Original article

Laser therapy in oral mucositis control: a meta-analysis ☆

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ABSTRACT

Objective: To perform a systematic review and meta-analysis of the effectiveness of laser therapy (LT) in the prevention of oral mucositis (OM) in patients undergoing oncotherapy.

Methods: A search was conducted in the MEDLINE, LILACS, and Cochrane databases using the keywords "laser therapy" and "oral mucositis" in order to perform this systematic review and meta-analysis. The case-control studies included were submitted to odds ratio (OR) analysis, whose cut-off for statistic calculation was OM grade $\geq$ 3. Calculations were performed with the BioEstat program, release 5.0, using DerSimonian-Laird's random effects statistical analysis.

Results: In this systematic review, twelve studies were included; the meta-analysis of seven of them demonstrated that LT in patients undergoing oncotherapy is approximately 10 times more effective in the prevention of OM grade $\geq$ 3 than in patients without laser treatment (OR: 9.5281; 95% CI: 1.447-52.0354; p = 0.0093).

Conclusion: The data demonstrated the significant prophylactic effect of OM grade $\geq$ 3 in patients undergoing LT. Further studies, with larger sample sizes, are needed for better evaluation of LT's prophylactic effect on OM grade $\geq$ 3.

Laser terapia no controle da mucosite oral: um estudo de metanálise

RESUMO

Objetivo: Realizar uma metanálise da eficácia da laser terapia (LT) na prevenção da mucosite oral (MO) em pacientes submetidos à oncoterapia.

Métodos: Foi realizada uma busca nas bases de dados MEDLINE, LILACS e Cochrane, utilizando as palavras-chave "laser therapy" e "oral mucositis". Os estudos de caso-controle incluídos foram submetidos à análise do *odds ratio* (OR), cujo ponto de corte para a estatística foi MO

grau ≥ 3. Os cálculos foram realizados com o programa BioEstat 5.0, utilizando a análise estatística de Efeito Aleatório de DerSimonian-Laird.

Resultados: Doze estudos foram incluídos na revisão sistemática. A metanálise de sete deles evidenciou que a LT em pacientes submetidos à oncoterapia é aproximadamente 10 vezes mais eficaz na prevenção de MO grau ≥ 3 do que em pacientes sem o tratamento com laser (OR: 9,5281; intervalo de confiança de 95% 1,447-52,0354, p = 0,0093).

Conclusão: Esses dados demonstraram efeito profilático significativo de MO grau ≥ 3 nos pacientes submetidos à LT. Estudos com maior tamanho amostral são necessários para melhor avaliação do efeito profilático de MO grau ≥ 3 por LT.

Introduction

Many patients with cancer are submitted to an initial therapy by radiotherapy (RT), surgery and chemotherapy (CT). RT is usually the treatment of choice in cases involving the head and neck, where the irradiation field involves the oral mucosa and salivary glands.[1] Alone or combined with CT, RT has a good clinical response in the treatment of stage I and stage II cancer. However, cancer therapy is closely related to the location of the tumor, its staging, its histological type, as well as the patient's status.[2]

Additionally, in cases of malignant and non-malignant hematological diseases, severe immunodeficiency, and bone marrow aplasia, one of the recommended treatments is hematopoietic stem cell transplantation[3] (HSCT). Therefore, bone marrow transplantations require the continuous use of a conditioning regimen responsible for myeloablation, in order to create space in the recipient's bone marrow.[4] Therefore, immunosuppression and destruction of neoplastic cells are other effects of high doses of CT drugs, whether or not combined with RT.

Mucosal inflammation is a frequent acute complication in patients with malignancies undergoing oncotherapy. Among patients with head and neck cancer treated with RT, 90% to 97% have some degree of oral mucositis[5] (OM). Literature indicates that the incidence of OM, in any degree, associated with oncotherapy for HSCT varies between 76.3% and 89%.[6] However, some risk factors appear to be implicated in the pathogenesis of OM, such as the location of the radiation field, preexisting dental disease, poor oral hygiene, low saliva production, compromised immune function, and focus of local infection.[7,8]

The toxicity produced by the treatment causes alterations that manifest as mucositis, in light of its action on cells with high mitotic activity.[9] Thus, there is an intense mucosal involvement, with a decrease in the capacity to overcome the natural exfoliation process, and consequent inflammation and edema.

Associated with a directly harmful effect on the mucous cells, pro-inflammatory cytokines play a role in the worsening of initial mucosal lesions. Tumor necrosis factor-α (TNF-α) and interleukin-1β, interleukin-11, and interleukin-6 appear to play an important role in tissue damage associated with oncotherapy.[10] According to the literature,[11] there are four stages in the mucosal lesion process: (1) white patches, with intra- and extracellular edema; (2) appearance of erythematous areas in mucosa, in addition to dysphagia; (3) raised areas of the superficial layers of the mucosa, with reddish borders and re-covered by serofibrinous pseudomembrane, (4) when erythematous areas or areas with pseudomembrane are not re-covered in time, there is a loss of mucous lining, increase of the pain, and fever can occur, and oncotherapy interruption becomes necessary.

The inflammatory picture causes pain and discomfort, with impairment of speech, deglutition, and feeding, and ulcerating lesions can lead to dehydration and poor nutrition. Furthermore, the ulcerations bring a high risk of microbial invasion, causing predisposition to local or systemic infections.[12] The increased severity of OM may cause fever, infection risk, need for total parenteral nutrition, need for intravenous analgesics, and mortality during the first 100 days.[13]

The severity of OM is commonly assessed by the Oral Toxicity Scale, a graduated scale established by the World Health Organization (WHO). This scale contains criteria such as the presence of erythema and ulceration, local pain, and deglutition capacity. When the score is 0 no abnormality has been detected; the presence of erythema without need for treatment characterizes a score of 1; a score of 2 indicates the presence of painful symptoms with no need for analgesics, with difficulty in feeding; a score of 3 indicates painful ulceration requiring the use of analgesics and preventing feeding; finally, a score of 4 indicates necrosis requiring parenteral nutrition.[14]

Another form of assessment that can be used to evaluate OM is the Toxicity Criteria recommended by the National Cancer Institute (NCI), which establishes grade 0 in the absence of OM; grade 1 when there are painless ulcers, erythema, or mild pain in the absence of ulcers; grade 2 in the presence of painful erythema, edema, or ulcers, but feeding or swallowing is possible; grade 3 in the presence of painful erythema, edema, or ulcers when there is need of parenteral nutrition; grade 4, in case of severe ulcerations or need for parenteral nutrition or prophylactic intubation; and grade 5, in case of death-related toxicity.[13] Among other scales used to classify the severity of OM, the Radiation Therapy Oncology Group (RTOG) scale must be cited, which also evaluates, in general, oral toxicity derived from the cancer treatment used.[13] The Oral Mucositis Index (OMI) is another tool used in the classification of OM.[15] In 1996,