Lasers in medicine past, present and future.

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Laser in medicine represents the "poor cousin" of lasers in surgery but, in spite of its low profile, is potentially the medicine of the future. Einstein formulated the hypothesis of the generation of laser in 1916 [1] but it was not until 1960 that Maiman, in the Bell Laboratories, generated laser from ruby crystal (λ = 694nm) [2]. A number of early studies initiated research on low-level laser therapy (LLLT) using this wavelength, both clinically and experimentally [3-5].

One of the seminal studies from this period was that of Endre Mester, who treated non-healing chronic ulcers with ruby laser and found a remarkable rate of healing, especially of venous ulcers [6, 7]. Mester's study was the springboard for the continuing use of lasers for wound healing and research into mechanisms for the biological effects underpinning tissue repair commenced. Strong evidence for numerous effects on the cascade of cellular involvement in wound healing continue to be demonstrated [8-17]. Somewhat disappointingly however, there is still variability in the outcomes of clinical studies and standard meta-analyses cannot provide evidence of a strong effect [18-20].

Nevertheless the trend is strong and Enwemeka has used a novel statistical technique to demonstrate a clinically useful benefit [21, 22]. Effects of laser irradiation (LI) in wound healing are especially dose sensitive and in this clinical domain, low doses of laser stimulate and high doses inhibit [23]. Understanding and applying the biphasic biological effects of laser on cells in tissue is critical to optimising the "dose" [24]. This is even more complex in an individual patient where variation in sensitivity to LI is a confounding factor in clinical studies.

Alongside the use of lasers in wound healing, treatment of painful conditions was one of the other early clinical applications of LLLT [25-28]. Many different painful musculoskeletal conditions have been the subject of investigation and, in contrast to wound healing, the evidence base is now strong [29-32]. For example, a meta-analysis of LLLT in neck pain [33], established it as one of the most strongly evidence based of all treatments for neck pain.

This has now been supported in the report assessing neck pain treatments, by the World Health Organisation Committee of the Decade of the Bone and Joint [34]. Other painful conditions have accumulating evidence, such as tendinopathy [32], and lateral epicondylitis [32]. Analysis of laser parameters to identify optimal doses in addition to methodological assessment, have been critical to these meta-analyses, differentiating them from standard meta-analyses where no technological assessment is made [32, 35, 36]. It appears that the balance between stimulatory and inhibitory effects of LLLT is not as critical in pain modulation as in tissue repair. Importantly, the critical concept of "dose" is again emphasised in these studies.

Various mechanisms for the pain relieving effects of LLLT have been proposed since the first clinical studies were performed. These have included the gate control theory [37], endorphin release [38-40], serotonin increase [41, 42], neural inhibition [43-48] and anti-inflammatory effects [49-52], with these latter two effects the focus of intense investigation. The anti-inflammatory effects of laser have now been well documented in many experimental studies as well as clinical studies [50, 53-57], demonstrating that these effects are of the same order of magnitude as anti-inflammatory drugs, and indeed more effective in some instances. In one of the most difficult areas of management, LLLT for the treatment of chemotherapy-induced oral mucositis is one of the most important recent applications, which should be introduced without delay into mainstream practice, as this condition carries significant morbidity [58].

The capacity of LLLT to reduce inflammation is one of the most promising areas in medicine as the ease of application in primary care practice and safety, compared with NSAIDs, would make it an extremely cost-effective option for introduction to mainstream medicine. Other mechanisms for pain relieving effects which focus on neural inhibition, also underlie the benefit where drug therapies are limited by side effects and lack of efficacy. This is particularly so in chronic pain states, which is reaching epidemic proportions [59]. Specific anti-nociceptor effects are strongly supported in the literature as is the capacity to reduce acute pain following injury and to prevent the progression from acute to chronic pain in the short term. Such "preventative" effects of "pre-emptive" treatment significantly reduced pain scores and drug intake when laser therapy was applied immediately post-operatively [60] and prevented recurrence of neck pain six months after treatment of an acute episode [61]. Neural inhibition may also have the capacity to reduce "wind up" as well as peripheral and central sensitisation by a cascade of effects from the peripheral nerve to the spinal cord and pain matrix [62]. These mechanisms are implicated in the progress of acute to chronic pain and induce long-term depression of pain in chronic pain states, such as fibromyalgia, which are very difficult to treat using conventional therapies.

Wound healing and treatment of painful conditions have been studied for many years, however, the first decade of the twenty-first century has seen research into a range of applications that offer novel treatment options for a range of neurological conditions.

Laser therapy as an adjunct to peripheral nerve and spinal cord repair presents an option for management for the near future [63-67]; laser therapy to the scalp within 24 hours of stroke reduces disability by about 25%[68]; laser (and LED) therapy for traumatic brain injury [69, 70] and depression [71] are also in the early stages of clinical development and offer novel approaches for difficult to treat conditions. Animal studies using models of myocardial infarction suggest another option for adjunctive treatment for minimising ischaemic damage [72]. Other areas at the frontier of research involves enhancement of stem cells viability [73-75] and enhancement of sperm motility [76, 77].

With all the potential of this therapy as well as the current evidence base for applications in pain and inflammation, one might ask why the notion that light might have a therapeutic potential in this new form is greeted with responses ranging from indifference to outright hostility, which was certainly the situation with the early literature [78]. There are many examples of currently applied light therapy such as the treatment of neonatal hyperbilirubinaemia, light therapy for psoriasis and seasonal affective disorder. The Nobel prize was won in 1903 by Neils Finsen for the treatment of tuberculosis with light. One reason for the resistance may have come about because the adoption of LLLT in clinical practice initially outstripped the evidence base, in addition to a lack of understanding of any mechanisms for the effects. This is very different from the introduction of drugs which undergo a series of experiments over many years from the Phase I laboratory based investigations to Phase III human clinical trials before finally, if at all, the drug becomes available to the public.

With LLLT, the safety and ease of application, meant that manufacturers could make and sell the devices to a wide variety of health practitioners, particularly alternative medicine practitioners, who rapidly took to the devices. The response of the medical profession was to attribute any benefits to placebo effects and therefore not attribute any credibility to LLLT. Manufacturers continued to make what appeared to be outrageous claims, further confirming in the medical profession's conservative and drug-oriented view that LLLT, which did not even have a heating effect, could "do anything".

One of the problems in critiquing laser therapy studies comes from both inside and outside the field. Firstly, many authors evaluating studies do not have the expertise to assess whether the technical aspects of the study fulfil the minimum criteria of effective dose and application, and conversely, those conducting studies either use inappropriate parameters or do not report them in sufficient detail to permit replication of the study. Added to this is the difficulty in measuring the precise "dose", and, even then, there is debate about what is the correct "dose".

In spite of these difficulties, there continues to be research into mechanisms of LLLT as well as clinical studies, which confirm significant benefit. While problems exist, mostly relating to understanding dosage, there is no doubt that laser medicine offers the potential for benefit across a range of difficult-to-treat clinical conditions. Patients will be the beneficiaries of the acceptance of LLLT into mainstream medicine. Laser Medicine is the energy medicine of the future.

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