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Effects of Low-Level Laser on the Repair of Orthodontically Induced Inflammatory Root Resorption: A Systematic Review of Studies in Rats

Efectos del Láser de Bajo Nivel en la Reparación de la Reabsorción Radicular Inflamatoria Inducida por Ortodoncia: Una Revisión Sistemática de Estudios en Ratas

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SUMMARY: Orthodontically induced inflammatory root resorption (OIIRR) is a complication of dental treatment which consists of the degradation of local tissue due to an inflammatory reaction provoked by inappropriate orthodontic stimulus. The aim of the present systematic review was to assess the effectiveness of low-level laser therapy (LLLT) in reducing orthodontically induced inflammatory root resorption (OIIRR) in animal models. A systematic review was carried out in the MEDLINE, EMBASE and LILACS databases. Studies of interventions in animals were selected which analysed the effect of LLLT on OIIRR repair. The risk of bias was analysed through the 10 domains of the SYRCLE RoB tool for animal studies. Seventy-one studies were found; 27 were eliminated as duplicates and 44 titles/abstracts were analysed. Of these, 38 were excluded, and five studies were included for qualitative analysis. In 66.6 % of the studies included, the authors state that LLLT was effective in the inhibition/repair of OIIRR. In histological analysis it was observed that root resorption was significantly less in animals treated with laser as compared to the control. Furthermore, LLLT accelerated cicatrization after OIIRR. Laser proved effective in reducing root resorption lacunae and shortening the inflammatory process induced by the application of orthodontic force.

KEY WORDS: Animal model; Inflammatory root resorption; Low-level laser therapy; Orthodontic treatment; Histology; Systematic review.

INTRODUCTION

Orthodontically induced inflammatory root resorption (OIIRR) is a complication of dental treatment which consists of the degradation of local tissue due to an inflammatory reaction provoked by inappropriate orthodontic stimulus (Brezniak & Wasserstein, 2002; Krishnan & Davidovitch, 2006; Vasconcelos *et al*., 2016). Dental movement should occur slowly in order to avoid the negative effects of orthodontic force, such as bone necrosis or OIIRR (Seifi *et al*., 2014). When a very high orthodontic force is applied, higher than 2000 m, it may cause a decrease in bone formation and a slower rate of dental movement, as well as serious pain in the patient (Seifi *et al*., 2003; Cruz *et al*., 2004). Root resorption (RR) may occur on both the pressure side and the traction side. Small lacunae are observed at first, which gradually grow deeper and end in flattening of the radicular apex or shortening of the root (Altan *et al*., 2015). The incidence of apical RR may be as high as 53.1 % (Maués *et al*., 2015), and severe resorption presents in 2.9 % of cases (Sousa *et al*., 2014). This is a cause of grave concern for both clinicians and patients, and determines the need for techniques which help to reduce OIIRR. Some researchers have used local or systemic application of hormone-like molecules, such as calcium ions and prostaglandins, in order to observe their effect on OIIRR; however no evidence has been found that their administration has determined a variation in RR (Spoerri *et al*., 2018). One alternative treatment for repairing OIIRR is low level laser therapy (LLLT), a non-invasive treatment which promotes

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an analgesic effect. It can be used to minimise the patient's pain during dental treatment (Deana *et al*., 2017) by modulating the inflammatory process (Altan *et al*.), reducing the oedema and the number of inflammatory cells in the conjunctive tissue (Albertini *et al*., 2007), and promoting bone remodelling thus accelerating dental movement (Habib *et al*., 2010; Doshi-Mehta & Bhad-Patil, 2012; Sandoval *et al*., 2017; S. Suzuki *et al*., 2018). Recent studies have shown that laser can repair OIIRR (Altan *et al*.), reducing the area and volume of the resorption lacunae generated by the application of orthodontic force (Suzuki *et al*., 2016). However some authors report finding no reduction in OIIRR in groups treated with laser (Vasconcelos *et al*.), indicating that the action of LLLT on OIIRR is still controversial. Experimental studies in animals form part of the basic evidence for decisions in clinical practice (de Vries *et al*., 2015). They are fundamental for understanding the mechanisms of a disease, and important for testing the effectiveness of new interventions safely (Vesterinen *et al*., 2014). The research question for this work was therefore as follows: Is low-level laser therapy effective in reducing orthodontically induced root resorption in animal models? Therefore the aim of the present systematic review was to assess the effectiveness of LLLT in reducing OIIRR in animal models.

MATERIAL AND METHOD

Protocol and registration. A systematic review (SR) 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 for Systematic Reviews and Meta-Analysis (PRISMA) (Higgins & Green, 2011). The study was not registered.

Eligibility Criteria. The studies included were experimental studies in rats, randomised or not, which analysed the effects of low-level laser (red or near infrared) on repair of OIIRR. The exclusion criteria were: in vitro studies, studies in humans, studies in other animal model, systematic reviews and meta-analyses, unpublished theses, high level laser and light therapy using LED, studies with no comparison group.

Sources of Information and Search Strategy. An electronic search of the following databases was carried out on 17 April 2018, with no date or language restrictions: PubMed, LILACS and EMBASE. The search was complemented by a manual review of the references of the included studies.

The search in Pubmed is shown below: (((("Root Resorption"[Mesh]) OR root resorption*)) AND ((((orthodontic*) OR orthodontic tooth movement) OR "Tooth Movement Techniques"[Mesh]) OR tooth movement)) AND (((((((((diode laser) OR near infrared laser) OR red laser) OR "Laser Therapy"[Mesh]) OR laser therapy) OR "Phototherapy"[Mesh]) OR phototherapy) OR "Low-Level Light Therapy"[Mesh]) OR low level laser*).

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

The data from each article selected were analysed to obtain sample size, sex, age range, laser used, wavelength, output power, spot size, number of application points, treatment time, application points, days of LLLT application, total energy, energy density, study design, orthodontic force applied, method used for measuring the results, follow-up time, and the principal results found for the LLLT group and the control/placebo group.

Assessment of Risk of Bias. Two review authors (V.S.B. and P.S.) independently assessed the risk of bias of the eligible trials according to the SYRCLE risk of bias tool for animal studies (SYRCLE RoB) (Hooijmans *et al*., 2014). In cases of discrepancy, consensus was obtained by consulting a third reviewer (N.F.D.). The domains assessed were: 1- Random sequence generation; 2- Baseline characteristics, 3- Allocation concealment; 4- Random housing; 5- Blinding of operator; 6- Random outcome assessment; 7- Blinding of outcome assessment; 8- Incomplete outcome data; 9- Selective reporting; 10- Other biases. The potential risk of bias for each study was classified as 'No' (high risk), 'unclear' (unclear risk), or 'Yes' (low risk) (Hooijmans *et al*.).

RESULTS

Study Selection. A flow chart of the study selection process at each stage of the review is shown in Figure 1. The search identified 71 references. After excluding duplicates and reviewing titles and abstracts, the full texts of five experimental studies in rats were finally included for qualitative analysis.

Study Characteristics

Study design. Randomised and non-randomised studies were included. The principal characteristics of the studies are summarised in Table I.

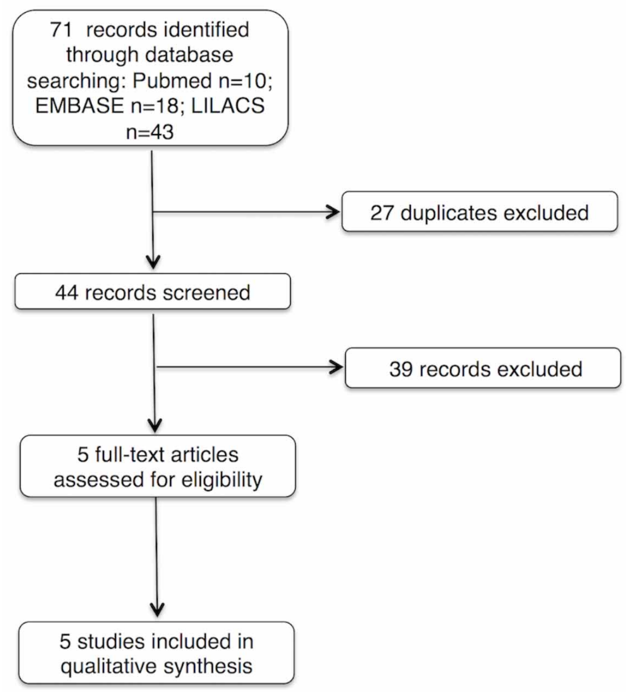

Fig. 1. Flow diagram for the identification and selection of studies in this systematic review.

LLLT. The laser parameters used in the studies are reported in Table II. It was observed that all the studies used near infrared laser (808-820 nm), with power between 50 and 100 mW. The energy densities were quite variable, between 4.8 and 580 J/cm^2 per point, with energy between 0.6 and 96 J. Laser was generally applied with an optic fibre at 1, 2, 3 or 4 points. The application frequency varied between 1 and 7 applications. Some studies did not present complete information on the LLLT protocol used, however the missing parameters could be calculated from the data reported.

Animal population. All studies used male Wistar rats (Marquezan *et al*., 2013; Altan *et al*.; Suzuki *et al*., 2016; Vasconcelos *et al*., 2016; Suzuki *et al*., 2018). The sample size with rats varied between 30 and 54 animals. The follow-up time of the studies ranged from 3 to 25 days.

Application of orthodontic force. One study applied a force of 25 g, used to move the left maxillary first molar (Vasconcelos *et al*.); three studies applied a force of 50 g to the upper first molars (Altan *et al*.; Suzuki *et al*., 2016, 2018), and 1 study used 40 cN on the upper incisors (Marquezan *et al*.) .

Outcomes. Laser was effective in reducing OIIRR in 60.0 % of the studies (Seifi *et al*., 2014; Altan *et al*.; Suzuki *et al*., 2016, 2018). The principal results and the techniques used to analyse the results in the studies included can be observed in Table III.

Risk of bias. The results of the risk of bias assessments of the studies included in this systematic review are shown in Figure 2. All the studies presented a high risk of bias. All five studies included presented high risk of bias for

Table I. Characteristics of the studies included.

Author	Animal species	*N (CG/IrG)*	Sex	Age	Weight	Appliance, force, location	Follow-up time
Altan *et al*. (2015)	Wistar rats	30 (16/14)	male	12 weeks	185 g (±10 g)	Coil spring, 50 g, maxillary left first molars	11 (Short term), 25 days (Long term)
Marquezan *et al*. (2013)	Wistar rats	36 (18/18)	male	12 weeks	250 g	Coil spring, 40 cN, maxillary first molar-maxillary incisors	2 (CG2, IrG2) and 7 (CG7, IrG7) days
Suzuki *et al*. (2016)	Wistar rats	68[a] (44^{CG}/30^{NG}/44 ^{IrG})	male	10 weeks	200-250 g	Coil spring, 50 g, left upper first molars, maxillary incisors	3, 5, 9, 14, 21 days
Suzuki *et al*. (2018)	Wistar rats	30[a] (20^{CG}/ 10^{NG}/30^{IrG})	male	10 weeks	300-350 g	Coil spring, 50 g, right and left upper first molars-distal to the upper incisors	14, 21 days
Vasconcelos *et al*. (2016)	Wistar rats	54 (18/36)	male	80 days	280-320 g	Coil spring, 25 g, left maxillary first molar-maxillary incisors	7 (CG, IDM, LD, HD) and 10 (CG, IDM, LD, HD) days

a Split mouth design, CG control group, IrG Irradiated group, NG negative group, IDM induced dental movement, LD low dose, HD high dose.

Table II. Low level laser treatment parameters used in the studies included.

Author	Laser type, _	Mode	Spot size	OP (mW)	ED (J/cm^2)	E (J)	Points	t	Number of sessions
Altan *et al.* (2015)	GaAlAs, 820 nm	continuous	0.031 cm^2 (OF)	50	4.8/point 19.2/total	0.6/point	4: 2 buccal, 2 palatal	12 s/point	6/7
Marquezan *et al.* (2013)	GaAlAs, 830 nm	NI	0.02 cm^2 (OF)	100	6000/day	54/total	3: 1 buccal, 1 palatal, 1 mesial	3 min/point	2 (IrG2) and 7 (IrG7)
Suzuki *et al.* (2016)	GaAlAs, 810 nm	NI	0.02 cm^2	100	75/point 150/total	1.5/point	2: 1 buccal, 1 palatal	15 s/point	every 48 hours
Suzuki *et al.* (2018)	GaAlAs, 810 nm	NI	0.02 cm^2	100	75point/ 150/total	1.5/point	2: 1 buccal, 1 palatal	15 s/point	7
Vasconcelos *et al.* (2016)	GaAlAs, 808 nm	continuous	0.6 mm (OF)	100	25^{LD} 580^{HD}	2.1/total^{LD} 96/total^{HD}	Buccal, palatal: 3^{LD}; 6^{HD}	7 s/point^{LD}; 2 min 43 s/point^{HD}	3

l wavelength, OP output power, t time, E energy, ED energy density, OF optical fibre, NI no information, LD Low dose, HD High dose

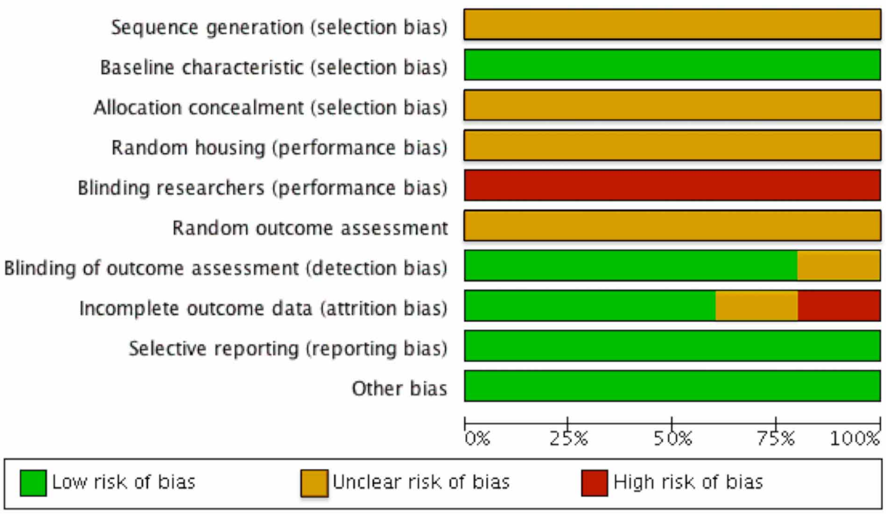

Fig. 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

'Blinding of operator'; two studies presented high risk of bias for 'Random sequence generation' (Altan *et al*.; Suzuki *et al*., 2016) and one study presented high risk of bias for 'Incomplete outcome data' (Vasconcelos *et al*.). None of the five studies offered sufficient information to judge the domains 'Allocation concealment', 'Random housing' and 'Random outcome assessment', and these risks were classified as unclear (Marquezan *et al*.; Seifi *et al*., 2014; Altan *et al*.; Suzuki *et al*., 2016, 2018; Vasconcelos *et al*.). One study presented unclear information for judging 'Blinding of outcome assessment' (Suzuki *et al*., 2016); one study did not offer sufficient information to judge 'Incomplete outcome data' (Altan *et al*.). The five studies presented low risk of bias for 'Baseline characteristic', 'Selective outcome reporting' and 'Other sources of bias' (Marquezan *et al*.; Seifi *et al*., 2014; Altan *et al*.; Vasconcelos *et al*.; Suzuki *et al*., 2016, 2018).

DISCUSSION

Summary of evidence. For orthodontic dental movement to occur, physiological forces must be applied which generate traction and compression stresses in the tooth support tissue (periodontal ligament – PDL) (Wise & King, 2008). The application of orthodontic force determines the start of an inflammatory process on the compression side, causing constriction of the microvasculature of the PDL. This results in local hyalinisation, with compensatory hyperaemia in the adjacent PDL and the vessels in the dental pulp (Long *et al*., 2001). One possible explanation for OIIRR during orthodontic treatment is that the production of excessive force limits the blood flow due to compression of the PDL space. The resulting oxygen deprivation determines ischaemic necrosis and the formation of hyalinised areas along the PDL space, death of the cementoblast and the PDL cells, and exposure of the root surfaces to osteoclast activity (Brudvik & Rygh, 1994; Brezniak & Wasserstein). OIIRR starts when the protective cementoblast layer, which interacts with the hyalinised PDL, suffers apoptosis, allowing the odontoclasts to resorb the cement and dentine (Brudvik & Rygh, 1994). Interrupting the application of orthodontic force may interrupt resorption, triggering repair or diminution of the process (Brudvik & Rygh, 1995). It should be noted that premature interruption of

Table III. Principal findings reported by the authors in relation to root resorption.

Author	Outcome measurements	Principal findings	Diminution of RR
Altan *et al.* (2015)	Histochemical evaluation (HE): analysis of the mesial aspect of the distopalatal root and adjacent structures.	- The inflammatory process occurred faster in the LLLT group than the control - LLLT applied after the cessation of orthodontic force significantly reduced resorption and accelerated wound healing of the OIIRR - Reparative effects on OIIRR were found, but preventive effects were not proved - In the Long-term Laser group (25 days follow-up), an important increase in osteoclasts and fibroblasts was observed, showing that the repair process was stronger than the resorption process.	Yes
Marquezan et al. (2013)	Histological evaluation (HE): analysis of the mesial, middle buccal, middle palatal, disto-buccal, and disto-palatal aspects of first molar roots. The resorption percentage (_m^2) was evaluated by digitized photomicrographs.	- Laser treatment was not effective in reducing RR - The group irradiated with laser presented twice the amount of root resorption, however no statistically significant differences were found between the experimental and control groups.	No
Suzuki *et al.* (2016)	The volumes of the root resorption lacunae were measured with ex vivo microcomputerized tomography in the tension and compression areas of the mesial and distal roots. The severity of root resorption was also measured on a scale of 1-5 by semi-quantitative analysis in scanning electron microscopy, where 1 presented no resorption and 5 presented more than 1/3 of the length of the root in root resorption lacunae at the dentine level	- The LLLT group presented a greater rate of dental movement than the control, with a pronounced difference in the first 6 days and no difference thereafter. - The root resorption score was lower in the laser group than the control. - The area of hyalinisation was significantly smaller in the laser irradiated group than the control. - In the control group, a larger number of roots was observed with more than 1/3 of the root length presenting dental resorption in the cement and dentine as compared with the LLLT group - In the laser group the volume of the resorption lacunae showed a significant reduction on the tension and compression sides, in the mesial and distal aspects - The compression side presented a greater volume of RR in both groups	Yes
Suzuki *et al.* (2018)	The root resorption craters were measured with *ex vivo* microcomputerized tomography. HE was used for descriptive analysis of the root resorption craters	- A smaller total root resorption crater volume was found in the LLLT group than the control group, on both tension and compression sides, mesially and distally. - In histological analysis, the irradiated groups presented smaller root resorption craters. - Laser treatment associated with corticopuncture produced greater dental movement and less RR than the separate application of the two techniques.	Yes
Vasconcelos *et al.* (2016)	Histological evaluation (HE) using a binocular microscope: measurement of the resorption percentage, the extent of resorption and the ratio between the resorption percentage and the root perimeter	- After 10 days, the group treated with a high dose of laser presented a better percentage of the total resorption area, extent of resorption and ratio between the resorption percentage and the root perimeter, but no significant difference was found between the experimental and control groups. - The wavelength 808 nm is safe for dental movement and does not stimulate resorption. - The dose used in the study is not recommended for clinical use.	No

OIIRR orthodontically induced inflammatory root resorption, RR root resorption, HE hematoxylin-eosin.

orthodontic treatment may mean that the patient's aesthetic and/or functional recovery may not be complete. However, shortening the inflammatory process may have the effect of reducing RR, since the cementoblast will not be exposed to a high level of stress over a long period of time (Suzuki *et al*., 2016). Thus it is important to find treatment techniques which reduce OIIRR and can be applied in combination with orthodontic treatment.

LLLT can accelerate the migration of macrophages, increasing their phagocytosis; it can also increase cytokine production, stimulate the metabolism of bone tissue and improve angiogenesis, which is essential during wound healing (Núñez *et al*., 2013; Paolillo *et al*., 2014). In the present review we assessed the effectiveness of LLLT in reducing OIIRR, finding it to be successful in 60.0 % of the studies. Altan *et al*. indicate that laser irradiation increases tissue response, accelerating the inflammatory process, showing that laser irradiation was able to reduce RR by promoting a shorter inflammatory process. Suzuki *et al*. (2018) indicated that LLLT promotes a reduction in the volume of RR lacunae by strengthening bone remodelling, determining greater bone resorption on the compression side and stimulating bone formation on the tension side. In another study, Suzuki *et al*. (2016) observed that laser acts at the same time on the biomodulation of bone resorption and OIIRR, stimulating bone resorption by activating the osteoclasts and inhibiting RR by preserving the cementoblast layer, avoiding damage to the roots even when there is high bone resorptive activity (Suzuki *et al*., 2016). Another important effect of laser is to stimulate the proliferation of osteoblast and fibroblast cells, improving the OIIRR repair process (Altan *et al*.). On the other hand, Marquezan *et al*. reported observing greater RR in the laser-treated group, while Vasconcelos *et al*. reported finding a reduction in RR with the use of a higher energy density; however the results were not significant in either of these studies. The effect of laser is dose-dependent, and an effective dose for OIIRR repair needs to be established. Very high doses of laser may cause inhibitory effects, while very low doses may be insufficient to trigger biomodulation (Hawkins & Abrahamse, 2006).

Various parameters need to be considered when choosing a laser treatment protocol, such as wavelength, spot area, number of applications, number of application points and energy density (ED). All the studies included in the present review used near-infrared laser, which has higher penetration power than infrared (Bagnato, 2008). The number of irradiations was between six and seven in the studies which reported successful results (Seifi *et al*., 2014; Altan *et al*.; Suzuki *et al*., 2016, 2018) and between two and seven in the studies which found no differences between the treatment group and the control group (Marquezan *et al*.; Vasconcelos *et al*.). The ED was between 4.8 and 75 J/cm2 per application point in the results which found that laser was effective in reducing OIIRR (Seifi *et al*., 2014; Altan *et al*.; Suzuki *et al*., 2016, 2018). Marquezan *et al*. observed a contrary effect to that expected with LLLT, although there was no statistically significant difference. These authors reported that the group irradiated with laser presented greater RR than the group not irradiated with laser; this may have occurred due to the high doses applied in this work, of up to 6000 J/cm^2 per day. Vasconcelos *et al*. indicated that neither of the protocols used in their study were effective in reducing OIIRR. The results presented by Marquezan *et al*. and Vasconcelos *et al*. corroborate the dose-dependent effect of laser, and show the importance of finding ideal doses which can be used in the routine treatment of dental patients.

Few SR have been carried out of experimental studies with animals, however such studies are important as they are able to assess not only the effects of an intervention, but also the risks of bias in investigations. Studies with high risk of bias may present overestimated results, which will determine that the study presents a low level of evidence (Faggion *et al*., 2017; Higgins & Green). Studies in animals which present a high risk of bias may fail to reflect the mechanism of the disease, or offer inaccurate results about the effectiveness of an intervention (Faggion *et al*.). In the present work, all the studies presented a high risk of bias. This was due to the difficulty of blinding the operators during laser application, since many types of equipment emit light, sound or both during laser emission. However we consider that this bias may have little influence on estimation of the effect if the researchers manage to minimise the other risks of bias included in the SYRCLE RoB tool, especially if the study applies 'Random sequence generation', 'Blinding of outcome assessment' and 'Random outcome assessment' correctly. 'Blinding of outcome assessment' was carried out in 80 % of the studies; the other 20 % did not provide sufficient information to judge this bias. Randomised and non-randomised studies were included in the present SR, however it should be noted that none of the four studies which reported carrying out 'sequence generation' explained how the randomisation was done, making it impossible to judge whether the method was carried out correctly; the risks were therefore considered 'unclear'. The difficulty of judging the risk of bias in the absence of information was observed in other domains such as 'allocation concealment', 'random housing' and 'random outcome assessment' in all the studies included in the qualitative analysis. It should be noted that when a domain is classified as 'unclear', the study may present a high or low risk of bias (Faggion *et al*.), and this may have a direct influence on the estimation of the effect of the intervention being assessed. We believe that the information is absent because the researchers did not know how to report their study properly, and we emphasise the importance of including all the information in future interventions carried out in animals, to allow consistent analysis of the evidence provided by every study.

Study limitations. One limitation observed in the present research is related with the risk of bias in the studies included in the qualitative analysis. Because the studies omitted much of the information it was impossible to judge properly the risk of bias in various domains of the SYRCLE RoB tool, resulting in doubts as to whether the estimation of the effect reported by the studies is overestimated or not. Another limitation of the present review arises from the lack of similar results which could be combined; the studies assessed the OIIRR in different ways, making it impossible to carry out a meta-analysis.

CONCLUSIONS

Laser proved effective in reducing the root resorption lacunae and shortening the inflammatory process induced by the application of orthodontic force.

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RESUMEN: La resorción radicular inflamatoria inducida por tratamiento ortodontico (RRIITO) es una complicación del tratamiento odontológico que consiste en la degradación del tejido local debido a una reacción inflamación provocada por un estímulo ortodóntico inadecuado. El objetivo fue analizar la efectividad de la terapia láser de baja intensidad (LBI) en la disminución de RRIITO en ratas. Se realizó una revisión sistemática en las bases MEDLINE, EMBASE y LILACS. Fueron utilizados los términos 'resorción radicular', 'láser de baja intensidad', 'fototerapia', 'tratamiento ortodóntico', 'movimiento dental'. Fueron seleccionados estudios de intervención en animales, que analizaron el efecto del LBI en la reparación de la RRIITO. Los riesgos de sesgos fueron analizados mediante los 10 domínios de la herramienta SYRCLE RoB para estudios en animales. 71 estudios fueron encontrados, siendo eliminados 27 duplicados, y analizados 44 títulos/abstracts; de estos, fueron incluídos 5 estudios para análisis cualitativa. El 66,6 % de los estudios incluidos afirman que el LBI fue efectivo em reparar la RRIITO. En el análisis histológico se observó que la RRIITO fue significativamente menor en animales tratados con láser en comparación con el control. Además de eso, el LBI aceleró el proceso de cicatrización de la RRIITO. El láser se mostró efectivo en reducir las lagunas de resorción radicular y acortar el proceso inflamatorio inducido por la aplicación de fuerzas ortodonticas.

PALABRAS CLAVE: Modelo animal; Resorción radicular inflamatoria; Terapia láser de baja intensidad; Tratamiento ortodóntico; Histología; Revisión sistemática.

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