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Effects of Photobiomodulation Therapy on Levels of Inflammatory Cytokines in Gingival Crevicular Fluid during Orthodontic Tooth Movement: A Meta-analysis

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ADMINISTRATIVE INFORMATION

Support - None.

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 February 2024 and was last updated on 26 February 2024.

INTRODUCTION

Review question / Objective This meta-analysis was to systematically evaluate the impacts of photobiomodulation therapy (PBMT) on levels of inflammatory cytokines during orthodontic tooth movement (OTM).

Condition being studied Orthodontic treatment, majoring in the alignment of teeth and improvement of occlusion, commonly requires long-term treatment of 2 to 3 years. Long-term orthodontic treatment might result in complications, such as dental caries, periodontal disease, root resorption, and loss of patient cooperation. Therefore, to eliminate the adverse impact of long-term orthodontic treatment, several techniques were adopted to promote rapid orthodontic tooth movement (OTM), including vibration, low-intensity pulsed ultrasound, medicinal drugs, and surgical corticotomy. However, most of these procedures have insufficient scientific evidence or cause side effects such as pain, inflammation, or damage to the roots, dental pulp, and alveolar bone. Among these techniques, photobiomodulation therapy (PBMT), which has fewer clinical side effects and better stimulating impacts, has been widely applied to accelerate tooth movement in orthodontics.

The OTM phenomenon is a highly complex mechanism involving adaptive biological responses in the physiological equilibrium of tooth-bone structures mediated by external mechanical forces. Remodeling of periodontal tissue and bone is a biological mechanism involved in an inflammatory reaction. Inflammatory cytokines, produced in autocrine and paracrine settings in response to external stimuli, are mainly responsible for the inflammatory reaction in the periodontal tissue after the force application during orthodontic movement. Inflammatory cytokines can induce cellular proliferation and differentiation, thereby regulating cell communication and function. These inflammatory cytokines, including interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor (TNF)-α, act as key mediators of tissue damage, bone turnover,

and bone remodeling during orthodontic tooth movement.

PBMT has been shown to be effective in accelerating OTM and lowering orthodontic discomfort. Through the intracellular assimilation of the laser beam, PMBT leads to a biological stimulation effect of oral tissues, resulting in the amplification of intracellular signaling sequences. During the process, it enhances the metabolic process and modifies the expression of cytokines, which may reduce inflammation and relieve pain.

A few articles have assessed the influence of laser therapy on the rate of OTM and accompanying changes in the levels of inflammatory cytokines in gingival crevicular fluid (GCF). For example, Varella et al. proposed that laser irradiation can accelerate tooth movement with an increase in the level of IL-1β in GCF. Zheng et al. observed reductions in OPG levels and an increase in IL-1β and RANKL levels in irradiation groups compared to non-irradiation groups. Additionally, Reis et al. conducted a systematic review, including nine trials, to evaluate the impacts of photobiomodulation on the levels of inflammatory mediators during orthodontic tooth movement. Their meta-analysis was performed with 2 articles, which included trials adopting low-level laser therapy to assess levels of IL-1β. The result showed that PBMT was statistically associated with an increase of IL-1β level(SMD=1.99;95%CI=0.66,3.33), but it cannot lead to a firm conclusion because only two studies were added to the analysis. The systematic review lacked evaluation of other inflammatory mediators and subgroup analysis from different perspectives. Therefore, we undertook this meta-analysis to systematically evaluate the impacts of PBMT on different inflammatory mediators during OTM. In this analysis, we attempted to include more trials to generate a unified and firm conclusion and conduct a subgroup analysis to assess the impact factors regarding the efficacy of PBMT toward inflammatory mediators.

METHODS

Participant or population Patients in orthodontic tooth movement treatment were included in this meta-analysis. Patients should have permanent dentition, healthy periodontium, and adequate oral hygiene.

Intervention Photobiomodulation was conducted in experimental groups.

Comparator Non-use of photobiomodulation was adopted in control groups.

Study designs to be included We included studies designed to explore the effects of PBMT on GCF cytokines in patients undergoing orthodontic tooth movement.

Eligibility criteria Articles were excluded if: published studies lacked the required control groups; published studies lacked sufficient extractable data or calculable effect size; written language was not English. For studies lacking the required data, such as average means and SDs, we contacted the authors by email. If we could not obtain the required data, studies would be excluded.

Information sources Data were collected up to February 12th, 2024 from the following databases: Cochrane Library, PubMed, Embase, Scopus, Web of Science, Wiley, and Ovid. The following keywords were selected:((photobiomodulation) OR (laser)) AND (orthodontic) OR (tooth)) AND ((cytokine) OR (GCF) OR (gingival crevicular fluid)) The search strategy was imported as a string and searched independently in these seven databases.

Main outcome(s) Levels of cytokines in GCF served as leading indicators to evaluate the impacts of PBMT on cytokines during toothmovement.

Quality assessment / Risk of bias analysis Due to its suitability for both RCT and quasi-RCT, the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool was adopted to assess the methodological quality of studies. Based on the EPHPP tool, the following items were taken into consideration: selection bias, study design, confounding factors, study blinding, data collection, withdrawals, and dropouts. The quality of studies was rated as Strong, Moderate, and Weak. Based on the number of weak ratings they received, the overall rating was also rated as three levels: Strong (no weak ratings), Moderate (one weak rating), and Weak (two or more weak ratings).

Strategy of data synthesis Qualitative analysis was undertaken by the Stata/SE version 18 (StataCorp LLC, College Station, TX). Mean changes and their SDs of levels of cytokines in GCF were utilized to obtain the overall effect. The standard mean difference (SMD) with the random-effects model, suitable for different outcomes and units of measure, was adopted for data pooling. I-squared statistics and the Cochran Q test were conducted to evaluate the heterogeneity of effect sizes. A value of I2> 50% or <0.05 for the Q test was considered a significant heterogeneity between studies. Since the included articles study

different cytokines in different periods after delivering laser therapy, several study groups were identified based on the same cytokines and the same GCF collection days. If it shows a high heterogeneity, a subgroup analysis will be performed to evaluate the source of the heterogeneity, including laser irradiation parameters, research design, etc. Begg's and Egger's regression tests were used to assess the publication bias quantitively, while visual analysis from the funnel plot was explored simultaneously.

Subgroup analysis Subgroup analysis was performed to evaluate the source of the heterogeneity, including laser irradiation parameters, research design, etc.

Sensitivity analysis None.

Country(ies) involved China.

Keywords photobiomodulation therapy, meta-analysis, inflammatory cytokines, gingival crevicular fluid, orthodontic tooth movement.

Contributions of each author

Author 1 - Xinyu Xie performed the statistical analysis and wrote the first draft.
Email: xxy770323639@163.com
Author 2 - Xiaolong Liang wrote the first draft.
Author 3 - Chuang Li carried out data collection.
Author 4 - Nan Zhang carried data coding.
Author 5 - Xinxin Jin contributed to the revision of the manuscript.
Author 6 - Xuefei Zhang contributed to the revision of the manuscript.
Author 7 - He Cui contributed to the revision of the manuscript.