

USE OF LASER THERAPY IN THE MANAGEMENT OF LYMPHOEDEMA

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The use of laser therapy has been slow to develop and not without controversy along the way. Forty years have passed since initial research reported positive biological effects from laser light (Carney et al, 1967). Despite the publication of over 2,500 titles relating to therapeutic light, there is still debate over its clinical use particularly for lymphoedema management. Limited research is available compared with other conditions such as pain and wound management. This article gives an overview of what laser is, how it works, current research trends and some clinical protocols in the management of lymphoedema.

Key words

Low level laser therapy (LLLT)
Postmastectomy lymphoedema
Biostimulation
Laser parameters

Laser is amplified electromagnetic radiation in a particular wavelength range (measured in nanometres [nm]) produced by electronically stimulating a medium to release photon bundles of energy. Medical lasers can be broadly generalised into:

- ▶ High output lasers that produce power outputs up to hundreds of watts. They are used for hair removal, ophthalmology and general surgery
- ▶ Low output lasers which are in the visible to infrared range of wavelength (670–950nm). Average power output is usually in milliwatts (mW). They are known as low level laser, soft laser or cold laser — referred to here as low level laser therapy (LLLT).

Laser therapy can be delivered by:

- ▶ Probes in direct contact with skin which minimise loss due to scatter/radiation
- ▶ Scanning which reflects the beam using motorised mirrors over areas up to 20x20cm. Some light may be lost in scatter but the output power is greater in such units than with hand-held models
- ▶ Fibre optics which can be used intravenously, transcutaneously and intracranially.

Lasers have international classifications according to their wavelength, acceptable emission limits and hence risk for eye damage. These are set by the International Electrotechnical Commission and the International Organisation for Standardisation. Lasers are classified in increasing order of eye hazard from class 1, class 2, class 3, class 3b to class 4.

Different laser characteristics' effects on treatment outcome

The laser medium determines the wavelength produced. Different wavelengths have varying penetration depths and so the appropriate choice can maximise the effect. For example, 810nm and 830nm lasers appear to be most effective in treating pain and musculoskeletal conditions (Laakso et al, 1994). Their penetration depth is 2–3cm, compared with 632nm which is more effective in wound

healing (Al-Watban and Zhang, 1996) with a shallow penetration depth of up to 8mm. Reduction of fibrosis in chronic lymphoedema is best treated using a 904nm laser due to a superior penetration depth of 3–5cm (Thelander, 1994).

Depth is also affected by:

- ▶ Skin pigmentation: melanin has a high absorbency coefficient which results in reduced depth of penetration in dark skin
- ▶ Haemoglobin level: this has a high absorbency coefficient and so vascular tissue such as muscle will absorb more light than fat
- ▶ Skin contaminants: dirty skin reduces the depth of penetration (Melo et al, 2001).

Some lasers have pulsed light, whereby the light is switched on/off at a chosen frequency (measured in hertz [hz]). Others, such as those with a 904nm wavelength, are super-pulsed, which may reduce the required dosage time for effective treatment compared with other wavelengths. Some research has been dedicated to determining which frequency is more effective in treating certain conditions (Mohkhtar et al, 1993), but lymphoedema has yet to be investigated.

As treatment dose can markedly affect the outcome, this parameter is arguably the most important to

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consider (Bolton et al, 1995). The dose is calculated on the product of the average power output and treatment time per area of treatment. It is expressed as joules per square cm (j/cm^2) and is known as the energy density (Figure 1).

A systematic review of the effects of LLLT on joint pain and investigating five different wavelengths reported that the optimal dose for biostimulation was 5–4 j/cm^2 (Bjardal et al, 2003). Doses too low can have little or no effect and doses too high can have a bio-inhibitory effect (Karu, 1989).

Effect of low level laser therapy (LLLT)

With over 2,500 titles in scientific literature relating to the therapeutic use of LLLT, 100 of these being positive double-blinded studies on patients, it is no longer valid to consider LLLT as a sophisticated placebo. The objective effects of laser have been measured using microscopy, thermography, magnetic resonance imaging (MRI), ultrasound, collagen tensile strength, nerve conduction studies, metabolite secretion and blood studies (Tuner and Hode, 1999). The balance of literature certainly supports the bio-stimulatory effects of laser therapy. The debate continues, however, mainly due to lack of large population studies of humans and the lack of consensus regarding optimal doses, pulse frequency and intervals between treatment sessions. Unfortunately, some substandard laser units together with less skilled therapists have left a negative legacy. On objective analysis, however, negative studies can still provide useful information for future research. Many of these studies had small populations, used doses that were too low and were not controlled in areas such as frequency.

Mechanism of effect

Effects from photostimulation can be summarised as primary and secondary mechanisms.

The primary mechanism occurs at a cellular level and several concepts

$$\text{Energy density} = \frac{\text{average power output (watts)} \times \text{time (seconds)}}{\text{area (cm x cm)}}$$

Figure 1. Energy density.

exist as to the actual molecular process (Karu, 1999). One common feature is that photoreceptors in mitochondria (known as cytochromes and porphyrins) absorb the light. Singlet oxygen is produced, the cellular respiratory chain is enhanced and adenosine triphosphate (ATP) and DNA synthesis are boosted (Karu et al, 1993). LLLT seems to have no effect on normal tissue but stimulates cell metabolism when tissue is in a depressed state (Karu, 1989).

Recently, the importance of laser speckle formation in the tissue has been reported as the phenomenon which sets LLLT apart from other forms of therapeutic light such as light-emitting diodes (LEDs) (Rubinov, 2003). This effect, caused by scattered light interference patterns, occurs only with coherent light. Coherence is a characteristic unique to laser and refers to the light waves being in order or in 'phase' for long trains of up to a metre. This attribute enables a much greater depth of penetration than other forms of light (Kamikawa, 1989). The speckle formation also produces local pressure gradients and temperature changes across a cell membrane of $.01^\circ\text{C}$. Although not a perceptible heat change, this causes increased membrane permeability to calcium, sodium and potassium. This can set off a chain reaction of chemical changes which include increased plasma endorphin and serotonin levels (Laakso et al, 1994), and reduced bradykinin and C-fibre activity which result in pain relief (Tsuchiya et al, 1993).

Increased ATP synthesis triggers an immunological chain reaction resulting in macrophage and fibroblast activation, as well as mast cell proliferation (Young et al, 1989). Fibroblast stimulation causes procollagen synthesis which promotes

wound healing. It is the proliferation of the phagocytic cells that is believed to be a crucial factor in reduction of fibrosis caused by the accumulation of protein in the perilymphatics (Piller et al, 1995).

Interestingly, tissue responses can be experienced systemically following LLLT. One example is with a study on wound healing in which non-irradiated wounds on the contralateral side to a treated wound healed faster than in non-treated controls (Rochkind et al, 1989).

Evolution of LLLT in the management of lymphoedema

In 1917 Albert Einstein introduced the concept of stimulated emission from which the term LASER (light amplification by the stimulated emission of light) was derived. In 1960 the first Ruby laser was developed by Ted Haiman. It had a wavelength of 694nm and was soon used for ophthalmology and dermatology.

Shortly after, in 1961, the first helium/neon (He-Ne) laser of 632nm was invented and became the first commercially available laser.

Using this laser, Professor Endre Mester from Hungary became the pioneer of biostimulation research at a cellular level. In the late 1970s interest grew in Italy, Japan, China, Russia and the UK, as technology advanced from expensive units to smaller, more powerful semiconductors.

Research in LLLT has mainly centred on wound healing (Bounko et al, 2000; Woodruff et al, 2004).

The use of LLLT in lymphoedema management was pioneered in Australia in 1988 by Ann Thelander who based her work on Lievens' (1985) studies of improved motoricity

of lymphatics and vascular tissue in wounds of mice. Lievens also determined microscopically that LLLT had a dilatatory effect on those lymphatics in which oedema had been artificially induced, but had little or no effect on vessels not subjected to trauma (Lievens, 1991). The large population study of 100 mice and 600 controls also showed that no adhesions developed in the wound to underlying tissue in any of the LLLT group after day four. Yet, on day seven, 90% of controls had adhesion formation. Complete regeneration of lymphovessels occurred at day nine in the LLLT group and at day 55 for the controls. There was increased permeability (and hence potential for increased extracellular volume as filtration pressures allow) in 50% of the control subjects after six months, but in no vessels in the LLLT group after day six.

Similar treatment dose and wavelength were used in clinical practice in Australia leading to the first clinical trial in 1995. The effects of LLLT in the management of post-mastectomy lymphoedema were examined (Piller et al, 1995). With a study population of 10, a scanning laser of dual wavelengths 632nm and 904nm was used in 16 treatments over 10 weeks, providing doses of between 2–4 J/cm². Plethysmography measurements showed a mean volume reduction in the affected arm of 19%. Ranges were between 17% and 40%. Tonometry indicated that a significant degree of fibrotic softening had occurred in both the upper and forearm regions. Bioimpedance is a sensitive and accurate method of determining extracellular volume (ECV) changes (Ward, 2006). Data from this study using bioimpedance measurement showed a large statistically significant reduction of ECV in the affected arm. The results correlated with subjective improvements in heaviness, aching and tightness. A follow-up study conducted two years later (Piller et al, 1998) indicated that most subjective and ECV data had a trend towards pre-treatment levels. Interestingly,

however, tonometry and volume data had a trend towards maintenance of any improved values from the original study, except in the upper arm where fibrotic induration tended to worsen.

Several theories explaining the long-term maintenance of some measurement parameters such as volume and tonometry have been put forward:

- ▶▶ Lysis of collagen and fibrosis reduction enables more rapid collateral vessel development (Piller and Thelander, 1995)
- ▶▶ The stimulation of lymphovenous vessel regeneration (Lievens, 1991; Kipshidze et al, 2001)
- ▶▶ Reduction in incidence of cellulitis resulting from stimulation of the auto-immune system (Piller and Thelander, 1995)
- ▶▶ A number of repeated laser sessions has a cumulative response (Kert and Rose, 1989). This may indicate that the frequency of treatments can be reduced after the initial sessions without complete regression to pre-treatment levels of some parameters (Laakso et al, 1994).

Carati et al (2004) performed the first randomised double blind study (n=64) using a class I hand-held unit of 904nm in a spot application of 1.5J/cm² to the axillae of arms affected by post-mastectomy lymphoedema. Compared to the placebo group no immediate effect occurred, but at one- and three-month follow-up, there was a mixture of clinically and statistically significant outcomes. At three months, 31% of subjects showed at least a 200ml volume reduction compared with only 4% in the control group. ECV values using bioimpedance were significantly reduced in 52% of those receiving all sessions of LLLT compared with 24% of the placebo group. At three months there was also a significant softening of tissues in the upper arm using tonometry readings. Of note also are the systemic changes found in both this and the Piller study (Piller and Thelander, 1998). Sustained ECV changes were found in the torso and unaffected limb despite no direct laser irradiation.

An unpublished Australian pilot study in the late 1990s used an 18-spot application of 1J/cm² 780nm laser over the deltoid and cubital fossa regions for three sessions per week for two weeks. Statistically significant reductions in volume using circumferential measurement were found.

A more recent study (Kaviani et al, 2006) reported a reduction in arm circumference and pain using an 890nm laser of 1.5J/cm² spot application for 18 sessions over four months (n=8). Unlike some studies, the laser parameters were thoroughly defined but the population was again small and limited objective measurements were examined.

Treatment protocols

Non-uniform methodological design and the wide variety of laser parameters used make comparisons between studies difficult. It cannot be unequivocally stated which parameters are the most effective for LLLT in lymphoedema management. A further complication is the effect of external factors such as body mass index (BMI), the degree of fibrosis, initial ECV values and the time lapsed from initial lymphoedema symptoms, all of which could influence treatment outcome (Carati et al, 2004).

The most commonly studied wavelength in research related to lymphoedema has been the 904nm. As yet, no studies have compared the different modes of application and only class 3b dual wavelength scanning and hand-held class I models of lasers have been used in robust studies in Australia (Piller et al, 1995, 1998; Carati et al, 2004). As a result, the Australasian Lymphology Association (ALA) has been unable to reach a consensus on the use of laser therapy. However, some common protocols have been adopted by centres as a result of available research and anecdotal sharing of knowledge through the Australian Medical Lasers Association (AMLA) and recommendations set by the World Association of Laser Therapy (WALT).

1. Area of treatment

Proximal nodes and vessels are irradiated before any distal areas (i.e. axilla in the case of upper limbs and groin for lower limbs) to stimulate the dilatory effect and flow proximally as with manual lymph drainage techniques (Oasevich and Shargorodskii, 1999). Direct irradiation is often performed over areas of fibrosis. In the case of scanning lasers, it is common practice in Australia to treat four to five areas of proximal to distal progression. The hand-held units are used directly over fibrotic or congested areas at a dose of 1.5j/cm² (equivalent to one minute of irradiation) per point.

2. Dose

As previously discussed, the therapeutic window is 0.5–4j/cm² per treatment area. Doses too high can be bio-inhibitory (Mester et al, 1989). The majority of studies researching lymphoedema have used 1.5j/cm² in spot application of up to 20 areas. Scanning lasers likewise treat multiple areas with energy densities generally between 0.5–2j/cm². Hence, the cumulative dose in one session could be up to 20–30j/cm². There have been no studies to the author's knowledge to compare the effectiveness of varied cumulative doses with respect to lymphoedema management. Some studies have compared cumulative doses in the treatment of joint pain but the suggested doses vary from 8–9j/cm² in North America (Castel, 1985) to 30–50j/cm² in Europe and Japan (Kert and Rose, 1989). It is clear that controversy still exists over optimal doses.

3. Treatment frequency

Research indicates that due to a cumulative effect over several sessions, the frequency of treatments can be reduced while still achieving or maintaining positive results (Piller and Thelander, 1998; Carati et al, 2003). In the studies discussed, treatment frequency was three times per week for several weeks at a time (interspersed with a block of no treatment), with up to 18 sessions in total over three to four months. The

reality is that treatment frequency in both private and public centres can be as much driven by economics as optimal treatment plans.

Contraindications

There are few true contraindications indicated by research. Avoiding direct irradiation over a foetus is prudent, not because of proven negative effects but to avoid the burden of proof if complications arose. For a similar reason, direct irradiation over silicon implants is avoided in Australia due to lack of manufacturers' guarantee.

LLLT is another viable treatment option in the management of lymphoedema. It has been shown through extensive case reports and limited research to have positive and potentially long-term effects.

The thyroid gland is sensitive to light and so direct irradiation is avoided because of potential fluctuation of plasma thyroid hormones.

As per the international standard recommendations, to avoid retinal damage the client and therapist using laser units of class 3 and higher must wear goggles specific to the wavelength used. Warning signs must be displayed on entrances to areas containing class 3B and class 4 lasers.

An awareness of the use of photosensitive drugs such as anti-malarial and hyperthyroid medications might indicate the use of a lesser initial energy density to test client sensitivity.

Irradiation directly over untreated or active malignancy is avoided. Laser therapy is not carcinogenic and there is no research to indicate definitive negative or positive effects on existing cancer cells *in vivo*. Current research has shown no effect on osteosarcoma cells *in vitro* with 830nm irradiation, but a stimulatory effect was observed

with 780nm (Renno et al, 2007). An abstract recently presented at the New Zealand Laser 2008 Conference (Powell et al, 2008) indicated that human breast adenocarcinoma cells *in vitro* had no proliferative response to 830nm and 904nm irradiation. Certain single 780nm doses, however, caused some proliferation. Interestingly, multiple exposures (only performed on the adenocarcinoma lines) had either no effect or a decreasing effect on dose-response relationships. Breast ductal carcinoma cells, however, had no response to single exposures with any wavelengths. The authors concluded that definitive protocols could not be made until *in vivo* studies are produced. One must consider that absorbency coefficients will obviously be largely different in tissue mass as opposed to cell lines *in vitro* and, for this reason, *in vitro* studies alone cannot give definitive clinical guidelines.

Side-effects of LLLT

On rare occasions clients describe mild nausea or dizziness within 24 hours post LLLT (Kleinkort and Foley, 1984). This seems to be associated with doses that are too high. Anecdotally, one in 100 people may exhibit photosensitivity (Laakso, 2006). Extreme tiredness can be experienced which is believed to be due to metabolite release. In chronic musculoskeletal conditions there can be a short-term exacerbation of pain prior to positive response. Warnings for possible side-effects, though rare, should form part of the pre-treatment assessment.

Conclusion

LLLT is another viable treatment option in the management of lymphoedema. It has been shown through extensive case reports and limited research to have positive and potentially long-term effects. Factors that may influence the degree of positive outcome can be BMI, severity of lymphoedema, differing laser parameters and individuals varying absorption coefficients. Further research will need to be produced to define optimal parameters to maximise effect. JL

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Key points

- ▶▶ Low level laser therapy has been shown to reduce fibrosis and volumetric measurement in several studies of secondary upper limb lymphoedema.
- ▶▶ Laser parameters such as wavelength, frequency and dosage must be considered in order to maximise clinically-effective treatment.
- ▶▶ Further research involving larger population studies needs to be undertaken to further define optimal treatment regimes, such as treatment frequency and laser dosage.