Developments in low level light therapy (LLLT) for dentistry
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Review

Developments in low level light therapy (LLLT) for dentistry

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A B S T R A C T

Objectives. Low level light/laser therapy (LLLT) is the direct application of light to stimulate cell responses (photobiomodulation) in order to promote tissue healing, reduce inflammation and induce analgesia. There have been significant studies demonstrating its application and efficacy at many sites within the body and for treatment of a range of musculoskeletal injuries, degenerative diseases and dysfunction, however, its use on oral tissues has, to date, been limited. The purpose of this review is to consider the potential for LLLT in dental and oral applications by providing background information on its mechanism of action and delivery parameters and by drawing parallels with its treatment use in analogous cells and tissues from other sites of the body.

Methods. A literature search on Medline was performed on laser and light treatments in a range of dental/orofacial applications from 2010 to March 2013. The search results were filtered for LLLT relevance. The clinical papers were then arranged to eight broad dental/orofacial categories and reviewed.

Results. The initial search returned 2778 results, when filtered this was reduced to 153. 41 were review papers or editorials, 65 clinical and 47 laboratory studies. Of all the publications, 130 reported a positive effect in terms of pain relief, fast healing or other improvement in symptoms or appearance and 23 reported inconclusive or negative outcomes. Direct application of light as a therapeutic intervention within the oral cavity (rather than photodynamic therapies, which utilize photosensitizing solutions) has thus far received minimal attention. Data from the limited studies that have been performed which relate to the oral cavity indicate that LLLT may be a reliable, safe and novel approach to treating a range of oral and dental disorders and in particular for those which there is an unmet clinical need.

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Significance. The potential benefits of LLLT that have been demonstrated in many healthcare fields and include improved healing, reduced inflammation and pain control, which suggest considerable potential for its use in oral tissues.

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1. **Introduction**

Low level light/laser therapy (LLLT) is the application of light (usually delivered via a low power laser or light-emitting diode; LED) to promote tissue repair, reduce inflammation or induce analgesia. LLLT has been the subject of several systematic reviews for a range of musculoskeletal pathologies with favorable outcomes reported in The Lancet [1], British Medical Journal [2], International Association for the Study of Pain [3] and the World Health Organization [4]. Unlike many other laser treatments LLLT is not an ablating or heating based therapy but is more analogous to photosynthesis in its mode of action. LLLT also differs from photodynamic therapy (PDT), which utilizes light indirectly to trigger photosensitive dyes to produce bactericidal molecules that kill infecting microbes that cause disease. Indeed, current data indicates that PDT appears to be a useful adjunctive tool for treating oral infections in the dental specialties of oral surgery, endodontics and periodontitis (e.g. Periowave\textsuperscript{TM}) [5,6].

In contrast, LLLT or photobiomodulation uses the action of light and light alone to directly stimulate host cells in order to reduce inflammation, relieve pain and/or promote wound healing.

Dental applications for LLLT are not well documented in comparison with musculoskeletal applications; however, more studies are now being reported. Indeed, there is now encouraging data for LLLT application in a wide range of oral hard and soft tissues and covering a number of key dental specialties including endodontics, periodontics, orthodontics and maxillofacial surgery as described below. LLLT has also been shown to have efficacy in managing chronic pain and non-healing bone and soft tissue lesions in the maxillofacial region.

The laser or LED devices applied in LLLT typically emit in the 600–1000 nm spectrum range (red to near infrared), with typical irradiance of 5 mW/cm\(^2\) to 5 W/cm\(^2\) and generated by devices with as little power as 1 mW, and up to 10 W. Pulsed or sometimes continuous beams are delivered. Treatment time is typically for 30–60 s per treatment point (see Glossary of terms for an explanation of “per-point”; Table 4) and as little as one treatment point or a dozen or more may be treated at a given time. For acute and post-operative therapy one treatment is all that is usually required however for chronic pain...
and degenerative conditions as many as ten sessions may be necessary. Whilst other wavelengths outside the 650–850 nm spectrum can have similar effects they do not penetrate the tissues as well as those in the red and near-infrared range [7].

The following review provides an overview of LLLT, the background, our current mechanistic understanding, the clinical benefits and treatment parameters.

2. History and application of LLLT

In 1967, a few years after the first working laser was invented, Dr. Endre Mester at Semmelweis Medical University in Budapest, Hungary, attempted to identify if this newly developed ‘ray of light’ could induce cancer. In his experiment, hair was shaved from the backs of two groups of mice; one as the control, the other being exposed to treatment using a low-powered ruby laser. The treatment group did not develop cancer as had been predicted, however, the hair on the treated mice grew back at a faster rate than the untreated controls. Mester (1967) subsequently described this effect as “laser biosimulation” [8]. Forty-five years later, thousands of papers have been published with over 30 in-press every month related to LLLT and its mechanism of action, downstream physiological changes and the clinical benefits as demonstrated in both randomized clinical trials and in pooled data meta-analyzed in several systematic reviews [1-4,9].

To-date more than 300 randomized double blind placebo controlled clinical trials have been reported. This has resulted in publication of a number of expert consensus reports for utilizing LLLT as part of standard clinical management, including:

- The Lancet – systematic review of LLLT for neck pain [1].
- International Association for the Study of Pain (IASP) – fact sheets for myofascial pain syndrome, osteoarthritis and neck pain [3].
- The World Health Organization (WHO) – task force on neck pain systematic review [4].
- British Journal of Sports Medicine (BJSM) – systematic review for frozen shoulder [5].
- American Physical Therapy Association (APTA) – systematic review and clinical practice guidelines for achilles tendinopathy [10].
- Multinational Association for Supportive Cancer Care (MASCC) – clinical practice guidelines for oral mucositis [12].

Whilst most of the clinical evidence for LLLT has been obtained from treating musculoskeletal pain, many trials relating to oral and maxillofacial indications have also now been published (Table 1).

Apart from an enhanced rate of postoperative healing [80,126] and better tissue remodeling, LLLT is also a major benefit for patients who are in pain, are needle phobic or cannot tolerate non-steroidal inflammatory drugs (NSAIDs) [13–15].

3. Mechanism of action of LLLT

Most of the effects of LLLT can be explained by light absorption within the mitochondria [16–18] (Fig. 1). Cells can contain up to several thousand mitochondria, which generate cellular energy (ATP) from oxygen and pyruvate. In addition, in stressed or ischemic tissues, mitochondria synthesize nitric oxide (NO) from the respiratory chain and increasing levels of adenosine triphosphate (ATP) and reactive oxygen species (ROS). These changes act via intermediaries cyclic adenosine monophosphate (cAMP) and protein kinase D (PKD) to activate transcription factors AP-1 and NF-κB resulting in changes in gene expression and subsequent downstream production of chemical messengers implicated in the cellular changes seen following LLLT exposure.

3.1. The consequences of LLLT on hypoxic/stressed cells

3.1.1. Primary effect: absorption by cytochrome c oxidase

CcO absorbs red and near-infrared light, the transfer of light energy by this enzyme triggers a series of downstream effects [16,26–29] (Fig. 1).
Table 1 – Oral and maxillofacial indications of LLLT.

<table>
<thead>
<tr>
<th>Oral specialty</th>
<th>Application</th>
<th>LLLT effect</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endodontics</td>
<td>Dentinal hypersensitivity</td>
<td>Reduced tactile and thermal sensitivity, Improved dentin formation in the dental pulp, Promotion of HDP cell mineralization</td>
<td>[97–99]</td>
</tr>
<tr>
<td></td>
<td>Pulp</td>
<td>Improved dentin formation in the dental pulp</td>
<td>[94–96]</td>
</tr>
<tr>
<td>Maxillofacial</td>
<td>Bisphosphonate related osteonecrosis of the jaw</td>
<td>Reduced pain, reduced edema, pus and fistulas, Improved bone trabeculation and ossification</td>
<td>[91–93]</td>
</tr>
<tr>
<td></td>
<td>Mandibular distraction</td>
<td>Improved bone formation in condylar region</td>
<td>[88–90]</td>
</tr>
<tr>
<td></td>
<td>Mandibular advancement</td>
<td>Improved osteogenesis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Temporo-mandibular joint disorder</td>
<td>Reduced pain, Improved range of mandibular movement, Improved bone healing</td>
<td>[85–87]</td>
</tr>
<tr>
<td>Oral pathology</td>
<td>Burning mouth syndrome</td>
<td>Reduced symptoms, reduced pain</td>
<td>[81–83]</td>
</tr>
<tr>
<td></td>
<td>HSV</td>
<td>Improved healing and reduced reoccurrence</td>
<td>[123–125]</td>
</tr>
<tr>
<td></td>
<td>Lichen planus</td>
<td>Reduced lesion size, less pain</td>
<td>[120–122]</td>
</tr>
<tr>
<td></td>
<td>Oral mucositis</td>
<td>Reduced incidence, duration and severity</td>
<td>[63,118,119]</td>
</tr>
<tr>
<td></td>
<td>Xerostomia/dryness</td>
<td>Regeneration of salivary duct epithelial cells, Improved salivary flow, improved antimicrobial characteristics</td>
<td>[115–117]</td>
</tr>
<tr>
<td>Oral surgery</td>
<td>Healing</td>
<td>Improved healing after gingivectomy, reduced gingival Inflammation</td>
<td>[56,60,80]</td>
</tr>
<tr>
<td></td>
<td>Paresthesia/ alveolar nerve</td>
<td>Improved mechanical sensory perception</td>
<td>[77–79]</td>
</tr>
<tr>
<td></td>
<td>Third molar extraction</td>
<td>Reduced pain, reduced swelling, improved trismus</td>
<td>[64,65,76]</td>
</tr>
<tr>
<td>Orthodontics</td>
<td>Orthodontic pain</td>
<td>Reduced pain, Faster remodeling</td>
<td>[42,112–116]</td>
</tr>
<tr>
<td></td>
<td>Titanium implants</td>
<td>Improved healing, Improved attachment, Improved osseointegration</td>
<td>[73–75]</td>
</tr>
<tr>
<td></td>
<td>Tooth movement</td>
<td>Accelerated tooth movement</td>
<td>[58,112,113]</td>
</tr>
<tr>
<td>Pediatric</td>
<td>Cavity preparation</td>
<td>Reduced pain, Faster healing</td>
<td>[56,88,111]</td>
</tr>
<tr>
<td></td>
<td>Mandibular distraction</td>
<td>Faster healing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gingivitis</td>
<td>Faster healing</td>
<td></td>
</tr>
<tr>
<td>Periodontics</td>
<td>Chronic gingivitis</td>
<td>Reduced inflammation, Improved healing</td>
<td>[56,57,110]</td>
</tr>
<tr>
<td></td>
<td>Periodontal ligament</td>
<td>Increased early hyalinization</td>
<td>[57,108,109]</td>
</tr>
<tr>
<td></td>
<td>Periodontitis</td>
<td>Improved pocket depth, Less inflammation</td>
<td>[105–108]</td>
</tr>
<tr>
<td>Prosthodontics</td>
<td>Denture stomatitis</td>
<td>Reduced yeast colonies, Reduced palatal inflammation</td>
<td>[102–104]</td>
</tr>
<tr>
<td></td>
<td>Implants</td>
<td>Faster bone formation, Improved bone-implant interface strength, Improved osseointegration</td>
<td>[74,75,101]</td>
</tr>
</tbody>
</table>

3.1.2. Secondary effect: modulation of ATP, nitric oxide and reactive oxygen species
Changes in ATP, reactive oxygen species and nitric oxide occur due to light absorption by CcO, which are redox state and dose dependent. In hypoxic or otherwise stressed cells it has been shown that following LLLT, nitric oxide is released from CcO, ATP synthesis is increased and oxidative stress is reduced [30–34].

3.1.3. Tertiary effect: downstream intracellular responses (gene transcription, and cellular signaling)
There are many downstream effects of LLLT including nitric oxide release, increased ATP synthesis and reduced oxidative stress. These effects are context and cell type dependent.

Either directly or indirectly these biochemical intermediates affect components in the cytosol, the cell membrane, and nuclear functions that control gene transcription and subsequently regulate cellular responses such as proliferation, migration, necrosis and inflammation [30–34].

3.1.4. Quaternary effect: extracellular, indirect, distant effects
Tissues that have not absorbed photons can also be affected indirectly via bioactive molecules released from cells that have been stimulated by absorbed light. Cells in the blood and lymph can also be activated and subsequently promote systemic effects such as autocrine, paracrine, and endocrine and termed as “bystander” effects.
There is laboratory evidence that LLT also improves lymphatic flow. A systematic review of eight clinical trials of LLT for post-mastectomy lymphoedema concludes that "There is moderate to strong evidence for the effectiveness of LLT for the management of breast cancer related lymphoedema" [36]. A controlled clinical trial on football players with second degree ankle sprains, found a significant reduction in edema volume in the laser group compared with the placebo [37]. A laboratory trial on Carrageenan-induced edema in the mouse paw also found that treating lymph nodes alone was sufficient to reduce the swelling [38]. The mechanism of action of the LLT however was not elucidated.

### Analgesia

Analgesic effects are probably a result of a different biological mechanism from those of the increased ATP/reduced oxidative stress model described above. According to a systematic review of laser analgesia mechanisms by Chow et al. [39], laser light with higher irradiance (>300 mW/cm²), when absorbed by nociceptors, exert an inhibitory effect on Aδ and C pain fibers, which slows conduction velocity, reduces amplitude of compound action potentials and suppresses neurogenic inflammation. Chow’s own laboratory studies suggest that LLT blocks anterograde transport of ATP-rich mitochondria in dorsal root ganglion neurons. Varicosities result from the inhibitive effect, which is normally associated with disruption of microtubules and the resulting block of anterograde transport of ATP-rich mitochondria. Interruption of fast axonal flow reduces the availability of ATP necessary for microtubule polymerization, and maintenance of the resting potential [39]. This effect is completely reversible and may last only 48 h [40–42], however, more work is needed to fully characterize the complex mechanism of action.

### Myofascial trigger points

The palpable nodules in taut muscle bands and contraction of muscle fibers that lead to muscle spasms and limited joint movement are referred to as myofascial trigger points.
They are a component of several pain conditions, including migraine, tension-type headaches, temporomandibular disorder and neck pain. The motor end plate is central to the etiology of the disorder and electromyography (EMG) studies have shown abnormally high electrical activity over trigger points. Electrical activity is reduced after LLLT and clinical studies have shown that LLLT has immediate and cumulative effects on reducing pain [43–46], however, the mechanism of action resulting on this effect is not yet fully elucidated.

### 4. LLLT parameters

For LLLT to be effective, the applied irradiation parameters including wavelength, power, irradiance, exposure time, and pulse need to be applied within limits.

#### 4.1. Irradiation parameters

If the incorrect irradiation parameters are used or applied for the incorrect period of time, then treatment will likely be ineffective. If the irradiance is too low and/or the delivery time is too short, then there will also be no significant effect. Alternatively, if the irradiance is too high and/or the treatment time is too long, then the benefit is abrogated and sometimes unwanted inhibitory effects occur [47–49].

Unfortunately, many researchers fail to accurately measure or even report some of these parameters in their studies. This is due, in part, to a poor appreciation of the relevance of these parameters and also because some of these measurements require the use of expensive instrumentation by trained engineers or physicists [50].

Parameters should be considered in two parts: the 'medicine' and the 'dose' and are described in Tables 2 and 3.

#### 4.2. Dose

Having established suitable irradiation parameters, they must be applied for the adequate exposure period. If the incorrect irradiation parameters are used or applied for the incorrect irradiation time, then treatment will likely be ineffective [47,48,52,53].

Energy (J) or energy density (fluence) (W/cm²) is often, incorrectly, referred to as "dose". These are different calculations and, on their own, are both potentially flawed methods of reporting this therapy. Table 3 provides the formulas, the correct radiometric terms and discusses the associated limitations.

### 4.3. Depth of penetration

Wavelengths in the range 700–850 nm penetrate tissues well and may achieve 5 mW/cm² at 5 cm depth when beam power is 1 W and irradiance is 5 W/cm² (unpublished data). Smith's [54] report on photobiological fundamentals provides data on light penetration through the human hand. Broad spectrum light projected through this tissue and measurements using a spectrophotometer demonstrated that most visible light does not pass through the hand but far red and near-infrared in the range 670–900 nm penetrates particularly well, with two peaks around 725 nm and 810 nm. Similar studies on rats identified a tissue penetration peak at 810 nm [55].

### 4.4. Treatment

There are four common clinical targets for LLLT and include:

1. The site of injury, disease or dysfunction to promote healing, remodeling and reduce inflammation [56–60].
2. Lymph nodes to help reduce edema and inflammation [36,38,61].
3. Nerves to induce analgesia [39,40,42,62].
4. Trigger points to reduce tenderness and relax contracted muscle fibers [43–46].

Treatment times per therapy point are typically in the range of 30–60 s. As little as one treatment point may be exposed in some cases, but as many as 15 points may be treated for more complex dysfunction’s such as temporomandibular joint disorder [43–46].
Table 4 – Glossary.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beam profiler</td>
<td>An instrument for measuring the beam intensity distribution</td>
</tr>
<tr>
<td>Laser speckle</td>
<td>A random fuzzy looking pattern produced by coherent laser light. Technically speaking they are a random intensity pattern produced by the mutual interference of a set of wavefronts</td>
</tr>
<tr>
<td>LED</td>
<td>Light emitting diode. A narrow spectral width (one color) semiconductor light source</td>
</tr>
<tr>
<td>Off-label</td>
<td>Use for a condition other than that for which it has been officially approved by a regulatory authority (e.g. FDA in USA, CE for Europe, Health Canada, TGA in Australia)</td>
</tr>
<tr>
<td>“Per point”</td>
<td>The region of treatment which may be a small area for a single laser beam (&lt;1 cm²) or a large area of many cm² for a cluster/array of incorporating many laser diodes or LEDs</td>
</tr>
<tr>
<td>Systematic review</td>
<td>A review in which research about a topic has been systematically identified, appraised and summarized</td>
</tr>
<tr>
<td>Tissue remodeling</td>
<td>The third phase of tissue repair after inflammation and cell proliferation.</td>
</tr>
<tr>
<td>1/e² point</td>
<td>Light beams do not typically have defined edges and the beam distribution is not usually uniform. To calculate power density laser physicists use the mathematical function 1/e² to define the area. This is the area in which 86.5% of the power is contained</td>
</tr>
</tbody>
</table>

5. Safety

There is less risk associated with LLLT (particularly the LED systems) than for the class IV surgical lasers most Academy of Laser Dentistry (ALD) members are familiar with. The potential hazards are mostly ocular rather than representing any risk from excessive temperatures, as most LLLT devices are class 3B lasers or LEDs, though some LLLT devices are defocused class IV lasers. In most cases, LLLT devices emit divergent beams (not collimated), so the ocular risk diminishes over distance (in the range of several meters). Indeed, manufacturers are obliged to provide the nominal ocular hazard distance (NOHD) within their user instructions. ANSI Z136.3 (2011) is the current definitive USA document on laser safety in healthcare environments (www.ansi.org) and IEC 60825 is the International Standard. Part 8 provides guidelines for the safe use of laser beams on humans (www.iec.ch) and there is also a European Union directive aimed to improve the health and safety of workers and reducing risks arising from exposure to artificial optical radiation (2006/25/EC; osha.europa.eu).

5.1. Contraindications

The North American Association for Laser Therapy conference in 2010 held a consensus meeting on safety and contraindications. Their recommendations were:

- EYES – Do not aim laser beams into the eyes and everyone present should wear appropriate safety spectacles.
- CANCER – Do not treat over the site of any known primary carcinoma or secondary metastasis unless the patient is undergoing chemotherapy; its use however can be considered in terminally ill cancer patients for palliative relief.
- PREGNANCY – Do not treat directly over a developing fetus (consequences unknown).
- EPILEPTICS – Be aware that low frequency pulsed visible light (<30Hz) might trigger a seizure in photosensitive, epileptic patients. It is essential that patients are adequately protected from pulsing beams.

5.2. Adverse effects

The Lancet review on neck pain [1] reported that “half of the studies obtained data for side-effects, with tiredness reported in the laser-treated group in three studies, and this was significant in one study. An oral mucositis review [63] reported: “all of the studies investigated possible side-effects, but none found side-effects or adverse effects beyond those reported for placebo LLLT. Five trials reported explicitly that LLLT was well tolerated among patients”.

A chronic joint disorder systematic review [44] reported: “In terms of side effects, six of the LLLT trials with optimal dose explicitly stated in their report that no adverse effects were observed. One trial however reported an incident of transient adverse effects for one patient in each group.”

5.3. USA Food and Drug Administration

There are no LLLT devices cleared specifically for use in treating oral conditions that are currently reported within the literature. However, there are many devices cleared for temporary relief of muscle and joint pain that could be applied to TMJ dysfunction. Currently, other applications are likely to be “off label” (Table 4).

6. Conclusion

LLLT is a safe effective treatment to enable enhanced healing, better tissue remodeling, reduced inflammation and analgesia for use in a wide range of oral pathologies. It is drug free and relatively side-effect free and appears to be efficacious where many current pharmaceuticals are not [13-15,64-66].

Acknowledgements

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