

Low-level laser therapy for oral mucositis in children with cancer

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ABSTRACT

Objective To assess the efficacy of oral low-level laser therapy (LLLT) – also known as photobiomodulation – in the reduction of oral mucositis experienced by children and young people with cancer undergoing chemotherapy.

Design A systematic review to evaluate the efficacy of oral LLLT for oral mucositis in children with cancer and the safety of oral LLLT in any age with cancer (International Prospective Register of Systematic Reviews/PROSPERO registration: CRD42018099772). Multiple databases and grey literature were screened. Randomised controlled trials were considered for assessing efficacy, and all studies were considered for assessing safety. Primary outcomes included severity of oral mucositis, oral pain and adverse events. Where results were compatible, meta-analysis was performed using a random-effects model. A narrative synthesis considered other outcome measures.

Results 14 studies (n>416 children) were included in the narrative synthesis of LLLT efficacy. 5 studies (n=380 children and young people) were included in the meta-analyses. Results demonstrate that LLLT may reduce the severity of oral mucositis and the level of oral pain, but further randomised controlled trials are needed to confirm or deny this. There is vast variation in different trial protocols. Insufficient blinding between LLLT or sham therapy/control led to a strong risk of performance bias. 75 studies (encompassing 2712 patients of all ages who had undergone LLLT) demonstrated minor and infrequent adverse reactions, but most studies had significant areas of weakness in quality.

Conclusion LLLT appears to be a safe therapy, but further evidence is needed to assess its efficacy as a prevention or treatment tool for oral mucositis in children with cancer.

INTRODUCTION

Inflammation and ulceration of the mouth (oral mucositis) is a significant and distressing side effect of chemotherapy and haematopoietic stem cell transplants (HSCTs). Oral mucositis can cause pain, problems with nutrition and psychological distress and may affect the patient's ability to continue the current chemotherapy regime.^{1,2} Up to 80% of children undergoing chemotherapy may be affected by oral mucositis.³ In blood and bone marrow transplantation, oral mucositis is associated with worse clinical and economic outcomes.⁴ One mother who took part in our patient and public involvement work described her daughter's experience with oral mucositis: 'She struggled to swallow her own saliva...[she was] not really with us 'cos she'd had

What is already known on this topic?

- Oral mucositis is a significant, common and distressing side effect of chemotherapy and haematopoietic stem cell transplants.
- National Institute for Health and Care Excellence guidance (2018) exists for low-level laser therapy (LLLT) for the prophylaxis and treatment of oral mucositis but is largely based on adult evidence.
- Paediatric-specific guidelines (2017) gave a 'weak recommendation' for LLLT for oral mucositis prevention, with questions around the feasibility of delivering LLLT.

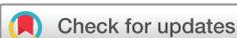
What this study adds?

- LLLT may reduce the severity of oral mucositis and the level of oral pain.
- Results are heterogenous and change over time; further research is needed.
- Minor and infrequent adverse device reactions were found and were poorly recorded.

so much morphine'. She required two 10-day-long stays in the hospital and asked her mum, 'Can't you just put me to sleep for 3 months...?'.

Guidance from The National Institute for Health and Care Excellence exists for the use of low-level laser therapy (LLLT)—also known as photobiomodulation—for the prophylaxis and treatment of oral mucositis, but is largely based on adult evidence, and no specific protocol for delivery is given.⁵ The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology produced recommendations for LLLT in 2019.⁶ This guidance recognises that different protocols are needed for different groups and indications and that further studies may be helpful.⁶ In 2017, paediatric-specific guidelines gave a 'weak recommendation' for LLLT for oral mucositis prevention because 'it is unknown whether it is feasible to deliver this therapy modality in routine clinical practice...'.⁷

LLLT is only being used for children and young people (CYP) in one centre within England and Wales.⁸ Therefore, we sought to undertake a systematic review.



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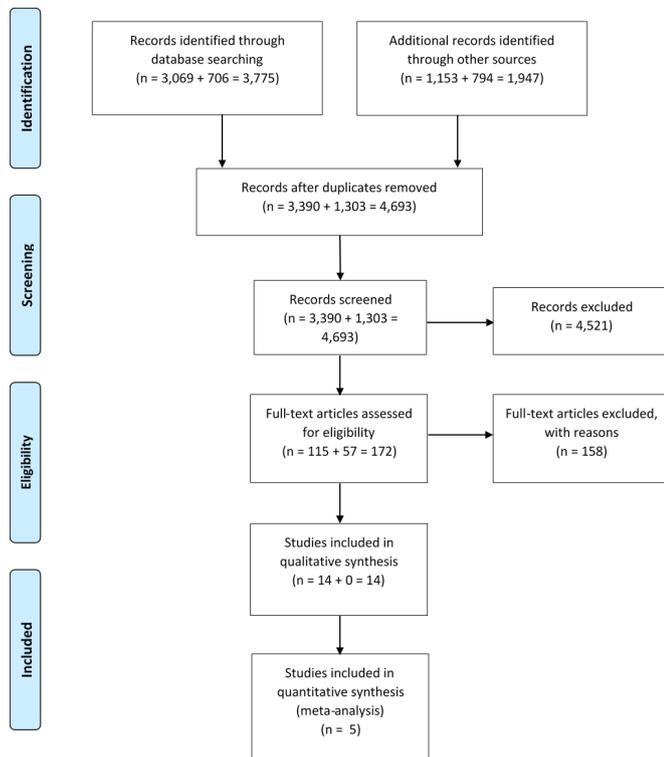


Figure 1 An adapted Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram¹³ showing the implementation of the search strategy for studies assessing efficacy identified through the first search in June 2018 and the additional studies included as a result of the update search in June 2020.

Objectives

- ▶ To assess the efficacy of oral LLLT in the reduction of oral mucositis experienced by CYP with cancer undergoing chemotherapy.
- ▶ To assess any adverse events associated with its use in patients with cancer of any age undergoing chemotherapy.

METHODS

The review protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) international database (CRD42018099772) using standard approaches.^{9 10}

Eligibility criteria

For assessing the efficacy of LLLT, randomised controlled trials (RCTs) considering CYP less than 18 years old with cancer were considered (online supplemental table 1). For assessing safety, all studies were considered for all ages of people with cancer (online supplemental table 2).

Search strategy

The 15 databases and sources searched are listed in online supplemental table 3. A 32-step search strategy was used for Embase, MEDLINE and Allied and Complementary Medicine Database (online supplemental table 4). Alternative search strategies were used for other sources. The search strategies ran from the earliest date available until 28 June 2020, including an update search. Searches were not restricted by age or language. Published and unpublished studies were considered. All studies included for efficacy had their reference lists reviewed. Additional unpublished material was sought from authors and experts in the field.

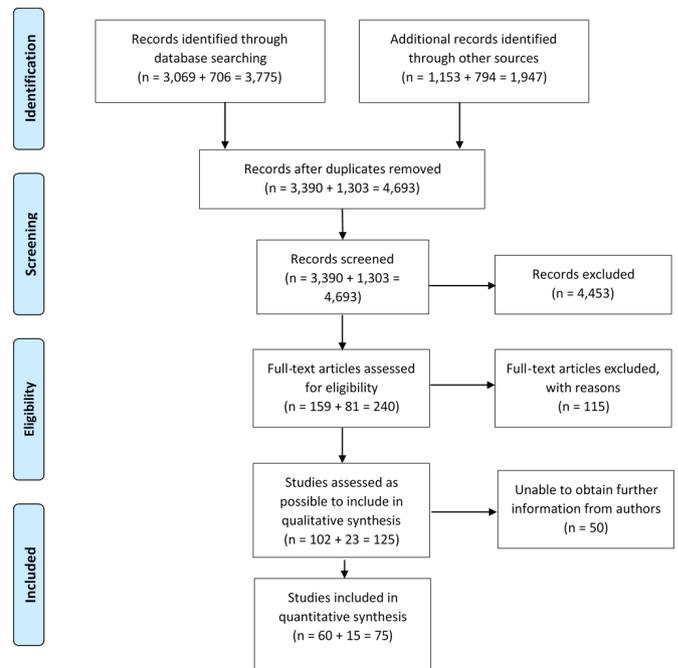


Figure 2 An adapted Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram¹³ showing the implementation of the search strategy for studies assessing safety identified through the first search in June 2018 and the additional studies included as a result of the update search in June 2020.

Data collection

Two reviewers (MGR/KH) screened all search results, obtaining full text where there was uncertainty about inclusion. Where the reviewers disagreed, a third reviewer (BSP) was consulted. Non-English studies were screened by experienced clinicians and/or academics (see the Acknowledgements section). Data extraction of the included studies was undertaken by KH or MGR and then counterchecked by the other (see online supplemental figure 1 for an example data extraction form).

Risk of bias

To assess the efficacy of LLLT, any RCTs that qualified for inclusion were analysed at a study level using the Cochrane risk of bias tool (Centre for Reviews and Dissemination, University of York, p37)[10]. When considering the adverse events associated with LLLT, studies were scrutinised using guidance provided by Loke *et al.*¹¹

Statistical analysis

Random effects meta-analysis was performed using RevMan V.5.4¹² where outcome measures were comparable. The principal summary measures were ORs and standardised mean differences. Pooling was not performed where there was substantial heterogeneity ($I^2 \geq 50\%$).⁹ Random effects were felt appropriate given the clinical heterogeneity of the interventions, and the Mantel-Haenszel method used as there were few events.⁹

Figures 1 and 2 adapted Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagrams¹³ demonstrate the flow of studies. Fourteen RCTs ($n > 416$ CYP) were included in the narrative synthesis of LLLT efficacy.^{14–27} Five RCTs ($n = 380$ CYP) were included for meta-analysis.^{15 16 19 21 22} Ahmed *et al.*¹⁵ declared that nearly half of their patients were below aged 17 (personal communications, MG Redman, 2020), and the other patients were young adults; we included these in

the meta-analyses. Seventy-five studies were included for safety analysis (online supplemental table 5). Relevant ongoing trials can be found in online supplemental table 6.

Quality of studies

When evaluating efficacy trials, there is a significant risk of performance bias as the outcome assessors were generally not blinded. Several RCTs provided insufficient data to assess selection bias (online supplemental figures 2 and 3).

Overall, studies included in the safety analysis provided insufficient assurance of quality. Of the quality assessment questions considered, 69.3% were 'unclear' or 'not applicable', particularly on how information about adverse events due to LLLT was collected.

Efficacy of LLLT

Intraoral LLLT was used by all studies, except Hodgson *et al*,²² who used extraoral LLLT. Studies considered prevention and/or treatment of oral mucositis. Protocols of LLLT administration varied widely (online supplemental table 7); wavelengths ranged from 632.8 to 955 nm. Energy delivery ranged from 1.5 to 8.0 J/cm². LLLT was mostly applied daily (apart from Abramoff *et al* and Fani *et al*^{14 20}), but duration ranged from 4 to 15 days.

Grade of oral mucositis

Two scales were used to assess oral mucositis grading: WHO oral mucositis scale/common toxicity criteria or National Cancer Institute Common Terminology Criteria [²⁸ p3-4]. Hodgson *et al*²² provided us with unpublished data using both grading systems, which allowed us to validate combining the grades for meta-analysis (online supplemental table 8). Patients aged > 18 or undergoing HSCT with no cancer diagnosis were removed from the dataset of Hodgson *et al*²² and Amadori *et al*.¹⁶ Abramoff *et al*¹⁴ included patients up to 23 years old; it was not possible to obtain the breakdown of data and thus all these are included.

For meta-analysis, three different timepoints were used, and results were grouped as low-grade (0–2) and high-grade (3–4) oral mucositis. A summary of the effect of LLLT on grade of oral mucositis in the included studies is presented in table 1. LLLT non-significantly reduced severe oral mucositis at all time points (days 3–5: OR 0.73, 95% CI 0.33 to 1.61; days 7–10: OR 0.35, 95% CI 0.12 to 1.03; days 11–17: OR 0.36, 95% CI 0.09 to 1.39; figure 3), but these results are heterogenous and change over time (figure 4).

Oral pain

Three studies had extractable data on oral pain. Median results from Gobbo *et al*²¹ and Ahmed *et al*¹⁵ were converted to estimates of means using an online tool.^{29–31} Similarly to observed grade of mucositis, there may be a trend towards less pain experienced

Table 1 Effect of low-level laser therapy (LLLT) on grade of oral mucositis

RCT	Effect of LLLT on grade of oral mucositis
Abramoff <i>et al</i> ¹⁴	For those undergoing prophylactic LLLT, at the third evaluation (between days 6 and 9 after commencing chemotherapy), 73% of the patients in the prophylactic laser group had grade 0 mucositis, compared with 27% in the placebo group (p=0.03).
Ahmed <i>et al</i> ¹⁵	Includes some adults. No statistically significant difference on daily evaluation of grade; however, authors report a risk ratio of 2.8 for the occurrence of grade 3 and grade 4 oral mucositis in the sham group compared with the laser group. OR of 0.22 (95% CI of 0.02 to 2.08) of grade 3 or more oral mucositis in the laser group on day 15.
Amadori <i>et al</i> ¹⁶	No statistically significant change. Day 4, oral mucositis median grade=2 for both laser and sham groups. Day 7, oral mucositis median grade laser=0, sham=1 (p=0.07). OR of grade 3 or more oral mucositis in laser group is 1.33 (95% CI 0.51 to 3.50) on day 4 and 0.18 (95% CI 0.01 to 3.88) on day 7.
Amadori and Bardellini ¹⁷	Abstract reports both prophylactic and therapeutic phases to result in a statistically significant reduction of OM in the laser group. Prophylactic phase reported as significant difference at day 4 (p=0.02) and therapeutic phase significant by the end of laser/sham treatment.
Cowen <i>et al</i> ¹⁸	Only 2 patients aged 17 out of group of 30 patients. Distribution of daily mucositis index statistically significantly lower in laser group compared with sham group on days 2–7 (inclusive) after bone marrow transplantation.
Cruz <i>et al</i> ¹⁹	Oral mucositis severity and prevalence were similar in the laser group and control group (p=0.208). OR of grade 3 or above oral mucositis was lower in the laser group (OR=0.34, 95% CI 0.01 to 8.80) on day 8 and lower in the laser group (OR=0.69, 95% CI of 0.11 to 4.47) on day 15, but not statistically significant.
Fani <i>et al</i> ²⁰	Unable to ascertain how many patients were children and met full inclusion criteria. Based on the WHO scale, there is no significant difference between the groups (p>0.05). However, based on the NCI scale, there is a significant reduction in oral mucositis between the groups (p<0.05).
Gobbo <i>et al</i> ²¹	On day 7, of those undergoing LLLT, one patient developed grade 4 oral mucositis, and 2 patients developed grade 3. Of those undergoing sham treatment, 8 patients developed grade 4 and 6 patients developed grade 3 oral mucositis (p<0.02). OR of grade 3 or above oral mucositis was lower in the laser group (OR=0.50, 95% CI 0.23 to 1.11) on day 4 but not statistically significant. It was also lower in the laser group (OR=0.17, 95% CI of 0.04 to 0.63) on day 7 and lower in the laser group (OR=0.08, 95% CI of 0.01 to 0.68) on day 11, and this was statistically significant.
Hodgson <i>et al</i> ²²	As displayed in the meta-analysis, OR of developing OM of grade 3 or above in laser group was lower at day 3–5 (OR=0.23, 95% CI 0.01 to 6.25) but then higher at days 8–10 (OR=1.25, 95% CI 0.23 to 6.71) and days 15–17 (OR=3.29, 95% CI 0.12 to 89.81). None of these were statistically significant.
Khoury <i>et al</i> ²³	Unable to ascertain how many patients were children and met full inclusion criteria. Mean grade of oral mucositis in the laser group was 1.75±0.45, compared with 2.45±0.93 in the control group (p<0.01). The laser group had a lower frequency of oral mucositis (p=0.02).
Kuhn <i>et al</i> ²⁴	Statistically significant reduction of oral mucositis in laser group (32% patients grade >0) compared with the placebo group (94% patients grade >0) on day 7 after oral mucositis diagnosis (p=0.001)
Salvador <i>et al</i> ²⁵	Unable to ascertain how many patients were children and met full inclusion criteria. Significant reduction in severity of oral mucositis from day +7 to day +11 (p<0.05).
Silva <i>et al</i> ²⁶	Unable to ascertain how many patients were children and met full inclusion criteria. Statistically significant reduction in grade of oral mucositis between laser and control group (p<0.001).
Silva <i>et al</i> ²⁷	Unable to ascertain how many patients were children and met full inclusion criteria. Less severe oral mucositis in the laser group on day 4, 7 and 8 (p<0.05). No significant difference on all other days of assessment (up to day 21).

NCI, National Cancer Institute; RCT, randomised controlled trial.

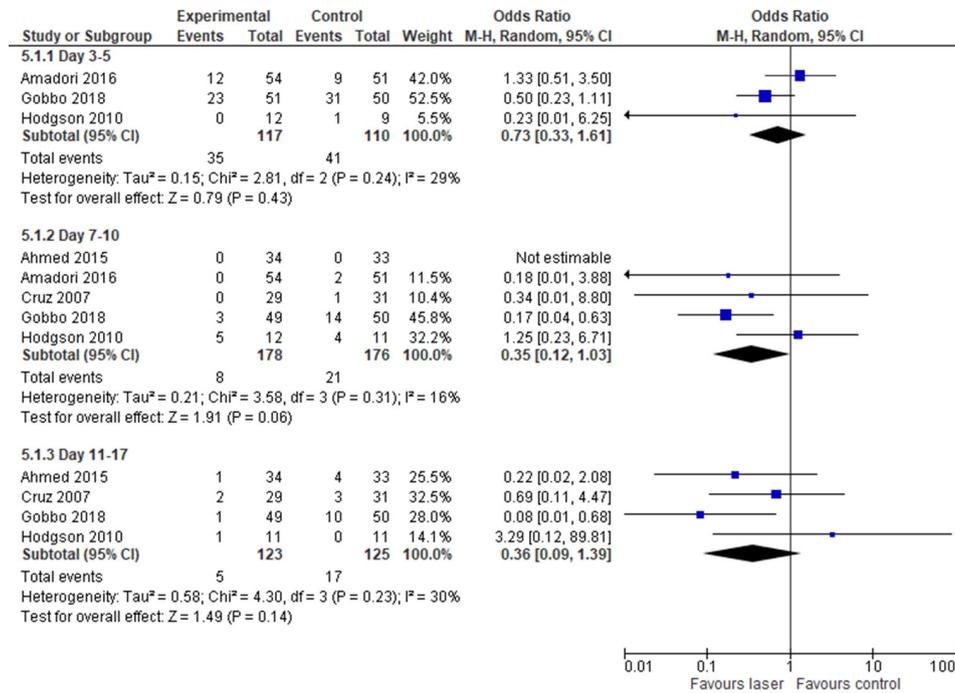


Figure 3 Forest plot of comparison: ORs comparing likelihood of patients developing grade 3+ (severe) oral mucositis in the laser group and the control group. Key: each study is labelled by its main author and year of publication and is represented by a square, the size of which reflects the relative size of the study, and the horizontal line passing through it represents the 95% CI. Random indicates the random-effects model; for CIs, the bracketed region denotes the upper and lower ends; I^2 represents heterogeneity between the randomised controlled trials; the 'p' value after 'test for overall effect' represents the probability that the overall effect is due to chance; the black diamond on each plot represents the pooled OR, with its breadth including the CIs. M-H, Mantel-Haenszel meta-analysis method.

from day 7 onwards after LLLT had been commenced (online supplemental figures 4 and 5 and online supplemental table 9).

Other outcome measures

Three RCTs^{16 19 21} considered the use of analgesia, with one suggesting reduced use in the treated arm (online supplemental table 10). Three RCTs^{18 19 22} considered the impact on diet, but no difference was found between the two groups (online supplemental table 11). One RCT looked at interruptions to cancer treatment; results are awaiting publication.¹⁷ No RCTs looked at

duration of hospitalisation. One study looked at quality of life,²⁷ but these results cannot be extracted for children alone (online supplemental table 12).

Safety of LLLT

As oral mucositis is an adverse event associated with chemotherapy/radiotherapy, LLLT, if effective, may have appeared to induce fewer or less severe adverse events than any control group. Therefore, where there was any ambiguity about wording around the monitoring or occurrence or causality of adverse

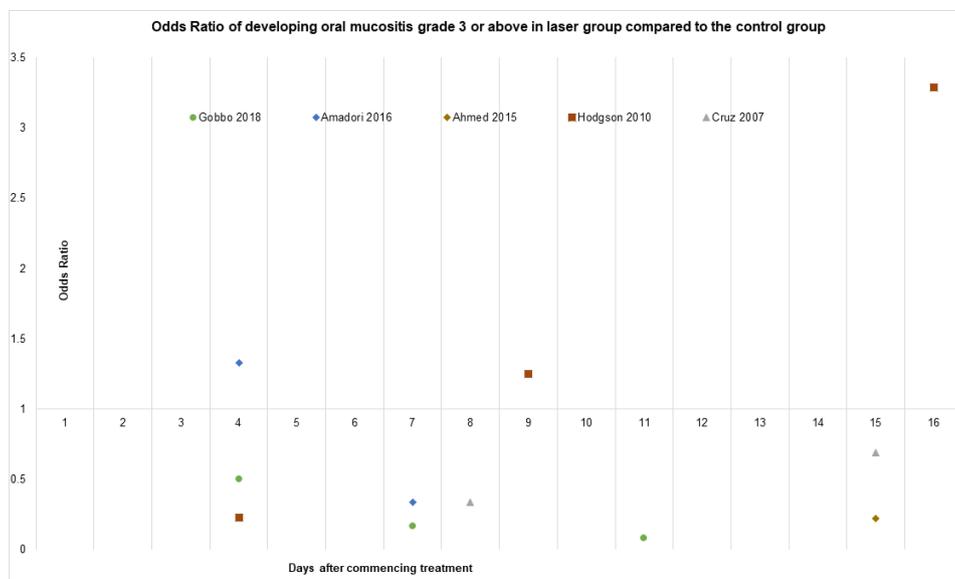


Figure 4 Graph comparing the ORs of developing oral mucositis grade 3 or more (severe to lifethreatening) in the laser group compared to the control group.

events, attempts were made to contact authors. Adverse reactions or adverse device effects which could be related to LLLT were sought.

A total of 125 identified studies would be expected to provide some information on the safety of LLLT. Despite attempts to contact authors, data were unavailable on adverse device effects or adverse reactions from 50 studies (which would have provided information on >1459 individuals who had LLLT).

Of the 75 included studies (encompassing 2712 patients who had LLLT), 24 studies were known to include children. The documentation of how adverse events were monitored was generally limited, affecting the quality assessment for the studies. There is a real challenge of monitoring and identifying adverse events due to LLLT. For example, Elad *et al* state, 'The treatment was well tolerated with no adverse events related to the study device'.³² However, they discuss adverse events found in the treatment (LLLT) group of 10 patients (they report 2 patients with a traumatic ulcer from self-biting and 1 patient with herpes simplex virus type 1 positive ulceration) and go on to explain that the oral adverse events are typical of HSCT.³² Definitions and monitoring methods regarding adverse events may be related to the cancer treatment and not to the LLLT. One study, where 22 children underwent LLLT, found adverse device events in 2 children and 1 issue with tolerability: 1 child was found to have some slight gingival bleeding after vomiting following laser treatment, and another child had a blood spot on the palate (attributed to mucositis rather than LLLT).³³ The same study also found that a 4-year-old boy refused to wear protective glasses, which are a necessary precaution for LLLT.³³ These issues were the only clear adverse device events indicated in 2420 patients.

A previous *in vitro* study raised concerns that LLLT exposure may lead to adverse effects on tumour behaviour, potentially affecting patient survival.³⁴ However, Antunes *et al* published a retrospective matched case-control study comparing those who had undergone LLLT with those who had not; this did not show any reduction in survival.³⁵ Genot *et al* retrospectively reviewed 361 patients and found that for the 62% who underwent LLLT, there was no statistically significant impact on overall survival, time to local recurrence or progression-free survival.³⁶ Fischlechner *et al* also considered overall survival and found no difference between 126 patients who had undergone LLLT and 126 matched controls.³⁷

Additional analyses

It was not possible to undertake subgroup analysis due to the small number of heterogeneous studies.

DISCUSSION

Fourteen studies (n>416 CYP) were considered in the narrative synthesis around LLLT efficacy and five studies (n=380 CYP) in meta-analyses. A robust search strategy was used to identify these studies, but the results are inconclusive. Insufficient blinding between LLLT or sham therapy/control meant a strong risk of performance bias. There is some potential that LLLT may reduce the severity of oral mucositis and the level of oral pain, but further larger randomised controlled trials would reduce uncertainty. Future RCTs should include protocols considering LLLT for both prevention and treatment, and should compare LLLT to sham therapy, ensuring appropriate blinding.

Heterogeneity between RCTs was anticipated, given a vast range of LLLT protocols used (online supplemental table 7). Some simplifications were made to pool the data, such as

combining NCI and WHO oral mucositis grades, and presenting efficacy over a group of days rather than identical time points.

This systematic review has highlighted some challenges of assessing the efficacy of LLLT. It is not clear what the optimal LLLT protocol is or the significance of different alternative parameters. This is in keeping with existing literature reflecting the challenges of assessing medical devices.³⁸

The meta-analyses demonstrated that LLLT may reduce the correlated outcomes of severe mucositis and oral pain. However, these findings are heterogeneous and imprecise. Seventy-five studies (encompassing 2712 patients of all ages who had LLLT) demonstrated minor and infrequent adverse reactions, but most studies had significant areas of weakness in quality. It is important to ensure accurate recording of adverse reactions/adverse device effects in future studies and interpret this with caution, given limitations around the quality assurance of these studies.

Antunes *et al* considered cost-effectiveness of LLLT for adults in Brazil and estimated the average cost of delivery of one 20 min session of LLLT was US\$41.18, including costs of equipment, furniture, facilities, salaries for a supporting team (including two dentists and two supporting staff) and medical supplies.³⁹ This may vary substantially, depending on the implementation of LLLT and the existing infrastructure.

Further work

While this review was robust in nature and included grey literature, there is currently insufficient direct data to draw any firm conclusions about the role of LLLT in children with cancer. Ongoing and unreported trials (online supplemental table 6) should be considered for inclusion in any future systematic review. Further studies to evaluate protocols, devices, timing and efficacy in prevention and treatment of oral mucositis in children with cancer are recommended.

CONCLUSION

LLLT appears to be a safe therapy in adults and children from available study data, and it may have the potential to provide some reduction in children's experience of oral mucositis and associated pain. However, LLLT is only being used for children and young people (CYP) in one centre within England and Wales.⁸ Where LLLT is used in other countries, protocols vary greatly between institutions, and clarity around the optimal delivery protocols is needed. For an institution to be able to introduce LLLT, some degree of dedicated infrastructure is needed to ensure laser safety. Further research is needed to assess if LLLT is an efficacious and cost-effective tool for the prevention or treatment of oral mucositis in children with cancer.

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