Photobiomodulation in the management of oral mucositis for adult head and neck cancer patients receiving irradiation: the LiTEFORM RCT

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Disclaimer: This report contains transcripts of interviews conducted in the course of the research and contains language that may offend some readers.

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Scientific summary

The LiTEFORM RCT

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Scientific summary

Background

Low-level laser therapy is purported in the literature to be the most effective treatment for oral mucositis caused by head and neck cancer irradiation. Oral mucositis is both the most common and the most devastating consequence of head and neck cancer radiotherapy. It affects around 97% of the 6000 people receiving radiotherapy or chemoradiotherapy for head and neck cancer in the UK each year.

This trial was motivated by the need to determine whether or not the positive results reported from several small studies overseas could be applied to the adult population receiving head and neck cancer irradiation in the UK, as well as considerations of feasibility of delivery within the NHS, cost-effectiveness and any possible harmful effects to patients and/or their care pathway.

Objectives

Primary objective

The primary objective was to examine the clinical effectiveness of low-level laser therapy in the management of oral mucositis for adult head and neck cancer patients receiving (chemo)radiotherapy.

Secondary objectives

- To explore the feasibility of site set-up and recruitment using an internal pilot.
- To investigate the short- and long-term harms and benefits for patients receiving low-level laser therapy in terms of clinical outcomes and quality of life.
- To examine the cost-effectiveness of low-level laser therapy by conducting an economic evaluation.
- To undertake a qualitative substudy to identify and understand the:
    - barriers to and facilitators of recruitment during the trial
    - barriers to and facilitators of the wider implementation of low-level laser therapy within the NHS
    - experience and impact of setting up and delivering low-level laser therapy services on patients and health professionals.

Methods

Design

This was a multicentre, Phase III, individually randomised, placebo-controlled superiority trial with an internal pilot and qualitative substudy, set in secondary care, comparing low-level laser therapy three times per week plus standard care with sham low-level laser therapy three times per week plus standard care for the prevention of oral mucositis in patients being irradiated for head and neck cancer. Participants, assessors and therapists were blinded. Participants were randomised in a 1 : 1 ratio, using a centralised random block allocation set by an independent statistician, and were stratified by planned treatment and radiotherapy field. This was a pragmatic trial and, for this reason, attempts were not made to standardise standard care for oral mucositis or radiotherapy regimes across sites.

Setting and participants

This trial was set in NHS head and neck cancer treatment sites in England and Wales.

Inclusion criteria

- Adults aged ≥ 18 years diagnosed with head and neck cancer.
- Patients who had the capacity to provide written informed consent.
- Patients who had received a histological diagnosis of head and neck squamous cell carcinoma. Primary sites included the oral cavity, oropharynx, nasopharynx, larynx, hypopharynx or unknown site.
- Patients who had been discussed in a head and neck multidisciplinary team meeting and were deemed medically fit for an agreed treatment plan for primary or adjuvant radiotherapy with our without concurrent cisplatin or cetuximab. Induction chemotherapy was also permitted.
- It had been planned for the patient to receive a minimum of 60 Gy to a defined clinical target volume in the oral cavity or oropharynx, or neck levels Ia/b.

Exclusion criteria

- Patients who were known to be pregnant or planning to become pregnant within the trial treatment period.
- Patients who had photosensitive epilepsy.
- Patients who had parotid tumours.
- Patients who had previous radiotherapy for head and neck cancer.
- Patients who were experiencing current/ongoing oral mucositis and trismus limiting access for treatment.
- Patients who were experiencing active heavy tumour bleeding from their mouth.
- Patients for whom the multidisciplinary team recommend short-course palliative radiotherapy.
- Patients on immunosuppressant drugs (except low-dose steroids).
- Patients who were participating in other trials assessing different treatments for oral mucositis.
- Patients who were unable to provide written informed consent.

Measurement of clinical outcomes

Primary

The primary outcome measure was the severity of oral mucositis, which was measured by the Oral Mucositis Weekly Questionnaire-Head and Neck Cancer (OMWQ-HN) score at 6 weeks and was completed by the participant. This was collected at baseline, weekly during radiotherapy and at the 4-month and 14-month follow-ups. It is a nine-item patient questionnaire that measures symptoms of mucositis and their impact on patient well-being over the past 7 days. A higher score indicates a worse outcome.

Secondary

The World Health Organization (WHO)'s Oral Mucositis Grading Scale score was recorded by a clinician at baseline, weekly during the 6-week treatment period and at the 4-month follow-up. All outcome assessors were unaware of treatment allocation.

The following measures were recorded at baseline, 6 weeks and at the 4-month and 14-month follow-ups:

- European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30 (EORTC QLQ-C30) (patient completed) (version 3.0) and the European Organisation for Research and Treatment of Cancer Quality of Life Module for Head and Neck Cancer 35 (EORTC QLQ-H&N35) (patient completed)
- the MD Anderson Dysphagia Inventory (MDADI) (patient completed) outcome measure
- the Performance Status Scale for Head and Neck Cancer Patients (PSS-HN) (rated by the research nurse, speech and language therapists or health professional)
- the 100-ml water swallow test (assessed by a speech and language therapist or trained research nurse)

- weight and body mass index.

The use of a feeding tube, use of analgesics, topical treatments and mouthwash, visits to an oral hygienist, and pain scores [as measured using the EuroQol-5 Dimension, five-level version, (EQ-5D-5L) descriptive questionnaire] were recorded at baseline and weekly during the 6-week treatment period.

Adverse events attributed to low-level laser therapy and clinical complications, notably the number of days as inpatient hospital admissions and interruptions in cancer treatment, were recorded weekly.

Data on disease recurrence and persistence of disease were recorded at 14 months.

Statistical considerations

The minimal clinically important difference for the OMWQ-HN is 4 points. We assumed a standard deviation of 10.7 points at 6 weeks. The trial was powered with a 5% alpha and 90% power. The sample size calculation required 190 participants in each treatment arm, allowing for 20% loss to follow-up or missing data.

Owing to under recruitment, the statistical analyses performed were descriptive and no formal statistical testing between arms was carried out. All analyses were performed on a modified intention-to-treat basis, defined as all randomised participants, and included seven participants who randomly received treatment that was the opposite to what they should have received according to the original randomisation schedule.

Summary statistics were calculated for the OMWQ-HN by treatment arm for each time point. The difference between treatment arm means at 6 weeks was reported with a 95% confidence interval. For the secondary outcome measures, questionnaires were scored in accordance with their manuals and any missing data were handled as recommended. Outcomes were summarised descriptively as frequencies (and percentages) or means/medians (and standard deviations/interquartile ranges). Where appropriate, the difference between arms has been reported with associated 95% confidence intervals.

Health economic analysis

Low-level laser therapy treatment costs were determined by microcosting equipment and human resources required to run the service. An electronic case report form was used to establish health service utilisation during the intervention phase and a Health Service Utilisation Questionnaire was used to collect information at 4 months post treatment. Details of prescribed medications were collected from the trial participants at each clinic visit.

Completion rates and domain scores for the EQ-5D-5L and EuroQol-5 Dimensions visual analogue scale (EQ-5D-VAS) were initially computed for the two treatment arms. The health state utilities calculated from the responses to the EQ-5D-5L were used to estimate mean quality-adjusted life-years for both treatment arms at 4 months.

Qualitative analysis

The qualitative process evaluation involved interviews and observations with a diverse sample of patients and hospital staff at all LiTEFORM trial sites.

The analysis was theoretically informed by normalisation process theory and was conducted in accordance with the standard procedures of rigorous qualitative analysis, including open and focused coding, constant comparison, memo taking, deviant case analysis and mapping. A proportion of data were analysed collectively in ‘data clinics’, where the research team shared and exchanged interpretations of key issues emerging from the data.

Results

In total, 221 patients were screened between November 2017 and April 2019. Of these, 87 were randomised and 71 were included in the primary analysis. Participants across the two arms had similar baseline characteristics. There were 37 participants in the low-level laser therapy arm and 34 in the sham arm. The mean (standard deviation) OMWQ-HN total score at 6 weeks was 33.2 points (10.0 points) in the low-level laser therapy arm and 27.4 points (13.8 points) 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 low-level laser therapy arm than in the sham arm, with a higher score indicating poorer well-being and oral function. For the WHO Oral Mucositis Grading Scale score, the low-level laser therapy arm had, on average, 10% fewer participants with grades III/IV oral mucositis at 6 weeks (95% CI −32.7% to 12.7%) than those in the sham arm.

Unsurprisingly, participants were most burdened by being unable to eat normally. This is illustrated by PSS-HN data, feeding tube use and quantity of oral diet. At 6 weeks, 33 out of 37 (85%) participants in the low-level laser therapy arm and 32 out of 34 (91%) participants in the sham arm were, at best, able to consume only very soft food textures. The proportion of participants using a feeding tube was the same in both treatment arms [25/37 (66%) in the low-level laser therapy arm and 23/34 (66%) in the sham arm]. There were relatively more participants in the low-level laser therapy arm who had total dependence on a feeding tube (15/25, 60%) than in the sham arm (9/23, 39%). Just over two-thirds of participants in each arm [low-level laser therapy arm, 25/37 (68%); sham therapy arm, 23/34 (70%)] were achieving an oral intake level of > 25%.

Participants' social confidence was impaired, with 28 out of 37 (78%) participants in the low-level laser therapy and 26 out of 34 (74%) participants in the sham arm eating only in the presence of selected persons in selected places.

The results from the following measures provided the secondary outcomes and they showed a decline during the 6 weeks of treatment, consistent with the cumulative side effects from (chemo)radiotherapy, in both arms: MD Anderson Dysphagia Inventory, EORTC QLQ-C30 and EORTC QLQ-H&N35, the timed 100-ml water swallow test, weight and body mass index.

The dramatic decline in the quality of life experienced by participants across both arms (mean decline in the EORTC QLQ-C30 global score of 24.6 points in the low-level laser therapy arm and 24.5 points in the sham arm) was consistent with previously reported studies.

Pain scores and concomitant analgesic use increased in a similar way over the 6 weeks of treatment. Overall, 83% of participants [33/37 (87%) in the low-level laser therapy arm and 28/34 (78%) in the sham arm] required opioid medication at 6 weeks, which is in accord with the high levels of pain reported on the EORTC QLQ-H&N35 and similarly high feeding tube use.

In total, 69 out of 87 (79%) (36/44 in the low-level laser therapy arm and 33/43 in the sham arm) participants experienced an adverse event. For each system organ class, adverse events appeared balanced across the two treatment arms.

Health economic evaluation

The total cost of delivering the intervention was estimated to be £802 per patient.

In the 6-week modified intention-to-treat sample, the average total costs of using hospital services during the intervention period (i.e. weeks 2–6) were £1615 in the low-level laser therapy arm and £1613 in the sham arm.

The average per-patient inpatient costs at the 4-month data collection point were £881 in the low-level laser therapy arm and £1417 in the sham arm. The average per-patient outpatient costs at the 4-month data collection point were £528 in the low-level laser therapy arm and £625 in the sham arm. The average per-patient primary care costs at the 4-month data collection point were £107 in the low-level laser therapy arm and £150 in the sham arm. These figures must be interpreted with caution because of the small sample size.

The mean costs of the medications prescribed before the 4-month post-intervention data collection time point were £284 in the low-level laser therapy arm and £217 in the sham arm.

The mean EQ-5D-5L utility scores at baseline were 0.729 points in the low-level laser therapy arm and 0.772 points in the sham arm. The mean utility scores at 6 weeks were 0.559 points in the low-level laser therapy arm and 0.626 points in the sham arm. The mean utility scores at 4 months were 0.736 points in the low-level laser therapy arm and 0.768 points in the sham arm. The mean accumulated quality-adjusted life-years at 4 months were 0.218 in the low-level laser therapy arm and 0.231 in the sham arm.

The mean EQ-5D-VAS scores at baseline were 72 points in the low-level laser therapy arm and 71 points in the sham arm. The mean EQ-5D-VAS scores at 6 weeks were 54 points in the low-level laser therapy arm and 57 points in the sham arm. The mean EQ-5D-VAS scores at 4 months were 72 points in the low-level laser therapy arm and 71 points in the sham arm.

Qualitative findings

The capacity to deliver low-level laser therapy (or sham), rather than the capacity to recruit, was the central problem that inhibited the successful conduct of the trial. The failure to recruit to target was not tied to recruiters' views and personal preferences. Instead, the pressures around the practical enactment of the scheduling, staffing and physical location of low-level laser therapy could neither introduce nor sustain the expected throughput of trial participants. The initial work of set-up, which involved finding suitable rooms and suitable staff and then adequately adjusting the room and training the staff, as well as receiving appropriate organisational approvals, took considerable time. Cognitive participation was very high in that staff and patients were very willing be involved and commit to the implementation of the trial. Staff reported a positive impact for the oral mucositis of some of their patients. Some participants perceived a positive impact on their oral mucositis. Others benefited from the additional time and care that they had received.

Conclusions

The LiTEFORM trial had a robust design but fell short in recruitment, in spite of high levels of participation and perceived value, because of the lack of site capacity. This, in turn, was caused by the excess treatment cost model within which it had to be delivered. Nevertheless, to our knowledge, the LiTEFORM trial recruited faster than all but one other low-level laser therapy trial and opened more sites than these other trials. The lack of power prevents any meaningful clinical conclusions about the clinical effectiveness and cost-effectiveness of low-level laser therapy in head and neck cancer irradiation. The health economic evaluation demonstrated that low-level laser therapy is relatively inexpensive. Qualitative data show that low-level laser therapy sessions can be challenging for patients. This, along with the low rate of completing all 18 low-level laser therapy sessions, means that we can conclude that low-level laser therapy is not tolerated as easily as previously described. The duration of low-level laser therapy sessions is, therefore, an important consideration. Clinicians experienced in oral cavity work most readily adapted to delivering intraoral low-level laser therapy, although other allied health professionals can be trained. Overall, the LiTEFORM trial shows that there are important human resource, real estate and logistical considerations for those setting up low-level laser therapy services.

Future work

1. Further adequately powered multicentre randomised controlled trials with robust allocation concealment are required.
2. Future studies designed to address the capacity constraints identified are required.
3. Studies should investigate low-level laser therapy protocols with less onerous treatment sessions.

Trial registration

This trial is registered as ISRCTN14224600.

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