rather than the timing of treatment initiation, initial PEV at baseline is the most significant determining factor of treatment outcome.

Future studies could also examine safety of the long-term use of LLL at currently established wavelengths. Current recommended dose for lymphedema treatment determined by the U.S. Food and Drug Administration is 650 to 1000 nm (Ridner et al., 2013). However, the possible correlation between long-term use of LLL at the indicated wavelength and increased risk of metastatic recurrence has not been studied (Lima et al., 2012). So far, an *in vitro* study conducted by Leeuwen, Dekker, Byers, Vermeer and Grevelink (1996) has shown that LLLT decreased expression of a protein that may be responsible for cell adhesions during metastasis.

Aside from the obvious necessity of treatment advancement of lymphedema to promote patient return to pre-morbid level of activities, the importance of patient education on health and wellness must be advocated by all medical professionals. Obesity, defined as body mass index (BMI) greater than 30 kg/m^2, has been shown to increase the risk of developing lymphedema by threefold (Helyer, Varnic, Le, Leong & McCready, 2010). Although cancer stages, age, type of surgery and adjunct treatment are considered to be associated risk factors to development of lymphedema, BMI is an important predictor for lymphedema (Helyer et al., 2010).

Patient education post-mastectomy is also crucial in preventing post-surgical complications and early detection of lymphedema. Patients should be instructed to conduct frequent skin inspections to prevent delayed wound healing and post-operative infections, which are associated risk factors for development of lymphedema (Javid & Anderson, 2013). A study conducted by Lao, Li, Huang, Chen, Kuo, Chen and Wei (2013) emphasizes the importance of patient education for early detection of lymphedema well into the post-ALND period, as average onset of lymphedema post-ALND is 36 months. In addition, early detection of seemingly mild lymphedema is critical, since 20% of mild lymphedema has been shown to progress into a more severe form of lymphedema within 1 year (Bar, Cheville, Solin, Dutta, Both & Harris, 2010).

Conclusion

Although there is not yet statistically significant evidence for the long-term efficacy of LLLT, the most recent literature along with our findings may suggest the following possibilities: Use of LLLT in conjunction with CDT may be indicated for long-term management of lymphedema; Either CDT alone or LLLT with CDT may be effective in short term management of lymphedema up to 6 months post treatment; Use of LLLT may have a more significant effect post 6 months after the initiation of treatment. With continuation of the study and more subjects followed to 18 months, there may be stronger evidence to support these initial findings.

Appendix

Limb circumference and limb volume

Protocol previously established by Armer, et al. (2004) and Armer and Stewart (2005); was used for circumference measurement for limb volume. Circumference of both the affected and unaffected limbs was measured using a non-stretch tape at the following locations: at the hand proximal to the metacarpals, wrist, and every 4 cm from the wrist to axilla (Callaway et al., 1988; Hutzschenreuter, Wittlinger, Wittlinger, & Kurz, 1991). Non-stretch tape was used to measure the circumference in order to ensure constant tension over soft tissue, muscle, and bony prominence, a flexible non-stretch tape measure was used for circumferential measurement (Callaway et al., 1988; Petlund, 1991). Circumference of affected and unaffected limb was used to calculate the limb volume of each limb. The following formula was used: $V= \sum(X^2 + Y^2 + XY)/ 3\pi$. **V** is the sum of the limb volume, **X** is the circumference at one point on the limb and **Y** is the circumference at a point 4 cm proximal to **X**. (Stantou et al., 1997).

Total limb volume

Total limb volume of affected and unaffected limb was measured using the Perometer 350S. Procedures for perometry as outlined by Armer & Stewart (2005); and as described by the equipment manual were followed. The perometer generated a 3-dimentional image of the limb to calculate the total limb volume. There is a standard deviation of 8.9 ml of arm volume, less than 0.5% of LV with repeated measuring using this method.

Total extra-cellular fluid volume in limb

Extra-cellular fluid volume in the affected and unaffected limb was measured using the L-Dex XCA U400, a bio-impedance analyzer that measures resistance and impedance to calculate extracellular fluid volume. The equipment manual provided by the manufacturer was followed for all procedures.

Tissue texture

A physical therapist palpated the affected and unaffected limb to compare and assess changes in skin compressibility. Skin compressibility is indicative of the extent of fibrosis present in a limb (Piller & Thelander, 1998).

Percent of Body Fat

Percent of body fat was measured using the DF 50 BIA and InBody 230 Body Composition Analyzer. This device sends an extremely weak electrical current of 50 kHz and less than 500 μA through the body to determine the amount of water in each tissue. Standard protocols established by each of the manufacturers were followed for all measurements. Participants were requested to remove all jewelry and metal objects, before being positioned in stand and supine position. The validity of using the BIA as the reference method ranged from 0.84–0.96 in white women (Pineau, Guihard-Costa, & Bocquet, 2007). The reliability (ICC) of BIA ranged from 0.97–0.99 (Jackson et al., 1988).

Body Mass Index

Body Mass Index was calculated by entering the body weight and height into the DF50 BIA &InBody 230 device. The device uses the following formula to calculate BMI

based on a ratio between body weight and height: BMI = weight (lb) / height (inches) /height (inches) x 703 (Callaway, Chumlea, & Bouchard, 1988).

Pain intensity

Pain intensity associated with lymphedema was measured using a self-reported, numeric pain scale. Participants quantified their pain on a numeric scale from zero to 10. A rating of zero signifies no pain while a rating of 10 signifies severely debilitating pain. It is a validated scale and a standard tool for rating pain.

Symptom experience of lymphedema

The study used the Lymphedema and Breast Cancer Symptom Experience Index in order to monitor the participants' overall experience of the lymphedema. This index was a structured interview tool adapted from the Lymphedema and Breast Cancer Questionnaire (LBCQ) (Armer, Radina, Porock, & Culberston, 2003; Fu et al, 2008). The content of the Breast Cancer Symptom Experience Index is described under *Materials*.

Perceived health outcome

The Short-Form Health Survey version 2 [SF-36v2] was utilized to assess the well-being of physical and mental health of each participant. The content of the survey is described under *Materials*.

Photography of limbs

Photographs of the chest, affected and unaffected extremity were taken for each participant in order to monitor any visual changes over the upper quadrants of the body. Each subject was given the right to refuse the photo. If photos were taken, they were

managed using the Individual Identifier Number. Photos were stored in a locked cabinet in a locked office of the Principal Investigator.

Demographics and Medical Information

A Demographics and Medical Information Tool as previously outlined by Fu, Axelrod and Haber (2008) was used to record the age, diagnosis, treatment, nodal status, numbers of lymph nodes removed, co-morbidities, and family medical history (breast cancer history, breast cancer gene status, morbidity of lower extremities).

Throughout the 18 month study period, patients were instructed to report any adverse changes to their affected limb such as rash, blister, redness swelling and/or increased temperature of the tissue. Participants were also instructed to receive any blood pressure evaluation, drawing of blood, injections and vaccinations on the unaffected upper limb whenever possible.

At the end of the study, participants were contacted and informed about whether they were part of the placebo or an intervention group. In the event that a medical problem arose, participants were instructed to contact Teresa Denham, PT, MA, Principal Investigator and Outpatient Physical Therapy Manager at New York University Medical Center/Rusk Institute of Rehabilitation Medicine, at (212) 263-8466.

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