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Review

Effectiveness of photobiomodulation therapy in accelerating orthodontic tooth movement: a meta-analysis of randomized clinical trials.

Efectividad de la terapia de fotobiomodulación en la aceleración del movimiento dental de ortodoncia: metaanálisis de ensayos clínicos aleatorizados.

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Abstract: To assess the effectiveness of photobiomodulation therapy (PBMT) in accelerating orthodontic tooth movement (OTM). Material and Methods: A systematic review was carried out in *MEDLINE, Cochrane Library, EMBASE* and *LILACS* of articles in English, Portuguese and Spanish. Additional studies were identified by searching bibliographies. The search terms included: randomized controlled trial (RCT), low-level laser therapy, phototherapy, orthodontic wires, orthodontic anchorage procedures, activator appliances. Study Selection: Only RCTs which analyzed the effect of PBMT in accelerating OTM were included. Independent extraction of articles by two authors using predefined data fields, including study quality indicators was performed. The risk of bias of the eligible trials was assessed using the Cochrane Collaboration's risk of bias tool. Mean difference was calculated and pooled by meta-analysis using random effect models. The quality of the evidence was assessed using GRADE Pro. Results: Fourteen RCTs analysing tooth movement in the canine retraction (CR) phase and two studies in the tooth alignment phase were included in the qualitative analysis; 68.75% of the RCTs reported that PBMT was effective in accelerating OTM. Nine studies presented 'unclear risk of bias' and seven presented 'high risk of bias'. Mean difference was calculated and pooled by meta-analysis using random effect models. Twelve studies presented sufficient information for inclusion in the meta-analysis. Photobiomodulation doses between 50 and 75 J/cm^2 were effective in accelerating OTM in months 1, 2 and 4 of CR, and in increasing the accumulated CR rate. The quality of the evidence was downgraded due to the risks of bias, imprecision or considerable heterogeneity of the studies. Conclusions: PBMT treatment with low or very high application of total/per tooth ED is not effective in accelerating OTM. Application of energy density (ED) between 50 and 75 J/cm^2 per tooth was effective in accelerating OTM after 1 and 2 months of CR, as well as in increasing the accumulated CR rate.

Keywords: Tooth movement techniques; low-level light therapy; photobiomodulation therapy; phototherapy; orthodontic space closure; orthodontics.

Resumen: Evaluar la efectividad de la terapia de fotobiomodulación (PBMT) para acelerar el movimiento dentario ortodóncico (MDO). Material y Métodos: Se realizó una revisión sistemática en *MEDLINE, Cochrane Library, EMBASE* y *LILACS* de artículos en inglés, portugués y español. Se identificaron estudios adicionales mediante la búsqueda de bibliografía. Los términos de búsqueda incluyeron: ensayo controlado aleatorio (ECA), terapia por luz de baja intensidad, fototerapia, alambres para ortodoncia, métodos de anclaje en ortodoncia, aparatos activadores. Selección del estudio: solo se incluyeron los ECA que analizaron el efecto de PBMT en la aceleración del MDO. Se

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realizó una extracción independiente de artículos por dos autores utilizando campos de datos predefinidos, incluidos los indicadores de calidad del estudio. El riesgo de sesgo de los ensayos elegibles se evaluó mediante la herramienta de riesgo de sesgo del Cochrane Collaboration. La diferencia de medias se calculó y se combinó mediante metanálisis utilizando modelos de efectos aleatorios. La calidad de la evidencia se evaluó utilizando GRADE Pro. Resultados: Catorce ECAs que analizaron el movimiento dental en la fase de retracción canina (RC) y dos estudios en la fase de alineación dental se incluyeron en el análisis cualitativo; el 68.75% de los ECA informaron que PBMT fue eficaz para acelerar el MDO. Nueve estudios presentaron "riesgo incierto de sesgo" y siete presentaron "alto riesgo de sesgo". La diferencia de medias se calculó y se combinó mediante metanálisis utilizando modelos de efectos aleatorios. Doce estudios presentaron información suficiente para su inclusión en el metanálisis. Las dosis de fotobiomodulación entre 50 y 75 J/cm^2 resultaron efectivas para acelerar el MDO en los meses 1, 2 y 4 de RC, y para aumentar la tasa de RC acumulada. La calidad de la evidencia se rebajó debido a los riesgos de sesgo, imprecisión o considerable heterogeneidad de los estudios. Conclusiones: el tratamiento PBMT con una aplicación baja o muy alta de densidad energética (DE) total / por diente no es eficaz para acelerar el MDO. La aplicación de DE de entre 50 y 75 J/cm^2 por diente fue efectiva para acelerar el MDO después de 1 y 2 meses de RC, así como para aumentar la tasa de RC acumulada.

Palabras Clave: *Técnicas de Movimiento Dental; Terapia por Luz de Baja Intensidad; terapia por bioestimulación; fototerapia; cierre del espacio ortodóncico; ortodoncia.*

INTRODUCTION.

Tooth movement induced by orthodontic force determines a series of phenomena involving biological reactions in the alveolar bone and periodontal ligament.[1] In the first phase of orthodontics, tooth movement determines an acute inflammatory response.[2] This inflammatory response is essential for remodelling of the alveolar bone and the periodontal ligament (PDL) during orthodontic tooth movement (OTM). Increases in blood vessel size and permeability are necessary components of the inflammatory process and are also involved in bone remodelling.[1]

Orthodontic treatment (OT) may determine a growing risk of caries, gingival recession and root resorption. Furthermore, due to the length of the intervention period and concern associated with the pain caused by OT, some patients abandon the treatment;[3] it is therefore important to find methods of accelerating OTM. Many studies have examined different methods for accelerating OTM, including injections of prostaglandins[4] 1,25(OH)2D3,[5] or osteocalcin,[6] minimally invasive surgical procedures (Piezocision, micro-osteoperforations and interseptal bone reduction)[7] as well as photobiomodulation by LED[8] and the application of ultrasound.[9,10]

One alternative that has been studied is photobiomodulation therapy (PBMT), which has presented good results in accelerating tooth movement,[11-13] reducing orthodontic treatment time by up to 30%.[13] PBMT raises the osteoblast proliferation rate, improving the bone synthesis required to generate orthodontic movement.[14] It also improves the regeneration of periodontal tissue by increasing the proliferation and differentiation of osteogenic cells.[15] PBMT has been found to significantly increase cell viability, decrease cellular inflammatory marker expression, and increase osteoclast activity in PDL cells,[16] and to improve the quality of bone remodelling during OTM.[10] However, the literature reports conflicting results, since some authors say they found no differences in OTM acceleration between patient groups treated with PBMT and non-intervention groups.[17-19]

The hypothesis of the present study is that PBMT is effective in accelerating OTM. The research question for this work was therefore as follows: Is PBMT effective in increasing tooth movement in orthodontics patients as compared to groups with no intervention? The aim of this study was carry out a systematic review to assess the effectiveness of PBMT in accelerating tooth movement in patients receiving OT. In addition, the effectiveness of PBMT was assessed according to the energy density applied at four moments: in the 1st, 2nd and 3rd months of laser, and the accumulated tooth movement.

MATERIALS AND METHODS.

Protocol and registration

A systematic review of the published data was conducted in accordance with the Cochrane Handbook for the Systematic Review of Interventions and reported according to the guidelines of the Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA).[20,21] The study was not registered.

Eligibility Criteria

The study included randomized clinical trials which

analyzed the effectiveness of PBMT (red laser or near infrared laser) in accelerating tooth movement (canine retraction and tooth alignment); participants who received orthodontic treatment with total follow-up of at least 4 weeks; studies in English, Portuguese and Spanish. The exclusion criteria were: in vitro studies, studies in animals, systematic reviews and meta-analyses, high level laser and LED.

Sources of Information and Search Strategy

A search was carried out in the *PubMed, LILACS, EMBASE and Cochrane Library databases*. The search in Pubmed is shown below: ((((((("Activator Appliances"[Mesh]) or "Orthodontic Wires"[Mesh]) or "Orthodontic Anchorage Procedures"[Mesh]) or orthodontic*)) AND ((((((((((("Low-Level Light Therapy"[Mesh]) OR "Laser Therapy"[Mesh]) OR "Lasers, Semiconductor"[Mesh]) OR "Phototherapy"[Mesh]) OR low level laser [tiab]) OR near infrared [tiab]) OR infrared therapy) OR low level laser therapy [tiab]) OR red laser [tiab]) OR yag laser [tiab]) OR co2 laser [tiab]) OR diode laser [tiab])

The last search was carried out on 31 March 2018. No limit date was applied in the search for articles. The search was complemented by a manual review of the references of the studies included.

Titles and abstracts were selected independently by two investigators (N.F.D. and N.A.) to verify their eligibility. In cases of discrepancy, consensus was obtained by discussion or by consulting a third reviewer (P.S.). The references that appeared to fulfil the inclusion criteria were reviewed in full text by the same reviewers (N.F.D. and N.A.).

The data from each article selected were analyzed to obtain sample size, sex, age range, laser used, wavelength, output power, spot size, number of application points, treatment time, application points, days of PBMT application, total energy, energy density, study design, orthodontic treatment stage, method used for measuring tooth movement, and the principal results found for the PBMT group and the control/placebo group (mean and standard deviation of tooth movement).

Assessment of Risk of Bias

Two review authors (N.F.D. and P.S) independently assessed the risk of bias of the eligible trials according to the Cochrane Collaboration's risk of bias tool.[20] In cases of discrepancy, consensus was obtained by consulting a third reviewer (N.A).The domains assessed were:

(1) Random sequence generation;
(2) Allocation concealment;
(3) Blinding of participants;
(4) Blinding of personnel;
(5) Blinding of outcome assessment;
(6) Incomplete outcome data;
(7) Selective reporting;
(8) Other biases (baseline imbalance, similarity in using co-interventions between groups and inadequate statistical analysis). The potential risk of bias for each study was classified as high, unclear, or low.

Summary of Findings

We used the principles of the GRADE system to assess the overall quality of the body of evidence associated with the main outcomes and we constructed a "Summary of Findings" (SoF) table using the GRADEpro GDT software *(Avalaible to: http://gdt.guidelinedevelopment.org).* The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. We assessed the quality of the body of evidence with reference to the overall risk of bias of the studies included, directness of the evidence, inconsistency of the results, precision of the estimates, risk of publication bias, and magnitude of the effect.[21] Depending on the seriousness of the deficiency, the quality of the evidence can be downgraded by one or two levels for each aspect. We categorised the quality of the body of evidence for each of the primary outcomes as high, moderate, low, or very low.[22]

Data Synthesis

The principal results were the monthly OTM rates in the 1st, 2nd and 3rd months of treatment and the accumulated OTM. In studies which presented results for more than one arch, we opted to use the data reported for the maxilla. We pooled studies that compared PBMT with a control/placebo. The results were reported as continuous data with differences between means, grouped in the meta-analysis by the energy density used (33-42 J/cm^2, 50-75 J/cm^2, 200-214 J/cm^2).

For all measurements, forest plots were constructed

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showing the summary and 95% confidence interval (CI) estimated in the meta-analyses, together with the results from individual studies. We used the random effect model (DerSimonian-Laird method), as we expected variation in effects due to differences in study populations, methods of analysing OTM acceleration and the application of different doses of PBMT. The heterogeneity between studies was assessed using the I^2 statistical categorisation as follows: <30% not important; 30%–50% moderate; 50%–75% substantial; 75%–100% considerable.[20,23]

Data were analyzed by sub-group by energy density applied per tooth, since this could be a heterogeneity factor. To explore possible publication bias, a funnel plot was planned when the number of studies pooled was equal to or greater than 10. The software used was Review Manager 5.3 (Cochrane IMS, Copenhagen, Denmark).

RESULTS.

Study Selection

A flow chart of study selection at each stage of the review is shown in Figure 1. The search identified 128 references. After excluding duplicates and reviewing titles and abstracts, 14 articles were evaluated in full text. Subsequently, two potentially relevant studies were excluded and four were identified by hand search. Sixteen RCT were finally included.

Study Characteristics

The PBMT parameters used in the studies are reported in Table 1. It was observed that all the studies used near infrared laser. Some studies did not present complete information on the protocol used, however the missing parameters could be calculated from the data reported.

The base characteristics of the patients and the OT are reported in Table 2. We observed that only one study used a sample exclusively of women,18 while all the others used patients of both sexes, in different proportions. The age range of the patients included in the primary studies was quite broad.

All the studies of canine retraction (CR) used similar forces and included patients who needed extraction of their first premolars bilaterally (upper, lower or both); however only four studies stated that the extractions were carried out at least 3 months before the start of CR. The orthodontic diagnosis was presented in only six studies. The exclusion criteria for patients were variable, since it was not possible to judge whether all the patients presented the same conditions. In tooth alignment the authors included patients of both sexes and different age ranges.

Canine Retraction

Fourteen studies analyzed the acceleration of OTM during the CR phase; one study applied multiple CR while the other 13 applied individual CR. Of the 14 studies, nine reported acceleration of OTM using PBMT[11,13,24-29] and five reported finding no differences between the experimental group and the control.[17-19,30,31] All the studies used split-mouth design.

Tooth Alignment

Two studies analyzed the velocity of tooth movement during the alignment phase; increased velocity was observed in the laser-treated group compared to the control in both studies.[32,33] Both studies used parallel design.

Assessment of the acceleration of tooth movement and principal findings of the studies

The assessment of OTM acceleration and the principal findings of the studies are reported in Table 3.

The authors analyzed the monthly OTM rate and the accumulated OTM. Tooth movement was measured from 56 days to 10 months. It was observed that PBMT determined an increase in the monthly OTM rate in the first two months of CR; the acceleration percentage was lower in the 4th month of treatment.[13,27] The velocity of OTM under PBMT was between 34% and 65%, which was higher than in the non-intervention group.[11,13,24,29] Of the 16 studies included in the qualitative analysis, 11 reported an increase in OTM in patients treated with PBMT.[11-13,24-29,32,33]

Risk of bias

The results of the risk of bias assessments of the studies included in this systematic review are shown in Figure 2.

Of the total of 16 studies, seven presented high risk of bias,[13,24,26,30-33] nine presented unclear risk,[11,12,17-19,25,27-29] and none presented low risk. Two studies presented low risk of bias for 'blinding of personnel',[18,19] six studies did not report whether that domain was assessed, and seven studies did not carry out 'blinding of personnel',[13,24,26,30-33] which was the principal risk of bias found. Six studies were classified as having low risk of bias for 'blinding of outcome assessment',[13,18,26,27,31,32] two were classified

with high risk of bias for not complying with this domain,[24,33] and eight studies did not offer enough information to judge – these were classified as unclear risk of bias.[11,12,17,19,25,28-30] 'Blinding of participants' was carried out by eight studies;[13,18,19,24-27,30] two studies did not comply with this domain[32,33] and six studies did not provide sufficient information to judge whether they complied with the domain.[11,12,17,28,29,31]

Although only RCTs were included, it was observed that only eight studies reported how 'random sequence generation' was carried out; these were classified as low risk of bias.[13,17,24,27,31-33] The other eight studies did not provide sufficient information to judge whether randomization was carried out or not. The majority of the studies did not report whether or not they carried out 'allocation concealment' and were therefore classified as unclear risk of bias;[11-13,17-19,25-32] only two applied this domain correctly.[24,33]

Effectiveness of PBMT in increasing the velocity of tooth movement

First month

Eight studies provided sufficient information to assess the monthly OTM rate; they were subdivided into three groups, according to the energy density (ED) used per tooth (Figure 3). PBMT was not effective in accelerating OTM in comparisons between studies which used an ED of between 33 and 42 J/cm^2 (MD -0.01; 95% CI -0.16 to 0.14; I^2=0%). PBMT was effective in accelerating OTM in comparisons between studies which used an ED of between 50 and 75 J/cm^2 (MD 0.58; 95% CI 0.36 to 0.80; I^2=9%). The comparison between studies which used ED between 200 and 214 J/cm^2 per tooth marginally favoured non-intervention (placebo/control), but the result was not significant (MD -0.06; 95% CI -0.12 to 0.00; I^2=0%).

Second Month

Six studies provided sufficient information to assess the monthly OTM rate; they were subdivided into three groups, according to the energy density (ED) used per tooth (Figure 4). PBMT was not effective in accelerating OTM in the comparison between the studies which used ED between 33 and 42 J/cm^2 (MD -0.03; 95% CI -0.26 to 0.21; I^2=0%). Two studies with ED of between 50 and 75 J/cm^2 per tooth were compared; a better result was found for PBMT (MD 0.41; 95% CI 0.14 to 0.68; I^2=0%). Comparison between two studies which used an ED of 200-214 J/cm^2 per tooth showed no differences between the group irradiated with PBMT and the non-intervention group (MD -0.01; 95% CI -0.1 to 0.09; I^2 = 0%).

Third Month

Four studies provided sufficient information to assess the monthly OTM rate; they were subdivided into three groups, according to the energy density (ED) used (Figure 5). PBMT was not effective in accelerating OTM when the ED used was between 33 and 42 J/cm^2 (MD -0.05; 95% CI -0.22 to 0.12).

Two studies with ED 50-75 J/cm^2 per tooth were compared; no differences were observed in the monthly OTM rate between the PBMT group and the non-intervention group (MD -0.01; 95% CI -0.15 to 0.13). One study with ED 200-214 J/cm^2 per tooth was compared; no differences were observed in the monthly OTM rate between the PBMT group and the non-intervention group (MD 0.05; 95% CI -0.12 to 0.22).

Accumulated OTM rate

Nine studies provided sufficient information to assess the accumulated OTM rate. They were divided into three sub-groups, according to the energy density used (Figure 6). The application of PBMT at an ED of between 33 and 42 J/cm^2 was not effective in increasing the accumulated OTM rate (MD 0.48; 95% CI -0.06 to 1.02, I^2 = 96%). PBMT was effective in increasing the accumulated OTM rate when the ED used was between 50 and 75 J/cm^2 per tooth (MD 1.40; 95% CI 0.94 to 1.85; I2=90%). In a study which compared treatment with ED between 200 and 214 J/cm^2 per tooth against a non-intervention group, no differences were observed between the accumulated OTM rates of the two groups (MD -0.02; 95% CI -0.73 to 0.69).

Sensitivity Analysis

No sensitivity analysis was carried out because none of the studies presented a low risk of bias.

Quality of evidence

All the studies included were RCTs. However, methodological problems were observed related with the quality of evidence. The quality of evidence was reduced due to the presence of many 'unclear' assessments for random sequence generation, allocation concealment, blinding of participants, blinding of personnel, blinding

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of outcome assessment and incomplete outcome data.

A high risk of bias was found in the blinding of participants, blinding of personnel and blinding of outcome assessment. Moreover, the limited number of participants and the wide confidence interval determined downgrading for imprecision of the effect estimate.

The quality of evidence was also reduced by the considerable heterogeneity found in the comparison of the accumulated CR rate. It was classified as moderate, low or very low. (Table 3)

Figure 1. Flow diagram for the identification and selection of studies in this systematic review.

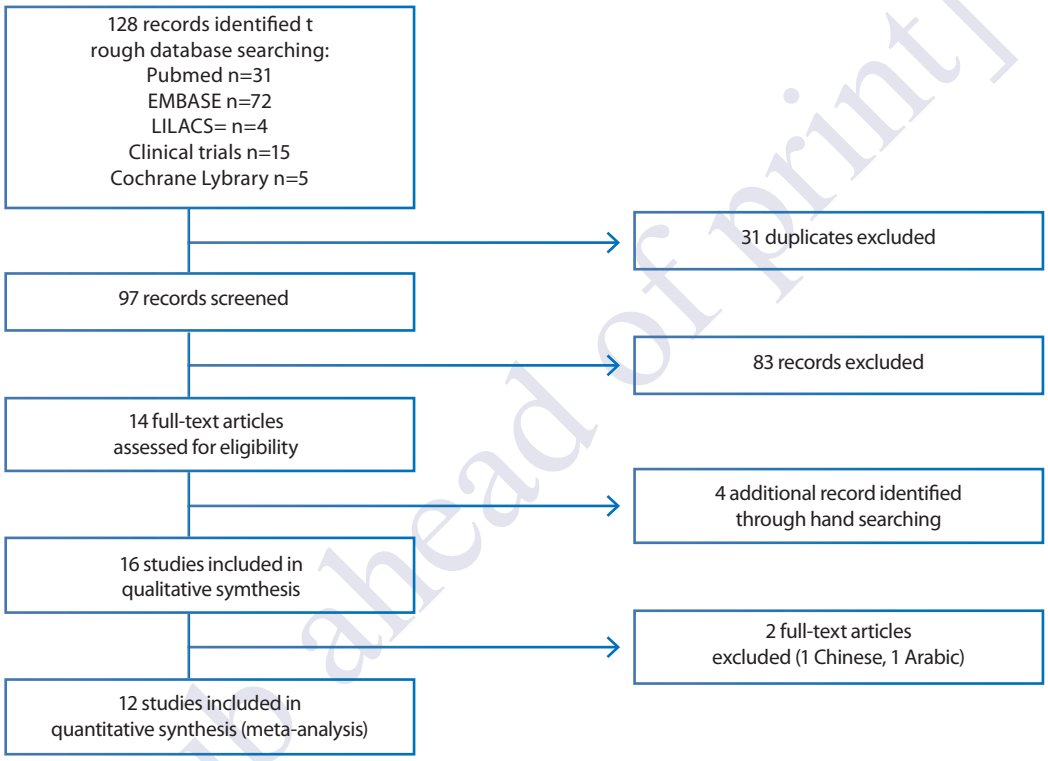

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each study included.

Table 1. Summary of PBMT parameters used in each study.

Author	orthodontic treatment	Type of laser	Output power (mW)	Spot size	Points	Time	Days of application	Energy density	E nergy
Al Sayed Hasan et al. [33]	Tooth alignment	GaAlAs, 830 nm, continuous mode	150	No information	4: 2 palatal, 2 lingual	15 s	0, 3, 7, 14, every 15 days	2.25/point	2/point 9/tooth*
Caccianiga et al. [32]	Tooth alignment	980 nm,conti-nuous mode100	100	1 cm^2 (optical fiber)	NI	150 s/entire mandibular arch	Single	150/total	No information
Cruz et al.[11]	Canine retraction	GaAlAs, 780 nm, continuous mode	20	4 mm^2	10: 5 palatal, 5 lingual	10 s/point	0,3,7,14,21,30,33,37,44, 51,60	5/point 50/tooth*	Nlo information
Dalaie et al. [17]	Canine retraction	GaAlAs 880 nm, continuous mode	100	No information	8: 4 palatal, 4 lingual	10 s/point	1, 3, 7, 30, 33, 37, 60, 63 and 67	5/point 40/tooth*	No information
Doshi et al.[13]	Canine retraction	GaAlAs 800 nm, continuous mode	0.25	4 mm^2	8	80 s	0, 3, 7, 14 (first month and thereafter every 15th day	5/point 40/tooth*	8/tooth
Guram et al. [29]	Canine Retraction	810 nm	0.2 W	No information	8: 4 palatal, 4 buccal	10 s/point	21 days (once per week)	5/point 40/tooth*	No information
Heravi et al. [30]	Canine Retraction	GaAlAs 810 nm, continuous mode	200	0.28 cm^2	10: 5 palatal, 5 lingual	30 s/point	0, 3, 7, 11, 15, 28, 32, 35, 39, 43, 56	21.4/point 214/tooth	6/point 60/tooth
Kansal et al. [31]	Canine Retraction	GaAs 904 nm	12	No information	10: 5 palatal, 5 lingual	10 s/point	1,3,7,14,21,28,35,42,49,56	42/tooth 4.2/point	No information
Kochar et al. [26]	Canine Retraction	GaAlAs 810 nm	100	0.4 cm^2	10: 5 palatal, 5 lingual	10 s/point	3rd and 7th of each month	5/point 50/tooth*	No information
Limpanichkul et al. [19]	Canine Retraction	GaAlAs 860 nm,	100	0.09 cm^2	8: 3 palatal, 3 lingual, 2 distal	23 s/point	0, 1, 2	25/point 200/tooth*	No information
Mal et al. [28]	Canine Retraction	940 nm, Continuous mode	0.2	3 mm	10: 5 palatal, 5 lingual	25 s	0, 3, 7, 14 (1st month), every 15th day for 4 months	5/point 50/tooth*	7J
Qamruddin et al. [24]	Canine Retraction	GaAlAs 940 nm, continuous mode	100	0.04 cm^2	10: 5 palatal, 5 lingual	3 s/point	every 3 weeks	7.5/point 75/tooth*	No information
Sandoval et al. [27]	Canine Retraction	AlGaInAs, 940 nm	100	0.4 mm^2 (optical fibre)	6: 3 palatal, 3 lingual	10 s/point	0, 7, 14 (1st month), every 15th day for 10 weeks	7.5/point 45/tooth*	6/total
Sousa et al. [12]	Canine Retraction	GaAlAs 780 nm	20	0.04 cm^2	10: 5 palatal, 5 lingual	10 s/point	0, 3, 7 of each month	5/point 50/tooth*	0.2/point 2/total
Üretürk et al. [25]	Canine Retraction	GaAlAs 820 nm	20	4 mm^2	10: 5 palatal, 5 lingual	10 s/point	0, 3, 7, 14, 21, 30, 33, 37, 44, 51, 60, 63, 67, 74, 81, 84, 90	5/point 50/tooth	0.2/point 2/total
Yassaei et al.[18]	Canine Retraction	GaAlAs 980 nm, continuous mode	100	No information	6: 3 palatal, 3 lingual	56 s/tooth	0, 7, 14, 21, 28 of each month for 6 months	5.6/point 33.6/tooth*	No information

*: data calculated by the authors.

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Table 1. Characteristics of the patients included in the primary studies.

Author	N	Females/ Males	Age	Study Design /Arch	OT/ Force	Extractions	Diagnosis	Exclusion
Al Sayed Hasan et al. 33	26	NI	16-24	Parallel/Maxilla	Tooth alignment Initial NiTi archwire 0.014, ending with 0.019x0.025 -inch stainless	Upper 1st PM	Moderate crowding (tooth-size–arch-length discrepancy of 3–5mm) in the anterior maxilla with Little's irregularity index (LII) of 7mm or more.	Poor oral hygiene, severe displacement (***e.g.*** ectopic canine)
Caccianiga et al.32	36	22/14	13-30 mean age: F =16.9 M =16.2	Parallel/ Mandible	Tooth alignment 0.022-inch slot Initial 0.014-inch thermal NiTi, final 0.017 x0.025-in thermal NiTi	No extraction	Angle Class I malocclusion, lower 6-6 mild crowding,	Ectopic teeth, spaces or diastema in the lower arch
Cruz et al. 11	11	NI	12-18	Split-mouth/ Maxilla	Canine retraction. NiTi closed-loop spring 150 g	Upper 1st PM	No information	No information
Dalaie et al. 17	12	9/3	mean age: 20.1	Split-mouth/Maxilla, Mandible	Canine retraction. NiTi coil springs 150 g	Extractions of upper and lower 1st PM 3 months before CR	No information	Absence of left and right canines, second premolars and first molars in maxillary and mandibular arches
Doshi et al.13	20	12/8	12-23	Split-mouth/ Maxilla, Mandible	Canine retraction. NiTi closed coil springs 150 g	Upper or lower 1st PM, or both	No information	Unilateral chewing or parafunctional habits, skeletal crossbite, occlusal interferences, impacted canines and canines with dilacerated roots
Guram et al. 29	20	12/8	17-24 mean age 19.75	Split-mouth/ Maxilla and mandible	Canine Retraction. Sectional closing loops	Extractions of upper and lower 1st PM 3 months before CR	Class I bimaxillary protrusion	Poor periodontal health
Heravi et al. 30	20	17/3	15-31 mean age 22.1	Split-mouth/ Maxilla	Canine Retraction.NiTi closed coil springs 150 g	Upper or lower 1st PM, where necessary	No information	Patients periodontally compromised
Kansal et al. 31	10	No information	No information	Split-mouth/ Maxilla	Canine Retraction. 150 g	Upper and lower 1st PM	No information	Patients needing extraction of other teeth in addition to first premolars
Kochar et al. 26	20	8/12	16-24	Split-mouth/ Maxilla, mandible	Canine Retraction. NiTi close-coil spring 150 g	Upper and lower 1st PM	Dental Class I bimaxillary protrusion	Dilacerated or impacted tooth, poor oral hygiene; crowding > 3 mm
Limpanichkul et al. 19	12	8/4	Mean age 20.11	Split-mouth/ Maxilla	Canine Retraction. NiTi close-coil spring 150 g	Extractions of 1st PM 3 months before CR	No information	No information
Mal et al. 28	10	No information	No information	Split-mouth	Canine Retraction. NiTi Coil Spring	1st PM	No information	Periodontal compromise, unilateral mastication habits, crossbite, occlu sal interference, impacted canines and canines with dilacerated roots
Qamruddin et al.24	20	11/11	12-25 mean age 19.8	Split-mouth/ Maxilla	Canine Retraction. NiTi Closed-coil spring 150 g	Upper 1st	Angle Class II Division 1; moderate to severe crowding	Patients with moderate to severe crowding who required extractions
Sandoval et al.27	20	12/8	18-25	Split-mouth/ Maxilla	Multiple Canine Retraction, 150 g	Upper 1st PM	No information	Periodontal compromise, unilateral mastication habits, crossbite, occlusal interference, impacted canines and canines with dilacerated roots
Sousa et al. 12	10	6/4	10.5-20.2 mean age 13.1	Split-mouth/both arches mixed	Canine Retraction.NiTi coil spring 150 g	Extractions of 1st PM 3 months before CR	Biprotrusion or dental crowding	No information
Üretürk et al. 25	15	8/7	12-19 mean age 16.2	Split-mouth/ Maxilla	Canine Retraction.NiTi Closed-coil spring 150 g	Upper 1st PM, 2 weeks before starting alignment and levelling	Angle Class II division 1	Poor oral hygiene
Yassaei et al. 18	11	11/0	14-25 mean age 19	Split-mouth/ Maxilla	Canine Retraction. NiTi Closed-coil spring 150 g	Upper and lower 1st PM three weeks before CR	Bimaxillary dentoalveolar protrusion with a convex profile and class I canine and molar relations	Poor oral hygiene, periodontal disease

Table 3. Methods for measuring orthodontic tooth movement, study design and principal findings of the studies included in the qualitative analysis

Author	Method for measuring orthodontic tooth movement	Principal findings	Effectiveness of PBMT in accelerating OTM
Al Sayed Hasan *et al.* [33]	Measuring the horizontal linear distance among adjacent contact points of the six anterior teeth.	PBMT was effective in accelerating movement of crowded maxillary incisors. PBMT accelerated the levelling and alignment time by 26%.	Yes
Caccianiga *et al.* [32]	Little's irregularity index was used before and after orthodontic treatment.	PBMT increases the efficiency of orthodontic treatment during dental alignment. Patients treated with PBMT required fewer control visits (7 visits) than patients in the control group (9.5 visits).	Yes
Cruz *et al.* [11]	The extent of canine movement was considered as the diminution of the distance between the distal slot of the canine support and the medial slot of the first molar support, measured in loco with a digital electronic calliper.	PBMT significantly accelerates orthodontic movement in human beings with a healthy response in the periodontal tissue. The group treated with PBMT presented 34% more tooth movement than the control group.	Yes
Dalaie *et al.* [17]	Distance between the canine cusp tip and first molar mesiobuccal cusp.	It was not possible to offer solid evidence to support the effectiveness of PBMT in accelerating tooth movement	No
Doshi *et al.* [13]	Distance between the cusp tips of the canines and the mesial cusp tips of the first molars	After CR, PBMT increased the velocity of tooth movement by 29% in the maxillary arch and 31% in the mandibular arch.	Yes
Guram *et al.* [29]	Distance between the canine cusp tip and mesiobuccal tip of the first molar on dental casts.	PBMT determined a CR time 65% shorter than in the control.	Yes
Heravi *et al.* [30]	Distance from the tip of the canine cusp to the tip of the mesiobuccal cusp of the first molar	There was no difference in the increase in canine movement between the PBMT and control groups.	No
Kansal *et al.* [31]	The extent of canine movement was considered as the decrease of the distance between the distal slot of the canine bracket and the mesial opening of the buccal tube of the first molar.	There were no differences between the PBMT and control groups.	No
Kochar *et al.* [26]	The distance between mesial cusp tip of the first molar and cusp tip of the canine for both the exposed and unexposed side in both the maxillary and the mandibular arch was recorded in millimetres using a calliper in all the models.	The increase in tooth movement velocity was greater in the PBMT group than the control. The maxilla presented greater velocity of orthodontic tooth movement than the mandible.	Yes
Limpanichkul *et al.* [19]	Measured on the Y-axis from the reference wire to the most mesial surface of canine at the new position	The mean difference of the cumulative distance of canine distal movement between the placebo side and the PBMT side for 3 months was 0.01 mm.	No
Mal *et al.* [28]	The amount of tooth movement was measured using a palatal plug. Each initial model was used for making a palatal plug, with reference wires pointing at the mesial contact of the canines.	Tooth movement in the PBMT group was more rapid in months 1, 2 and 4. PBMT increased the velocity of tooth movement by 30% compared to the placebo.	Yes
Qamruddin *et al.* [24]	The following method was used to measure canine displacement as elaborated by Gebauer.	PBMT can double the rate of tooth movement when applied every 3 weeks. The velocity of tooth movement presented no differences between the sexes. On the side treated with PBMT it was observed that the velocity of orthodontic tooth movement was 2.02 times greater than on the placebo side.	No
Sandoval *et al.* [27]	The tips of the mesial cusp of the first molar and the canine were used as intra-oral reference points.	Low-level light therapy increases the rate of orthodontic tooth movement. A 28% increase in orthodontic tooth movement was observed on the side which received PBMT.	Yes
Sousa *et al.* [12]	The tips of the canines on both sides, and the more cervical area of the papilla between the central incisors in the maxillary and mandibular arches, were the references for determining the linear distance between the papilla and the canines, either irradiated (PiCD) or not (PCD). Monthly canine retraction was measured by the difference against the PiCD or PCD obtained in the previous month .	PBMT accelerates orthodontic movement during the initial period of canine retraction, reducing the treatment period. The side irradiated with laser presented twice as much movement as the non-irradiated side.	Yes

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Üretürk *et al.* [25]	The tips of the canines of both sides, mesial cusp tips of the second molars, and the medial point of the 3rd palatine raphe were references to determine the linear distances both sides.	PBMT does accelerate tooth movement and could shorten the whole treatment duration. On the side irradiated with laser the mean increase in the rate of tooth movement at 3 months was 40%.	Yes
Yassaei *et al.* [18]	Distance from the tip of the canine cusp to the tip of the mesiobuccal cusp of the first molar.	There is no solid evidence that PBMT accelerates orthodontic tooth movement. Orthodontic tooth movement determined a significant increase in the IL-6 concentration, however no difference was observed between the side irradiated with laser and the placebo side.	No

PBMT: photobiomodulation therapy, OTM orthodontic tooth movement.

Table 4. GRADE summary findings table for the primary outcomes.

	Number of participants (studies)	Certainty of the evidence(GRADE)	Anticipated absolute effects Risk with non-intervention	Risk difference with low-level light Therapy
First Month ED 33-42 J/cm²/tooth	33 (3 RCTs)	⊕⊕◯◯ LOW [a,b,c]	-- -- -- --	MD 0.01 SD lower (0.16 lower to 0.14 higher)
First Month ED 50-75 J/cm²/tooth	38 (3 RCTs)	⊕⊕◯◯ LOW [b,d]	-- -- -- --	MD 0.58 SD higher 0.36 higher to 0.80 higher)
First Month ED 200-214 J/cm²/tooth	32 (2 RCTs)	⊕⊕◯◯ LOW [b,e]	-- -- -- --	MD 0.06 SD lower (0.12 lower to 0.00)
Second Month ED 33-42 J/cm²/tooth	21 (2 RCTs)	⊕⊕◯◯ LOW [a,b,c]	-- -- -- --	MD 0.03 SD lower (0.26 lower to 0.21 higher)
Second Month ED 50-75 J/cm²/tooth	23 (2 RCTs)	⊕⊕◯◯ LOW [b,d]	-- -- -- --	SMD 0.41 SD higher (0.14 higher to 0.68 higher)
Second Month ED 200-214 J/cm²/tooth	32 (2 RCTs)	⊕⊕◯◯ LOW [b,e]	-- -- -- --	SMD 0.01 SD lower (0.11 lower to 0.09 higher)
Third Month ED 33-42 J/cm²/tooth	9 (1 RCT)	⊕⊕◯◯ MODERATE [b]	-- -- -- --	MD 0.05 SD lower (0.22 lower to 0.12 higher)
Third Month ED 50-75 J/cm²/tooth	23 (2 RCTs)	⊕⊕◯◯ LOW [b,c,d]	-- -- -- --	MD 0.07 SD higher (0.20 lower to 0.34 higher)
Third Month ED 200-214 J/cm²/tooth	12 (1 RCT)	⊕⊕◯◯ LOW [b,f]	-- -- -- --	MD 0.05 SD higher (0.12 lower to 0.22 higher)
Third Month ED 200-214 J/cm²/tooth	12 (1 RCT)	⊕⊕◯◯ LOW [b,f]	-- -- -- --	MD 0.05 SD higher (0.12 lower to 0.22 higher)
Accumulated rate of tooth movement ED 33-42 J/cm²/tooth	62 (4 RCTs)	⊕⊕◯◯ VERY LOW [b,c,h,i]	-- -- -- --	MD 0.48 SD higher (0.06 lower to 1.02 higher)
Accumulated rate of tooth movement ED 50-75 J/cm²/tooth	59 (4 RCTs)	⊕⊕◯◯ VERY LOW [b,c,h,i]	-- -- -- --	MD 1.4 SD higher (0.94 higher to 1.85 higher)
Accumulated rate of tooth movement ED 200-214 J/cm²/tooth	20 (1 RCT)	⊕⊕◯◯ LOW [c,j]	-- -- -- --	MD 0.02 SD lower (0.73 lower to 0.69 higher)

CI: confidence interval. **MD:** mean difference. **GRADE:** working group grades of evidence. **high quality:** we are very confident that the true effect lies close to that of the estimate of the effect. **moderate quality:** we are moderately confident in the effect estimate. the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. **low quality:** our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect. **very low quality:** we have very little confidence in the effect estimate, the true effect is likely to be substantially different from the estimate of effect. **a:** Random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment 'unclear'; 'high risk of bias' for blinding of personnel. **b:** Very few participants. **c:** Wide confidence interval. **d:** Random sequence generation, allocation concealment, blinding of participants, blinding of personnel, blinding of outcome assessment, incomplete outcome data 'unclear'. **e:** Random sequence generation, allocation concealment, blinding of outcome assessment 'unclear'; 'high risk of bias' for blinding of personnel. **f:** Random sequence generation, allocation concealment, blinding of outcome assessment, blinding of outcome data 'unclear'. **g:** Random sequence generation, allocation concealment, blinding of participants, blinding of personnel, blinding of outcome assessment 'unclear'. **h:** Random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment 'unclear', incomplete of outcome data; 'high risk of bias' for blinding of personnel. iconsiderable heterogeneity. **j:** Random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data 'unclear'; 'high risk of bias' for blinding of personnel .

Figure 3. Forest plot of pooled standard difference in first month.

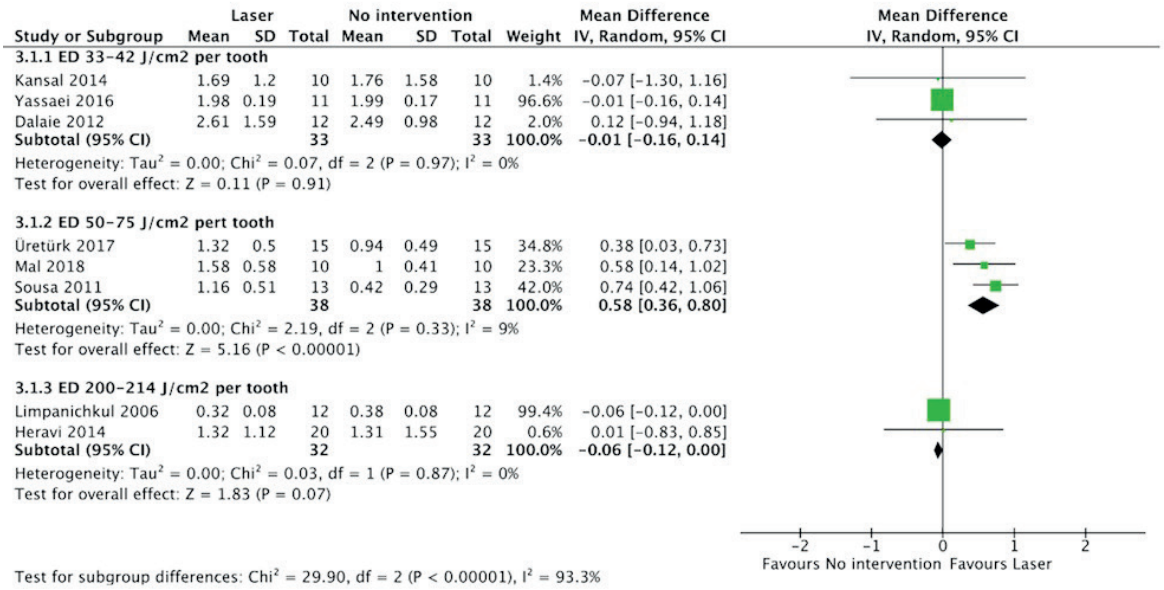

Figure 4. Forest plot of pooled standard difference in second month.

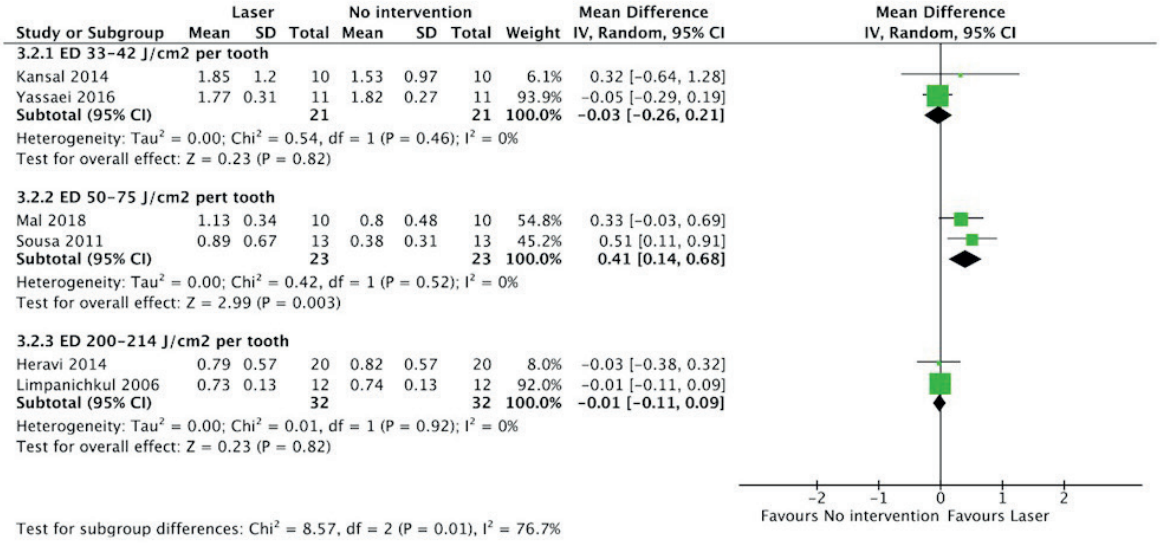

Figure 5. Forest plot of pooled standard difference in first month.

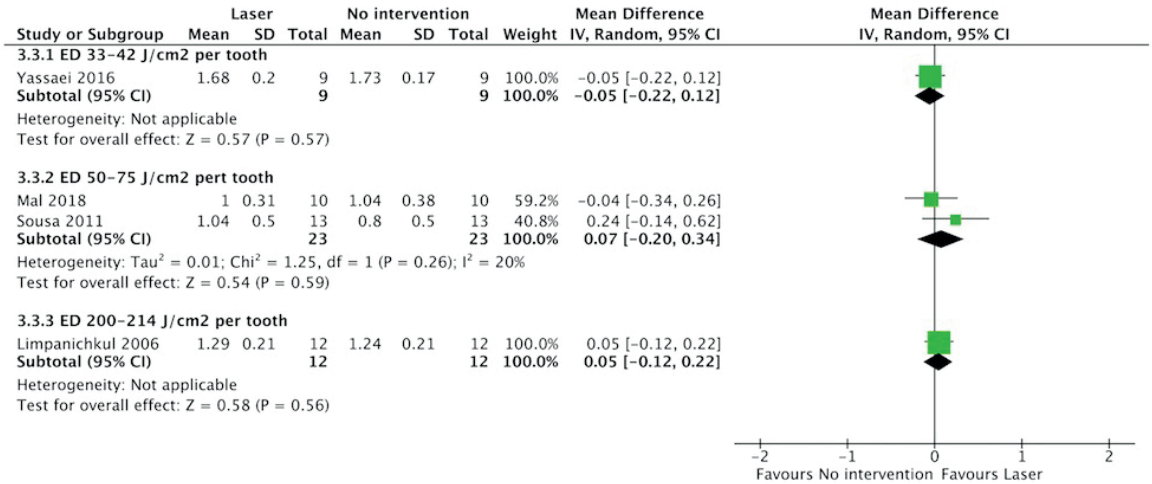

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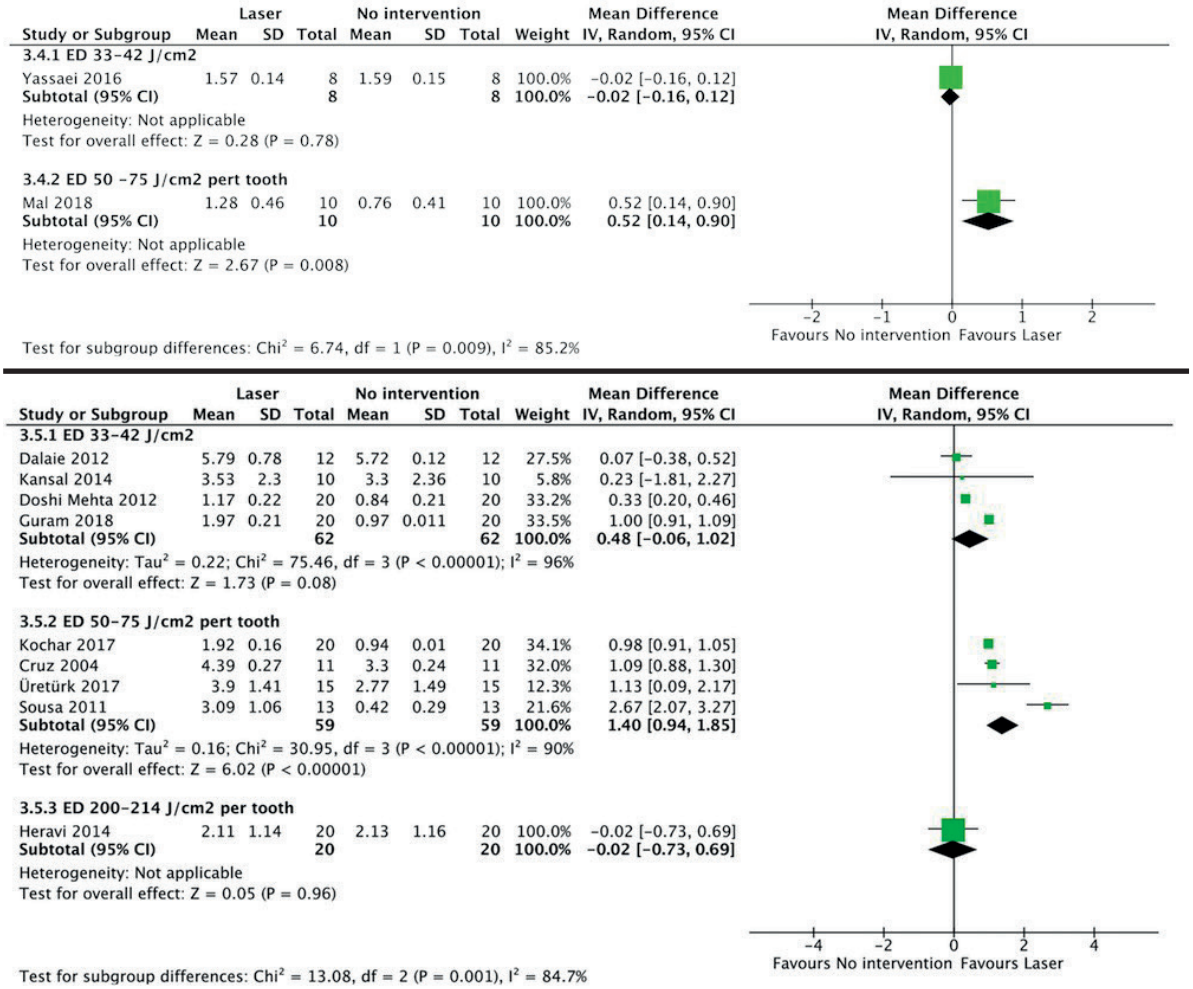
Figure 6. Forest plot of pooled standard difference in the accumulated CR rate.



DISCUSSION.

Summary of evidence

Orthodontic tooth movement is induced by therapeutic mechanical stress.[34] Mechanical stress leads to bone remodelling at a specific location; bone resorption occurs on the compression side due to osteoclast action, while bone is formed on the traction side due to osteoblast action.[35] The length of treatment time increases the risks of collateral effects such as root resorption, caries and decalcification.[36] Any increase in the OTM rate determines a shorter treatment time, potentially leading to beneficial effects for the patient through diminution in the collateral effects associated with OT.[37] Many factors may influence the rate of OTM, including bone density, the shape of the root and alveolar bone, occlusal forces and even the mastication habits of the individual.[38]

OTM may also be accelerated by treatments applied in conjunction with orthodontic treatment, such as corticopuncture and PBMT. Previous studies have shown that PBMT accelerates bone remodelling and consequently shortens the orthodontic treatment period.[39] PBMT has the potential to stimulate the maturing of osteoblast cells and accelerate synthesis of the organic matrix and mineralisation through increased osteoblast activity.[40,41] Furthermore, PBMT can accelerate tooth movement by increasing the activity of osteoclast cells, thus stimulating bone resorption on the compression side.[42]

In the present investigation we assessed the effectiveness of PBMT in accelerating OTM, observing that 68.75% of the RCTs reported an increase in the OTM rate with the application of PBMT as compared to non-intervention.[11-13,18,19,24-29] For successful treatment the PBMT application parameters must be chosen considering the dose-biphase response (Arndt Schulz

curve).[43] When the tissue is irradiated with a lower dose than the optimum (sub-optimal dose) it may not achieve such a significant therapeutic result, however when a very high dose is applied an inhibitory or contrary effect may occur. The energy density (ED) and the power density are parameters which determine the effectiveness of PBMT, since they are subject to thresholds, *i.e.* an upper and a lower limit.[43,44]

This finding was corroborated by the present review, since the effectiveness of PBMT in accelerating OTM was directly related with the dose applied. In the present study we carried out a meta-analysis of the data based on the ED used per tooth; it was observed that ED levels between 50 and 75 J/cm^2 per tooth were effective in accelerating the monthly OTM rate in months 1 and 2, and also in increasing the accumulated CR rate. However, authors who treated their patients with higher ED (between 200 and 214 J/cm^2 per tooth) did not succeed in accelerating OTM, and patients treated with a lower ED (between 33 and 42 J/cm^2 per tooth) experienced a beneficial effect but it was smaller than in patients treated with doses between 50 and 75 J/cm^2 per tooth. The findings of the present study coincide in part with the finding of Ge *et al.,*[45] who also indicated in an earlier meta-analysis that the effectiveness of PBMT was related with the ED used in the treatment. These authors say that the application of an ED between 2.5 and 8 J/cm^2 per point is effective in accelerating OTM.[45] In the present investigation we grouped the data according to the ED used on each tooth, as the different authors used different numbers of laser application points, determining the application of different total/per tooth ED in each treatment. Dalaie *et al.,*[17] Kansal *et al.,*[31] and Yassaei *et al.,*[18] used EDs of 4.2-5.6 J/cm^2/point and 33.6-40 J/cm^2/tooth, finding no increase in the velocity of OTM with PBMT; other authors using a similar ED/point (5-7.5 J/cm^2) report successful results by using a higher ED/tooth, of 50-75 J/cm^2.[11,12,24-28]

We note the importance of considering the total ED per tooth and not just the ED used in each point, since PBMT application at a different number of points modifies the total ED applied, which may determine the success or failure of the treatment. It should be noted that despite the important role of the ED, it is not the only parameter in PBMT that needs to be considered: the number of application points, frequency of sessions, final energy and wavelength of the equipment must all be taken into account. Previous studies have indicated that PBMT ED determines an important increase in the OTM rate, diminishing the time of OT; and that with the passage of time the OTM rate increases.[46]

However, some authors say that the acceleration percentage slows as the treatment progresses, a finding corroborated by the present study in which we observed that the monthly OTM rate is higher in the 1st month of OT than in the 2nd and 3rd months. Doshi-Mehta *et al.,*[13] reported that in the first 3 months of OT, tooth movement was increased by 56% with PBMT, while after 4.5 months the acceleration percentage of OTM on the experimental side was 30% higher than in the control.

This finding was corroborated by Sandoval *et al.,*[27] who observed an increase of 32% in OTM velocity in the 1st month of CR with PBMT as compared to the non-intervention group; however this percentage fell to 28% in the second month.

The correct choice of PBMT protocol is essential for successful treatment. The protocol must be chosen considering that the interaction of light with biological tissue depends on the penetration, absorption and distribution of light in the tissue.[47] It must be remembered that the dose delivered is not necessarily the same as the energy absorbed by the tissue. The absorption and distribution of light in the biological tissue depend on the wavelength and the chromophores.

The therapy window is limited in the first place by absorption, which in the case of longer wavelengths depends on the presence of water.[48] In the present review, all the studies used near infrared laser, which has greater penetration power in human tissue than red laser,[49] reaching 2-4mm below the skin surface.[47]

56.2% of the studies used wavelengths between 780 and 860nm,[11-13,19,25,26,29,30,33] and 43.8% used PBMT at very high wavelengths, between 880 and 940nm.[17,18,24,27,28,31,32] For studies which analyzed orthodontic movement during tooth alignment, the frequency of PBMT application was either a single application[32] or four times per month.[33] The frequency of PBMT must also be considered when choosing a protocol. The studies analysed in the present review indicate that to achieve an acceleration of OTM in

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CR, PBMT be applied at least twice per month,[24,26] and up to five times.[11-13,17,25,27,28]

In the present review only two studies used parallel design, both of which were studies of tooth alignment.[32,33] The other 14 studies used split-mouth design to analyse tooth movement during CR. An intact dentition is often found in orthodontics, making it possible to study comparable sites to analyse the effect of one treatment as compared to another or to a control. One advantage of split-mouth design is that it minimises biological variations in the comparisons. Another important point for studies of orthodontics patients is that in split-mouth design a smaller number of patients needs to be recruited than in a parallel design. One disadvantage is that the lack of follow-up may have a negative impact on the study, significantly reducing its power.

Some researchers say that PBMT has a systemic effect, 50 and therefore that split-mouth design is not appropriate. However, animal studies have shown statistically significant differences between the experimental group (treated with PBMT) and the control group,[51] demonstrating that even if systemic effects exist, they are not sufficient to influence significantly the side used as control.[42]

The conclusions on the effectiveness of PBMT in accelerating OTM are based on the results of 12 studies containing 175 patients. The evidence was down-graded to moderate or low quality because the studies present an unclear or high risk of bias, or imprecision (small samples and broad confidence intervals) or both. Very low quality was related with imprecision, risk of bias, and the considerable heterogeneity of the studies.

The principal risk of bias in the studies included in the present review was 'blinding of personnel', for which only two studies presented a low risk of bias;[18,19] seven studies did not report whether this domain was carried out and seven studies did not carry out 'blinding of personnel'.[13,24,26,30–33] It should be noted that 'blinding of personnel' is quite difficult to apply in PBMT, especially with operators who are familiar with the equipment; many types of equipment produce sound and emit light during treatment, making it very difficult to blind the procedure from the operator. In the present review only 40% of the studies carried out 'blinding of outcome assessment'.[13,18,26,27,31,32]

In clinical trials designed to assess acceleration of OTM, it must be remembered that the person who assesses the results must be blinded, not knowing whether the result refers to the placebo group or the treated group, since this knowledge might influence the results in some way. Although the present study included only RCTs, an important number of studies did not report how sequence randomization was carried out; only eight studies complied with this domain, in the others it was impossible to judge whether it was properly applied.[13,17,24,27,31–33]

We also note that an important number of studies did not comment whether 'allocation concealment' was carried out. In the present SR, there was a marked prevalence of 'unclear' judgements, while not a single study presented a low risk of bias. Of the 16 studies included in the qualitative analysis, 7 presented high risk of bias and 9 presented unclear risk of bias, determining a low quality of evidence. Bias may lead to under or overestimation of the results,[20] so future studies should consider the need to reduce the risk of bias in order to provide higher quality evidence.

The considerable heterogeneity found between the studies to analyse the accumulated CR rate may be related with the clinical characteristics of the patients.[52] Many individual factors may influence the OTM rate, for example the patient's sex and age. Female patients are affected by hormonal oscillations due to the menstrual cycle which may alter bone renewal during their monthly period.[53] In the present SR, only one study used a sample consisting exclusively of women;[18] all the others used combinations of males and females in different proportions, which may be a cause of the heterogeneity of the studies. Another factor which may affect the OTM rate is the patient's age, since pre-adolescents and adolescents (12-14 years) present a greater rate of movement than adults (21-45 years) under the same intensity of orthodontic force.[54]

Guram *et al.,*[29] included patients aged over 17 years, however other studies included younger patients and wider age ranges. An important aspect observed in the studies is that the majority do not report whether there were significant differences in the OTM rate between sexes and/or age ranges. We consider that the patients' different clinical characteristics related with age and sex may have determined the heterogeneity between the

studies. Furthermore, other factors may affect the rate of tooth movement, such as poor hygiene, periodontal disease, impacted canines or canines with dilacerated roots,[13,55] however not all the studies considered excluding patients with these characteristics, and it was impossible to judge whether or not these conditions may have affected the OTM.

Another important aspect which may alter the rate of tooth movement is tooth extraction, since extractions may increase the activity of inflammatory markers significantly, favouring increased tooth movement.[55] Of the studies included in the meta-analysis, only four authors reported that tooth extractions had been carried out in the three months before the start of CR[12,17,19,29] and one author reported extractions at least two weeks before CR.[25] The other studies did not report when the first pre-molars were extracted, making it impossible to judge whether the extractions may have influenced the acceleration of OTM.

Study limitations

We observed some limitations in our review process. Firstly, we may have failed to identify studies, since only publications in English, Portuguese and Spanish were included; this led to the exclusion of two studies, one in Arabic and one in Chinese. However, four studies were added by the manual search of the references, and the double independent review process was used. Another limitation of the present review was that four studies were not included in the meta-analysis because their data could not grouped due to the lack of the specific estimator needed; nevertheless their individual results were consistent with our findings.

The heterogeneity of the present review was substantial in the comparison of accumulated OTM rate; no sensitivity analysis could be carried out because none of the studies presented a low risk of bias. However it may be noted that all the other comparisons presented an unimportant I^2 (<30%), determining greater quality of the evidence.

We also consider that the presence of high risk of bias and a high prevalence of 'unclear' studies is not insignificant and may have affected estimation of the effect in the results. Finally, it was not possible to construct a funnel plot to explore the possible biases of the publications because we did not have more than 10 studies to pool in any meta-analysis.

CONCLUSION.

The present study determined the ideal dose (fluence) for accelerating OTM by photobiomodulation therapy. PBMT with a very low or very high ED/tooth is not effective in accelerating the OTM. PBMT with ED of between 50 and 75 J/cm^2 per tooth was effective in accelerating OTM in the first and second months of CR, and also increased the accumulated OTM rate.

Conflict of interests: No potential conflict of interest reported by the authors.

Ethics approval: Not applicable.

Funding: There was no funding for the study.

Author's contribution: NFD designed the study. NFD and NA carried out study selection by title, complete text and data extraction. NFD and PS carried out the risk of bias assessment of the studies. NFD carried out the quality of evidence analysis (GRADE). NFD and NA carried out the design and interpretation of the meta-analysis. NFD carried out the funnel plot. PS is the corresponding author and helped to draft the manuscript. NFD, NA and PS revised the final version of the manuscript. All authors read and approved the final version of the manuscript.

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