REVIEW ARTICLE

Efficacy of Laser Photobiomodulation in Accelerating Orthodontic Tooth Movement in Children: A Systematic Review with Meta-analysis

Chandrashekar M Yavagal[1], Sucheta P Matondkar[2], Puja C Yavagal[3]

Abstract

Aim and background: This systematic review aimed to investigate the efficacy of laser photobiomodulation (PBM) on the acceleration of orthodontic tooth movement (OTM).

Review methods: The study protocol was registered at PROSPERO (CRD42019121465). An extensive electronic search for randomized control trials and clinical control trials via Medline (via PubMed), The Cochrane Controlled Clinical Trials Register, and Scopus up to date 24/02/2019 was done. Hand searching was performed for relevant journals. Reference articles were retrieved and exported to Mendeley Desktop 1.13.3 software. The risk of bias was assessed using the Cochrane risk of the bias assessment tool. Articles were further analyzed using Revman5.3 software.

Results: A total of 14 articles were considered for systematic review and 9 articles were considered for meta-analysis. The results of the meta-analysis showed a significant difference between the laser group and conventional orthodontic treatment with Forest plots showing more tooth movement in the laser group compared to the control group in 2–3 months (mean difference = 1.73; CI: 0.9–2.57; $p = 0.00001$; $I^2 = 89$ %).

Conclusion: Although the analysis of the results shows that laser PBM favors OTM, the results are inconclusive as the heterogeneity across studies was high.

Clinical significance: Laser PBM may be considered as novel, safe, and noninvasive adjuvant therapy for the acceleration of OTM in children.

Keywords: Laser, Meta-analysis, Movement, Orthodontic, Photobiomodulation.

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Introduction

The most likely reason that leads patients to opt-out of orthodontic tooth correction is the rather tedious time frame required. Typically, it ranges from 24 to 36 months and may result in decreasing compliance from the patients.[1] Moreover, it is fraught with complications such as external root resorption, caries, and periodontal problems.[2] Therefore, shortening of the orthodontic treatment duration is much desired, by both the patient and the clinician. This reduction can be achieved by accelerating the rate of tooth movement. It has been well recognized that orthodontic tooth movement (OTM) is achieved under the stimulus of orthodontic forces triggering a series of biological events.[3] Alveolar bone remodeling is achieved by the mechanical forces applied during orthodontic treatment that stimulate cells responsible for bone turnovers such as fibroblasts, osteoblasts, osteoclasts, and myriad other cells.[4]

Several techniques have been quoted in past literature for accelerating OTM. Surgical options range from corticotomy, the distraction of dentoalveolar segment or periodontal segment. Other modalities include injection of biological substances such as vitamin D_3, prostaglandin E, parathyroid hormone, osteocalcin, etc.[5–7] However, the unpleasant experience caused by such techniques is rather high. Thus, more conservative approaches have been attempted. One such physical approach is by using low-level laser therapy (LLLT) or photobiomodulation (PBM). This is the application of light that lies between the 600 nm and 1000 nm range.[8]

The modus operandi of diode lasers is based on two determinants; the type of absorption (intermediate) and the wavelength that is responsible for the depth of penetration (inversely related). Low-level laser therapy has advantages such as accelerated healing, increased proliferation of osteoblasts and fibroblasts, which accelerates bone remodeling, stimulates nerve regeneration, decreases pain experienced.[9] It employs low-grade energy levels for an extended period of exposure. Photobiomodulation therapy encompasses a wide latitude of applications in modern dental practice. These include management of dentinal hypersensitivity, dealing with inflammation reduction in periodontology, enhanced bone repair, and superior osseointegration in implantology.[10] In the field of orthodontics, its use has been implicated with postoperative pain reduction and acceleration of tooth movement.[11] The mechanism of accelerated tooth movement has been explained

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at a cellular level by various *in vitro* studies. Diode lasers cause osteoblastic activity on the tension side and osteoclastic stimulation on the compression site to stimulate bone remodeling.[12] A proposed mechanism on osteoclastogenesis is via modification of the RANK/RANKL/OPG system, causing accelerated tooth movement. Its noninvasive effect has yielded promising results in animal models as well as human subjects with respect to accelerated OTM.[13] In the wake of clinical equipoise in this novel growing field with the number of studies examining the effect of LLLT on the rate of OTM reporting different results a systematic review pertaining to its outcome in humans was planned along with a meta-analysis with the research question: Does laser PBM accelerate OTM in human subjects? The research query was based on the patient, intervention, control, study design (PICOS) format (Table 1).

Review Methos

Protocol and Registration

The present systematic review was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).[14,15] The protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) under the number CRD42019121465.[16]

Table 1: PICOS (patient, intervention, control, study design) format protocol formulated to identify studies pertaining to research question formulated

Patient	Human subjects undergoing fixed orthodontic treatment
Intervention	Low-level laser therapy for orthodontic tooth movement
Control	Contralateral arch/side undergoing conventional orthodontic tooth movement
Study	Randomized controlled/clinical controlled trials

Research Question

Does laser PBM accelerate OTM in human subjects? The research query was based on the PICOS format (Table 1).

Search Strategy for Article Identification

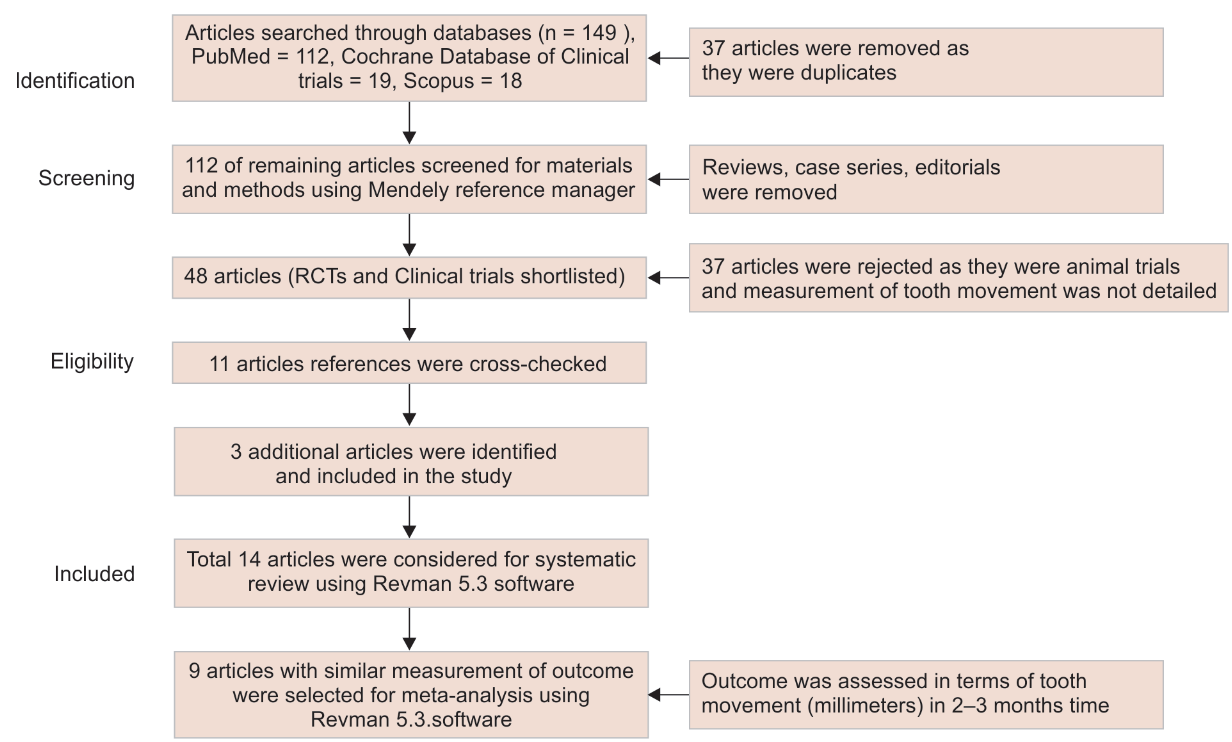
The methodology employed was the PRISMA statement instructions. An extensive electronic search for randomized controlled trials and clinical control trials via three databases namely Medline (via PubMed), The Cochrane Controlled Clinical Trials Register, and Scopus till 24/02/2019 was done. The outcome of the search, Medical subjects headings (MeSH) have been summarized (Flowchart 1). Hand searching was performed for relevant journals. Medical subjects headings terms used in the search included "tooth movement/orthodontic tooth movement", "laser/low-level laser/low intensity laser/soft laser/cold laser", "irradiation/light/phototherapy", "photobiomodulation". Boolean operators (OR, AND) were used in-between the MeSH terms. Reference articles were retrieved and exported to the Mendeley Desktop 1.13.3 software.[17] Duplicate records were removed out by the software. There were no language restrictions in the search. Filtered articles were then scanned by title and abstract by two reviewers to disclude articles not fitting the PICOS format. Thus, animal trials and study designs other than included criteria were discarded at this stage. The authors were not blinded to country or journal names.

Selection of Studies

Inclusion Criteria

- Clinical or randomized controlled trials were performed on humans performing laser PBM to accelerate the rate of OTM as compared to conventional OTM.

Flowchart 1: Flowchart of the study



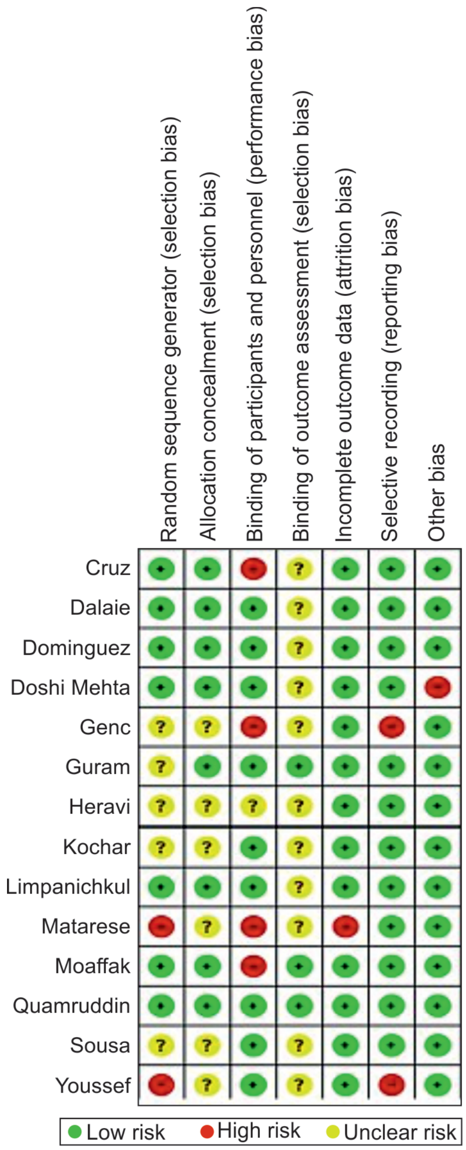


Fig. 1: Risk of bias assessment

- No restrictions on the year of publication, country, or language.
- Outcome based on reduction in treatment time due to accelerated tooth movement or distance (in millimeters) or speed of the tooth movement in treatment duration.
- Low-level laser therapy of any wavelength in pulsed or continuous wave mode.
- Excluding laser application, all other parameters are similar in both groups.

Exclusion Criteria

- Study designs other than those in the format such as case reports, experimental studies were not considered.
- Animal trials were not included.
- Studies involving participants suffering from metabolic disorders, or taking medications impeding or hastening tooth movement were excluded.
- Studies involving participants who had a high caries index or periodontal disease were not considered as well.

Data Extraction

One author searched the studies and screened the titles and abstracts of each study based on the criteria and extracted data. Two authors independently rechecked the full text of the screened studies. Data collected for every study included information pertaining to the year of publication, authorship, geographical area, sample size, study characteristics, laser parameters such as energy density, wavelength, mode of operation, frequency, and intervention sites on the tooth (Tables 2 and 3).

Risk of Bias Assessment of Included Studies

Studies were assessed for risk by using the Cochrane risk of the bias assessment tool.[18] Domains assessed for each included study were:

- Sequence generation.
- Allocation concealment.
- Blinding of outcome assessment.
- Completeness of outcome data.
- Risk of selective outcome reporting.
- Risk of other potential sources of bias.

A description of the risk of bias domains was tabulated for each included trial, along with a judgment of low, high, or unclear risk of bias, using the Revman 5.3 review manager software (Fig. 1). The risk of bias summary was expressed in red, green, and yellow colors which referred to high, low, and unclear risk of bias, respectively.

Statistical Analysis

A random-effects meta-analysis was done by Review Manager 5.3 (RevMan 5.3, The Cochrane Collaboration, Oxford, United Kingdom) using the mean difference (MD) and 95% confidence intervals (CIs) for the feasible data that were statistically pooled.[19] Heterogeneity between the estimates was evaluated by Cochrane's test (I^2 test) at $\alpha = 0.10$. Also, the statistical significance for testing the hypothesis was set at p value (two-tailed) <0.05. The unit of measurement of the distance of tooth movement was millimeters (mm).

Review Results

The search strategy yielded a total of 149 articles. Post removal of duplicates, 112 articles were retrieved, and their materials and methods were scanned. Forty-eight of those were of the desired study design. Thirty-seven articles were rejected as they were animal trials, had insufficient information pertaining to tooth movement or system of measurement was via biological markers. Eleven articles remaining were retrieved and their references cross-checked. This yielded an additional 3 articles making a total of 14 articles that were systematically reviewed[12,20–33] (Tables 2 and 3). Further nine studies were considered for meta-analysis with similar outcomes (Fig. 2).

Characteristics of the Studies

Studies included in the systematic review were reported in India, Thailand, Syria Brazil, Turkey, Columbia, Iran, Syria, Pakistan, and Italy. All the studies followed a randomized controlled split-mouth design. Eight studies reported single/double-blinding, five reported no blinding and one did not report on blinding. Studies reported intervention on canines and premolars of maxillary and mandibular arches. Out of 14 studies, 9 studies were included in the meta-analysis as their outcome was assessed in terms of tooth movement in a given time (2–3 months) and five studies were not considered as the outcome was assessed in terms of time taken

Table 2: Laser parameters used in the studies considered for systematic review

	Author, year	*Wavelength of laser, type of laser, waveform CW–continuous wave*	*Output power (MW–milliwatts)*	*Total time taken per tooth*	*Energy density (J/cm²)*	*Number of points per tooth*	*Frequency of application in days*
1	Cruz et al., 2004[20]	780 nm IR, GaAlAs diode, CW	200 mW	100 seconds	5 J/cm²	10 points, 5–Buccal, 5–Lingual	0, 3, 7, 14 days post-activation for 2 months
2	Limpanichkul, 2006[21]	860 nm IR, GaAlAs diode, CW	100 mW	160 seconds	25 J/cm²	8 points, 4–Buccal, 4–Lingual	3 consecutive days post-application for 3 months
3	Youssef et al., 2008[22]	780 nm IR, GaAlAs diode, CW	100 mW	60 seconds	8 J/cm²	6 points, 3–Buccal, 3–Lingual	0, 3, 7, 14 days post-activation
4	Sousa et al., 2011[23]	780 nm IR, GaAlAs diode, CW	20 mW	100 seconds	5 J/cm²	10 points, 5–Buccal, 5–Lingual	0, 3, 7 days post-activation for 0, 3, 5 months
5	Doshi Mehta et al., 2012[24]	800 nm IR, GaAlAs diode, CW	100 mW	400 seconds	8 J/cm²	10 points, 5–Buccal, 5–Lingual	0, 3, 7, 14 days post activation for 1 month; every 15 days till treatment completion
6	Genc et al., 2013[25]	808 nm IR, GaAlAs diode, CW	100 mW	100 seconds	7.1 J/cm²	10 points, 5–Buccal, 5–Lingual	0, 3, 7, 14, 21, 28 days post-activation
7	Dominguez et al., 2013[26]	670 nm IR, GaAlAs diode, CW	200 mW	40	80 J/cm²	2 points, 1–Buccal, 1–Lingual	0, 1, 2, 3, 4, 7 days post-activation
8	Heravi, 2014[27]	810 nm IR, GaAlAs diode, CW	200 mW	300 seconds	21.4 J/cm²	10 points, 5–Buccal, 5–Lingual	0, 3, 7, 15 days post-activation; repeated till treatment ends
9	Dalaie, 2015[28]	880 nm, GaAlAs diode, CW	100 mW	80 seconds	5 J/cm²	8 points, 3 buccal, 3 lingual 2 at line angles	1, 3, 7, 30, 33, 37, 60, 63 days
10	Moaffak et al., 2016[29]	800 nm IR, GaAlAs diode, CW	150 mW	120 seconds	22.5 J/cm²	8 points, 4–Buccal, 4–Lingual	0, 3, 7, 14 days post-activation for 1 month; every 15 days till treatment completion
11	Kochar et al., 2017[30]	810 nm IR, GaAlAs diode, CW	100 mW	80 seconds	5 J/cm²	8 points, 4–Buccal, 4–Lingual	3, 7, 21 days post-activation
12	Quamruddin et al., 2017[31]	940 nm IR, GaAlAs diode, CW	100 mW	300 seconds	7.5 J/cm²	10 points, 5–Buccal, 5–Lingual	0, 21, 42 days post-activation
13	Guram et al., 2018[32]	810 nm IR, GaAlAs diode, CW	100 mW	80 seconds	5 J/cm²	10 points, 5–Buccal, 5–Lingual	Weekly activation
14	Matarese et al., 2019[33]	810 nm IR, GaAlAs diode, CW	100 mW	90 seconds	8 J/cm²	6 points, 3–Buccal, 3–Lingual	3, 7, 14 days post-activation and subsequent every 15th day till space closure

GaAlAs, gallium-aluminum-arsenide

per tooth movement and nitric acid levels in the gingival crevicular fluid (Tables 2 and 3).

Methodological and Quality Assessment

Randomization was performed among all included RCTs. Eight of the included studies showed a moderate risk of bias, and six of them exhibited a high risk of bias. Reviews about the risk of bias for each included study (Fig. 1).

Effect of Laser Photobiomodulation on Orthodontic Tooth Movement

According to a systematic review, LLLT significantly increased osteoclastic but not osteoblastic activity during the initial phases of tooth movement, and that the osteoclastic activity was dose-dependent.[33] Cruz et al.,[20] Youssef et al.,[22] and da Silva Sousa et al.[23] found the significantly greater velocity of tooth movement with LLLT. Limpanichkul et al.[21] did not find an increase in tooth

Table 3: Interventional details of studies included for systematic review

S. no.	*Author, place of study*	*Study design*	*Blinding*	*Intervention site*	*Anchorage*	*Results (LG: Laser group) (C: control)*
1	Cruz et al. Brazil	RCT split mouth	Not specified	Maxillary canines	TPA + Nance palatal arch	Tooth movement: LG 34% faster than C
2	Limpanichkul Thailand	RCT split mouth	Double-blinded	Maxillary canines	Not mentioned	No significant difference in groups after 1, 2, 3 months
3	Youssef et al. Syria	CCT split mouth	No blinding	Maxillary canines	Stop loops mesial to molars	Tooth movement 1.98 times greater in LG than C
4	Sousa et al. Brazil	RCT split mouth	Double-blinded	Canines maxillary and/or mandible	Posterior segmental arch	Tooth movement 1.03 times greater in LG than C
5	Mehta et al. India	RCT split mouth	Single-blinded	Canine maxillary and mandible	TPA + solidarization of first molar and premolar	At the end of 3 months, Mean increased, tooth movement 29% maxilla, 31% mandible in the laser group
6	Genc et al. Turkey	CCT split mouth	No blinding	Maxillary canines and incisors	Mini implant	Tooth movement LG 20–40% faster than control group
7	Dominguez et al. Columbia	CCT parallel	No blinding	Maxillary canines/ premolars	Nance arch	Tooth movement LG 30% faster than control group
8	Heravi, Iran	CCT split mouth	Single-blinded	Maxillary canines	Stop loops mesial to molars	No differences between LG and C even after 56 days
9	Dalaie, Iran	RCT split mouth	Double-blinded	Maxillary canines	Sectional loops mesial to molars	No difference between LG and C even after 67 days
10	Moaffak et al. Syria	RCT split mouth	No blinding	Maxillary Incisors	Not specified	Tooth movement 26% faster in LG than C
11	Kochar et al. India	RCT split mouth	Single-blind	Maxillary canines	Nance arch Lingual arch	Tooth movement 67% faster in LG than C
12	Quamruddin et al. Pakistan	RCT split mouth	Single-blind	Maxillary canines	Stop loops mesial to molars	Tooth movement 2.02 times greater in LG than C
13	Guram et al. India	RCT split mouth	Double-blind	Maxillary canines	Stop loops mesial to molars	Tooth movement 1.6 times greater in LG than C
14	Matarese et al. Italy	RCT split mouth	No blinding	Maxillary canines	NiTi coil springs on canines	The laser group yielded significantly less mean time to accomplish space closure compared to the control group

RCT, randomized controlled trial; CCT, controlled clinical trial

velocity. While their total energy density was 25 J/cm^2 compared with the previous three studies at 5 J/cm^2 their area of application was smaller which may have accounted for their findings. Cruz et al.[20] found that their laser group demonstrated a 34% greater tooth retraction rate relative to the control group, and Doshi-Mehta and Bhad-Patil[24] found that their irradiated group had an increased retraction rate of 1.3 times greater compared to their control group. The study by Doshi-Mehta and Bhad-Patil has been critiqued for inappropriate use of statistical analysis, ordinal data had been represented with a parametric test, and thus data reporting was uncertain. The lack of effect found by Limpanichkul et al.,[21] Heravi et al.,[27] and Dalaie et al.[28] was hypothesized to be a result of an incorrect dose leading to reduced levels of arachidonic acid and PGE2, a key mediator in osteoclastic activity. Moaffak et al.,[29] Kochar et al.,[30] and Genc et al.,[25] showed positive results as well. Recent studies by Qamruddin et al.[31] and Guram et al.[32] showed greater tooth movement in the LLLT group with once in 3 weeks and weekly activation. Overall, the literature illustrated accelerated tooth movement in the LLLT group compared to conventional OTM without any side effects in human beings (Tables 2 and 3).

The meta-analysis was done to investigate the overall efficacy of LLLT on OTMs of canines post activation of archwires up to 2–3 months. The results showed that the orthodontic movement of canine was statistically increased in the LLLT group compared with the control group in 60–90 days (MD: 1.73; 95% CI: 0.9–2.57; $p < 0.0001$; $I^2 = 89\%$) (Fig. 2).

Discussion

Long-term orthodontic treatment is a major concern for pediatric patients, and reducing this time requires an acceleration of OTM. This meta-analysis showed that laser PBM (LLLT) significantly increased the OTM of human-canine/incisors/premolars in the patients compared with the controls after 2–3 months. With a rise in time, the rate of OTM increased. The findings of this meta-analysis are in agreement with a recent review done by Imani et al.[34]

The cellular responses assessed *in vitro* with LLLT/PBM are broadly classified under an increase in metabolism, migration, proliferation, and increase in synthesis and secretion of various proteins. *In vitro* studies have also shown upregulation of RANK/

	Laser Group			Control Group				Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Cruz 2004	4.39	0.27	11	3.3	0.24	11	8.8%	4.11 [2.53, 5.68]	2004
Limpanichkal	1.29	0.21	12	1.24	0.21	12	11.4%	0.23 [–0.57, 1.03]	2006
Sousa 2011	3.09	1.06	13	1.6	0.63	13	11.1%	1.65 [0.74, 2.57]	2011
Mehta 2012	2.3	0.45	20	1.98	0.46	20	11.9%	0.69 [0.05, 1.33]	2012
Heravi 2014	2.07	1.01	20	1.84	1.01	20	11.9%	0.22 [–0.40, 0.85]	2014
Dalaie 2015	4.98	0.78	12	4.5	0.23	12	11.3%	0.81 [–0.03, 1.64]	2015
Kochar 2017	1.13	0.13	20	0.86	0.02	20	11.1%	2.85 [1.94, 3.75]	2017
	1.81	0.26	22	0.79	0.4	22	11.2%	2.97 [2.09, 3.85]	2017
Guram 2018	1.78	0.28	20	0.79	0.4	20	11.1%	2.81 [1.91, 3.71]	2018
Total (95% CI)			150			150	100.0%	1.73 [0.90, 2.57]	

Heterogeneity: $Tau^2 = 1.43$; $Chi^2 = 71.69$, df = 8 (p <0.00001); $I^2 = 89\%$
Test for overall effect: Z = 4.06 (p < 0.0001)

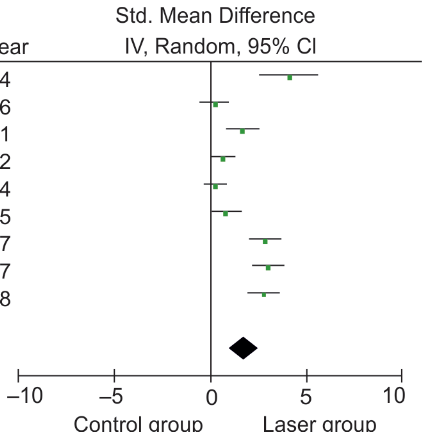


Fig. 2: Forest plot

RANKL and c-Fms gene expressions, which are known mediators for osteoclast activity,[35–37] demonstrating an enhanced proliferation of osteoblast-like cells.[21] Kim et al.[38] reported that the biomodulation effects of LLLT include fibroblast proliferation, collagen synthesis, and organization of collagen fibers. They also found that LLLT in combination with OTM resulted in increased vascularization. Youssef et al.[22] investigated the effect of LLLT on tooth movement and found that at each time point in their investigation their irradiated group had significantly greater tooth movement compared to their control group. This may be attributed to improved turnover of connective tissue by way of increased expression of fibronectin and collagen type I[39,40] as well as stimulating osteoblast and osteoclast cell proliferation.[41] Application of lasers intermittently for 8 weeks markedly elevated IL-1 beta levels on the laser-irradiated side compared with orthodontic force alone and was concurrent with increased rates of OTM. Dominguez et al.[26] conducted a clinical study assessing gingival crevicular fluid with LLLT to assess the levels of RANKL and OPG and found a slight improvement in OTM. They noticed a trend of increased tooth movement at the beginning of their observation period with a decrease to slower than their control group at 30–45 days. Overall, the laser group exhibited greater accumulated tooth movement with a change in the rate of movement that is similar to that observed in the animal studies.[42,43]

The difference observed between the results of the studies can be attributed to the different irradiation doses employed, which can cause variable PBM effects on laser-treated tissues.[24] Low-level laser as a beneficial method can double the rate of OTM if used at intervals of 3 weeks.[31] Researchers should not exceed the biostimulating dose range or reach the inhibition range (Arndt Schultz law) a significant increase in the total amount of tooth movement is reached in the group with low-level laser energy density (5–8 J/cm^2) compared to the group with high energy density (20–25 J/cm^2).[18,24] Results of a study done by Goulart et al.[36] indicated that teeth irradiated at 5.25 J/cm^2 (780 nm, 70 mW, and 3 seconds/day) showed faster orthodontic movements initially; whereas, those irradiated at 35 J/cm^2 (780 nm, 70 mW, and 20 seconds/day) showed slower movements.

What remains noteworthy is that current dosage calculations are not accurate attributing to failure in cases. This failure can be linked to dosimetry-related factors such as energy (too much or too little), irradiance, and time of exposure. Hadis et al.[44] summarized eight key factors that must be reported in all PBM studies. They are wavelength, power, time, beam area, pulse parameters, anatomical locations, number, and the interval between treatments. There were three significant limitations in this meta-analysis, including a low number of studies, variances in characteristics lasers used like power, wavelength, frequency, energy density, and a low number of teeth examined in the studies.

Conclusion

Based on the systematic review and meta-analysis, LLLT with laser wavelength between 780 nm and 940 nm has been shown to accelerate OTM in 2–3 months. A time interval of 3 weeks was sufficient for the acceleration to occur. Energy density was between 1 J/cm^2 and 2 J/cm^2 for each point, a total between 5 J/cm^2 and 8 J/cm^2. Failures were due to inaccurate calculation of dosage with an energy density of about 25 J/cm^2. This is in accordance with the Arndt Schultz law (stimulatory at low doses, inhibitory at high). Therefore, LLLT represents an appropriate adjuvant therapy for orthodontic treatment. However, findings of this review must be considered with caution due to heterogeneity of studies.

Clinical Significance

Laser PBM may be considered as novel, safe, and noninvasive adjuvant therapy for the acceleration of OTM.

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