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Editorial

The Evidence for Low-level Laser Therapy for Oral Mucositis in Head and Neck Cancer Radiotherapy

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Oral mucositis (OM) remains a significant toxicity for patients undergoing radiotherapy, with or without chemotherapy (C)RT, for the treatment of head and neck cancer (HNC) and is a burden on healthcare services. Reducing the negative effects of OM on patients' recovery from treatment is a major challenge for HNC researchers. Low-level laser therapy (LLLT), or photobiomodulation (PBM), is advocated as a therapy both to prevent and treat OM. This editorial aims to cast a critical eye on the evidence cited in support of LLLT to treat OM in patients undergoing (C)RT for HNC. In doing so, the authors accept there are many proposed regimens for LLLT but, for this pragmatic commentary, LLLT is referred to as a broad, all-encompassing intervention.

In 2018 the UK's National Institute for Health and Care Excellence (NICE) concluded that the evidence on LLLT in this patient population is adequate in quality and quantity, suggesting that the intervention can be used [1]. The Multinational Association of Supportive Care in Cancer and International Society for Oral Oncology (MASCC/ISOO) clinical practice guidelines recommend the use of intraoral PBM therapy using low-level laser therapy for the prevention of OM in adults receiving radiotherapy with chemotherapy (CRT) for HNC—citing level I evidence—and level II evidence for adults treated with radiotherapy (RT) alone [2]. This editorial summarises the studies highlighted through guidelines as supportive of LLLT and compares them to the broad findings from the ONLY two attempted multicentre studies. This commentary is not a scoping review of the many studies published in the field of LLLT in the management of HNC.

The use of LLLT for OM has received a lot of press, and much work has gone into the guidelines cited above. Much of the work appears to come from enthusiasts in the field of LLLT. The MASCC guidelines [2] rely heavily on a systematic review commissioned by the group and performed by Zadik *et al.*, in 2019 [3]. This review identified three 'flawless' trials according to specified criteria:

The first study by Gautam *et al.* [4] was a single-centre double-blind randomised controlled trial (RCT) in 22 participants receiving LLLT each day of radiotherapy and 24 receiving a sham/placebo intervention—all over 60 years old and receiving radiation therapy alone. The primary outcome was the Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer (RTOG/EORTC) scoring system for OM. The results suggested a large effect, with 58% in the placebo group and 18% in the LLLT group suffering severe OM at the end of RT. The participants were recruited between 2009 and 2012. Gautam and colleagues have published further clinical trials from the same period on different populations, all showing large effects of LLLT intervention. In 2012, an RCT of 239 patients undergoing CRT for oral and oropharyngeal carcinoma was published with participants recruited between 2009 and 2011. No upper age exclusion criteria was specified, but the mean age was approximately 55 with a standard deviation of 11, implying patients over 60 years old were included in this study [5]. In the same year—2012—an apparent subset of this population was published for patients with oral cavity cancer alone [6]. The three published trials appear to have recruited over the same time period. Multiple reports from potentially the same population can lead to sources of bias in meta-analyses, if reviewers do not scrutinise the data thoroughly.

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The NICE guidelines [1] summarise a number of studies, in particular a systematic review performed by Oberoi *et al.* [7], which concludes in favour of LLLT. In the principal Forest plot within this review are the two 2012 studies by the Gautam teams, duplicating the same patient population. These are the two largest studies to be included within the meta-analysis. The second study by Antunes *et al.* [8] was a single centre double-blind randomised trial that randomised 94 participants with nonoral cavity HNC treated with CRT. The primary outcome measure was the World Health Organisation OM scale (grade I − IV)—severe OM grades III and IV. At the end of CRT the incidence of severe OM was 6% in the LLT group (3 participants) and 40% in the placebo group (19 participants). The third study by Oton-Leite *et al.* [9] (n = 30) was an exploratory, unpowered, single-centre double-blind randomised trial aiming to analyse salivary inflammatory markers in addition to the incidence of severe OM, measured using the National Cancer Institute (NCI) and the World Health Organization (WHO) scoring systems. As with the other studies highlighted, this study used LLLT as a preventative measure throughout CRT. At the end of the treatment, 3/12 participants in the laser group suffered severe OM, compared to 7/13 in the placebo group.

Two well-designed multicentre randomised control trials have attempted to definitively ascertain whether LLLT for OM in this population is clinically and cost effective [10,11]. The two trials, performed in France (The laser mucositis study) and the UK (The LITEFORM trial) failed to recruit the numbers of participants they set out to include. In the case of LITEFORM, setting up a new laser service in enough institutions proved too challenging to achieve in the trial time period. The laser mucositis study took 8 years to recruit 97 participants between 2008 and 2016. The LITEFORM trial recruited 87 participants between November 2017 and April 2019, demonstrating that more rapid recruitment could be achieved over many centres, but not enough to meet the sample size calculation of 380.

The primary outcome for the laser mucositis trial was the incidence and duration of grade ≥ III on the WHO OM scoring system. Intervention commenced at the first visible signs of OM lesions; LLLT was used as a treatment rather than a preventative measure. The primary outcome was measured in 51 participants who suffered severe and reachable OM to treat with LLLT. Forty-one patients suffered with grade ≥ III OM, 23 in the active intervention arm (54.8%), and 18 (43.9%) in the placebo arm.

LITEFORM offered LLLT as a preventative treatment throughout the course of radiotherapy. Its primary outcome was the Oral Mucositis Weekly Questionnaire-Head and Neck Cancer (OMWQ-HN) score at 6 weeks. The total overall OMWQ-HN score ranges between 0 and 54 points, with a higher score indicating poorer well-being and oral function. Of the 87 randomised participants, 71 were included in the primary analysis. There were 37 participants in the LLLT group and 34 in the sham group. The mean (standard deviation) OMWQ-HN total score at 6 weeks was 33.2 (10) in the LLLT group and 27.4 (13.8) in the sham arm. The average score on the OMWQ-HN was 5.8 points higher (95% confidence interval 0.1 to 11.5 points) in the LLLT group than in the sham group. For the WHO OM scale score, the LLLT group had, on average, 10% fewer participants with grades III/IV oral mucositis at 6 weeks (95% CI −32.7%–12.7%) than the sham group [10].

Whilst there are clear limitations in drawing conclusions from these two trials, which failed to recruit the required number of participants, and in the case of LITEFORM recruited less than 25% of the anticipated numbers, the results are worthy of consideration. Neither multicentre trial shows a signal effect in favour of the active intervention. The single-centre studies cited above all demonstrated large effects with LLLT. The results from single-centre RCTs tend to overestimate the effects seen in multicentre RCTs [12,13]. The underlying evidence base for this intervention is reliant on a number of small single-centre randomised trials. As head and neck oncologists, we must question the evidence provided to us with critical rigour.

Patients undergoing (C)RT for HNC suffer with the side effects of treatment and are often at a low ebb during and after treatment. OM is a condition that resolves with time. Most patients will struggle with symptoms over a period of several weeks. Robust evidence is required to demonstrate the clinical efficacy of any intervention in such situations. One could envisage that many supportive interventions provided to this population would result in reported benefit. In the UK, to provide an LLLT service to all patients undergoing (C)RT would certainly require a discussion over the redistribution of personnel within services. The cost of delivering LLLT in the UK is approximately £800 per patient [11]. For a single large head and neck service treating approximately 150 new patients with radiotherapy per year would cost in the region of £120,000. This is a similar cost to employing two experienced clinical nurse specialists. Guideline conclusions regarding the clinical effectiveness of LLLT for OM in this population must therefore be robust and independent, as the implications are of great importance.

There are a number of more recent single-centre RCTs, many from Brazil, concluding that LLLT has a role in treating OM [14]. There is a multicentre study currently recruiting 80 patients in the USA [15]. This commentary concludes that the evidence cited in guidelines that support LLLT is not 'flawless'. Further high-quality multicentre trials are required for definitive evidence in this field. Without doing so, the intervention will continue in the hands of enthusiasts. If LLLT is truly effective, the evidence is required to support its broader adoption into clinical practice.

Conflict of interest

The authors declare no conflict of interest.

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