UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

BRENDA AI REFOSCO TAKAGI

EFEITO DA FOTOBIOMODULAÇÃO NA RESPOSTA HISTOLÓGICA DE REIMPLANTES TARDIOS EM DENTES QUE SOFRERAM AVULSÃO: REVISÃO SISTEMÁTICA DA LITERATURA

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Trabalho de Conclusão de Curso apresentado ao curso de Graduação em Odontologia da Universidade Federal do Rio Grande do Sul, como requisito parcial para a obtenção do título de Cirurgiã-Dentista

Orientador: Prof.ª Dra. Roberta Kochenborger Scarparo

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Porto Alegre, __ de ____________ de ____

BANCA EXAMINADORA

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Prof. Dr. Francisco Montagner

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RESUMO

Esta revisão sistemática avaliou estudos pré-clínicos para verificar se a fotobiomodulação apresenta uma resposta histológica mais favorável do que outros tratamentos anteriores ao reimplante tardio de dentes avulsionados, visando subsidiar futuros estudos clínicos na área. O estudo seguiu o *checklist* do PRISMA e foi registrado no PROSPERO. MEDLINE (PubMed), Embase, Scopus e Web of Science foram pesquisados desde o seu início até 29 de julho de 2021. Os dados foram extraídos independentemente por dois revisores. Informações sobre espécies, número de animais, número e tipo de dentes, grupos avaliados, tempo extra-alveolar, parâmetros para laser e outros grupos de estudo, presença e características de contenção, pontos de tempo de observação, métodos de avaliação, características avaliadas e resultados significativos foram coletados. As ferramentas ARRIVE e SYRCLE foram utilizadas para avaliar a qualidade metodológica e o risco de viés (RoB) dos estudos. Após a triagem, 6 estudos foram incluídos na síntese da revisão. Três dos quatro estudos que avaliaram a reabsorção radicular como resultado revelaram que a fotobiomodulação diminui sua ocorrência após o reimplante dentário tardio. Uma meta-análise não foi realizada devido à falta de dados dos estudos incluídos. Portanto, os resultados do estudo foram analisados qualitativamente. Metade dos estudos que avaliaram a anquilose observou um aumento na ocorrência desse desfecho após a fotobiomodulação. A resposta inflamatória foi avaliada em dois estudos avaliados que revelaram redução da inflamação após sua utilização. Em geral, os estudos incluídos apresentaram alta heterogeneidade metodológica, qualidade intermediária e alto risco de viés (RoB). Apesar das limitações dos estudos incluídos nesta revisão sistemática, a resposta histológica da fotobiomodulação após o reimplante dentário tardio foi mais favorável quando comparada ao seu não uso. Os estudos pré-clínicos apoiados por diretrizes pré-estabelecidas devem ser encorajados para definir parâmetros do laser a serem testados em estudos clínicos futuros.

Palavras-chave: Fotobiomodulação; trauma dental; reabsorção dentária, avulsão dentária, reimplante tardio

ABSTRACT

This systematic review evaluated preclinical studies to verify if photobiomodulation presents a more favorable histological response than other treatments prior to delayed replantation of avulsed teeth, aiming to support future clinical studies in the area. This review followed the PRISMA checklist and was registered in PROSPERO. MEDLINE (PubMed), Embase, Scopus and Web of Science were searched from their inception to July 29, 2021. Data were independently extracted by two reviewers. Information regarding species, number of animals, number and type of teeth, groups evaluated, extra-alveolar time, parameters for laser and other study groups, presence and characteristics of containment, observation time points, evaluation methods, characteristics evaluated, and significant results were collected. The ARRIVE and SYRCLE tools were used to assess the methodological quality and risk of bias (RoB) of the studies. After screening, 6 studies were included in the review synthesis. Three out of four studies that evaluated root resorption as an outcome revealed that photobiomodulation decreases its occurrence after tooth delayed reimplantation. A meta-analysis was not conducted due to missing data of the included studies. Therefore, study results were analyzed qualitatively. Half of the studies evaluating ankylosis observed an increase in the occurrence of this outcome after photobiomodulation. Inflammatory response was assessed in two studies evaluated that revealed reduction of inflammation after photobiomodulation. In general, the included studies presented high methodological heterogeneity, intermediate reporting quality and high RoB. Despite methodological quality and RoB limitations of studies included in this systematic review, the histological response of photobiomodulation after delayed tooth replantation was more favorable when compared to its non-use. Preclinical studies supported by guidelines should be encouraged to define laser parameters to be tested in future clinical studies.

Keywords: Photobiomodulation; Dental Trauma; Root resorption; Tooth avulsion; delayed replantation

APRESENTAÇÃO

O presente trabalho de conclusão de curso apresenta uma revisão sistemática da literatura sobre a resposta histológica em casos de reimplantes dentários tardios, com foco no potencial da fotobiomodulação em modificar a resposta inflamatória periapical e minimizar a ocorrência de reabsorções dentárias. O trabalho foi estruturado conforme os seguintes tópicos:

- Introdução;
- Artigo científico: Formatado de acordo com as normas da revista *Journal of Endodontics*, fator de impacto 4.171 (Qualis A1, CAPES);
- Considerações finais.

SUMÁRIO

1 INTRODUÇÃO

A avulsão dentária é caracterizada pelo completo deslocamento do dente de seu alvéolo (1). Mais comum em crianças na faixa de 7 a 10 anos, a incidência da avulsão varia entre 1 e 16% de todas as lesões traumáticas, sendo os esportes e os acidentes de carro os maiores responsáveis por esse tipo de lesão (2).

O tratamento das avulsões deve ter como objetivo mitigar a inflamação e a infecção decorrentes do trauma para que ocorra o reparo periodontal e, quando possível, a revascularização pulpar (2). Com exceção de algumas situações específicas, o reimplante do dente avulsionado sempre é a melhor conduta, sendo o melhor cenário aquele em que é possível a realização do reimplante imediato (3). O tempo que o dente ficou fora do alvéolo e as condições na qual o dente foi armazenado são cruciais e influenciam no seu prognóstico (4–6). Estudos clássicos indicam que quando o dente é mantido em meio seco por mais de 60 minutos ocorre dano severo às células do ligamento periodontal (LP) e que 90% dos dentes que são reimplantados dentro de 30 minutos após a avulsão não sofrem reabsorção (7,8). Atualmente, entende-se que quando o dente é reimplantado em até 30 minutos após a avulsão ou então é armazenado em um meio fisiológico por um curto período de tempo, o prognóstico é bastante favorável; já quando o dente é mantido em meio seco por mais de uma hora, é esperada a necrose do LP e a ocorrência de complicações como a anquilose, reabsorção radicular externa substitutiva (RRES) e/ou reabsorção radicular externa inflamatória (RREI) (3,9).

Logo, os casos de reimplante tardio são os que apresentam pior prognóstico a longo prazo, pois devido à inviabilização das células do LP o destino do dente é a anquilose e/ou a RRES, que em longo prazo culmina na perda do dente. É, portanto, preconizado pelo IADT (International Association of Dental Traumatology) que o objetivo do reimplante tardio é manter o dente por motivos funcionais, estéticos e psicológicos, bem como manter o contorno alveolar para que no futuro seja possível a colocação de um implante e a reabilitação protética desse espaço (3). Por essa razão, diversos protocolos têm sido investigados com o intuito de avaliar se o tratamento do alvéolo ou da superfície radicular previamente ao reimplante é capaz de estimular o reparo do periodonto e inibir ou retardar as reabsorções radiculares após reimplantes tardios (10–19). No entanto, apesar dos esforços desses e de outros estudos prévios, ainda não foi possível definir um protocolo eficaz que aumente a taxa de sobrevivência dos dentes avulsionados e reimplantados tardiamente.

Nesse sentido, a fotobiomodulação dos tecidos biológicos vem sendo amplamente investigada ao longo dos últimos anos e utilizada na Medicina em diferentes situações clínicas (20). A Odontologia já possui protocolos com resultados promissores para o tratamento da mucosite, herpes labial recorrente, estomatite aftosa recorrente, trauma em tecido mole, entre outros (21–24).

A palavra laser é a sigla de Light Amplification by Stimulated Emission of Radiation que significa “amplificação da luz por emissão estimulada de radiação” e sua aplicação em humanos iniciou na década de 60 (21). A partir de então, diversos estudos sobre os mecanismos de ação e dos efeitos da fototerapia a laser a nível celular, molecular e tecidual foram desenvolvidos (25–28). Os lasers podem ser divididos em dois grupos: os lasers de alta ou baixa intensidade. O laser de alta intensidade é utilizado na Odontologia para fins cirúrgicos, pois devido à produção de calor é possível manipular os tecidos biológicos através do corte, ablação, coagulação e vaporização (29). Já o laser de baixa intensidade é utilizado para a realização da terapia de fotobiomodulação a laser, também conhecida como Terapia Laser de Baixa Potência (TLBP) (21).

Como o nome sugere, na TLBP a luz é utilizada de forma terapêutica. Os fótons são absorvidos pelos cromóforos endógenos presentes nos tecidos vivos desencadeando uma cascata de alterações bioquímicas no metabolismo celular (30). É importante ressaltar que para se obter os benefícios da fotobiomodulação, a luz precisa ser absorvida pelos tecidos. Dessa forma, os comprimentos de onda emitidos pela radiação devem corresponder à região do espectro eletromagnético do vermelho e do infravermelho próximo (600 nm – 950 nm), pois estes comprimentos de onda estão dentro da chamada janela óptica (região do espectro eletromagnético onde a água, melanina e hemoglobina tem baixa absorção, permitindo a penetração efetiva da radiação nos tecidos alvo) (21,28).

A fotobiomodulação tem como efeitos celulares a proliferação, migração e adesão celular, além de prevenir a apoptose celular (21,31,32). Um estudo in vivo de Matos e colaboradores apontou que a fotobiomodulação foi capaz de promover a angiogênese no periodonto de dentes de ratos reimplantados tardiamente (33). Outro estudo in vivo em ratos também revelou que a fotobiomodulação reduziu a quantidade de células inflamatórias e áreas necróticas (34). Já em relação aos seus efeitos teciduais, a fotobiomodulação é capaz de promover a modulação da inflamação, a reparação tecidual e a analgesia (20). Safavi mostrou que a irradiação com laser de baixa intensidade modifica a expressão dos genes responsáveis pela produção de citocinas inflamatórias na gengiva de ratos (35).

Diante de tudo que foi exposto, é possível imaginar que a fotobiomodulação poderia atuar como uma terapia coadjuvante nos casos de reimplantes tardios de dentes avulsionados. Uma vez que se sabe que na RRES há uma intensa atividade das células osteoclásticas e osteoblásticas, é possível pensar que a propriedade biomoduladora dos lasers de baixa intensidade poderia cessar ou retardar o processo de reabsorção e substituição da raiz por tecido ósseo. Interessantemente, um estudo em ratos avaliou histologicamente o efeito da fotobiomodulação no cemento radicular e mostrou que a aplicação do laser por 2 semanas foi capaz de aumentar a espessura do cemento (36). Esse é um achado importante pois estudos indicam que a reabsorção radicular parece progredir mais rápido na dentina que no cemento, sendo interessante a preservação da camada de cemento quando for realizada a remoção dos remanescentes necróticos do LP previamente ao reimplante (37–40).

No entanto as vantagens da utilização da fotobiomodulação em tratamentos da superfície radicular previamente ao reimplante tardio de dentes que sofreram avulsão ainda é controversa. Logo, o objetivo geral desse estudo foi, por meio de uma revisão sistemática da literatura, comparar a resposta histológica da fotobiomodulação com outros tratamentos da superfície radicular prévios ao reimplante tardio de dentes avulsionados. Os objetivos específicos foram avaliar se a fotobiomodulação apresenta resposta histológica mais favorável que as outras terapias estudadas e analisar a qualidade metodológica e risco de viés dos estudos.

Essa revisão sistemática de estudos pré-clínicos é relevante para identificar qual terapia apresenta resultados mais promissores para suportar a realização de futuros estudos clínicos na área.

2 ARTIGO CIENTÍFICO

Histological effects of photobiomodulation on delayed tooth replantation: a systematic review

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ABSTRACT

Introduction: This systematic review evaluated preclinical studies to verify if photobiomodulation presents a more favorable histological response than other treatments prior to delayed replantation of avulsed teeth, aiming to support future clinical studies in the area.

Methods: This review followed the PRISMA checklist and was registered in PROSPERO. MEDLINE (PubMed), Embase, Scopus and Web of Science were searched from their inception to July 29, 2021. Data were independently extracted by two reviewers. Information regarding species, number of animals, number and type of teeth, groups evaluated, extra-alveolar time, parameters for laser and other study groups, presence and characteristics of containment, observation time points, evaluation methods, characteristics evaluated, and significant results were collected. The ARRIVE and SYRCLE tools were used to assess the methodological quality and risk of bias (RoB) of the studies.

Results: After screening, 6 studies were included in the review synthesis. Three out of four studies that evaluated root resorption as an outcome revealed that photobiomodulation decreases its occurrence after tooth delayed replantation. A meta-analysis was not conducted due to missing data of the included studies. Therefore, study results were analyzed qualitatively. Half of the studies evaluating ankylosis observed an increase in the occurrence of this outcome after photobiomodulation. Inflammatory response was assessed in two studies evaluated that revealed reduction of inflammation after photobiomodulation. In general, the included studies presented high methodological heterogeneity, intermediate reporting quality and high RoB.

Conclusions: Despite methodological quality and RoB limitations of studies included in this systematic review, the histological response of photobiomodulation after delayed tooth replantation was more favorable when compared to its non-use. Preclinical studies supported by guidelines should be encouraged to define laser parameters to be tested in future clinical studies.

KEY WORDS

Photobiomodulation; Dental Trauma; Root resorption; Tooth avulsion; delayed replantation

INTRODUCTION

Dental avulsion is characterized by the complete dislocation of the tooth from its alveolus (1). More common in children aged 7 to 10 years, the incidence of avulsion varies between 1 and 16% of all traumatic injuries, with sports and car accidents being the main cause for this type of injury (2). The treatment of avulsion cases should aim to mitigate inflammation and infection resulting from trauma, thus favoring periodontal repair and, when possible, pulp revascularization (2). Except for some specific situations, the replantation of the avulsed tooth is always the best approach (3). Extra alveolar period and storage conditions are crucial and influence its prognosis (4–6). Classic studies report severe damage to periodontal ligament cells (PL) in teeth kept in a dry environment for more than 60 minutes, while 90% of teeth replanted within 30 minutes after avulsion do not undergo root resorption (7, 8).

Delayed replantation has the worst long-term prognosis, especially if a physiologic storage medium is not available (3, 9). Complications such as ankylosis, replacement root resorption (RRR) and/or inflammatory root resorption (IRR) are expected due to difficulties in maintain viable PL cells, which culminates in tooth loss over time. Hence, it is recommended by the International Association of Dental Traumatology (IADT) that the purpose of delayed replantation is to maintain the tooth for functional, aesthetic and psychological reasons, as well as to maintain the alveolar contour so that in the future it is possible to place an implant and the prosthetic rehabilitation of this space (3).

Several protocols of root surface treatment have been investigated to stimulate periodontal repair and thus inhibiting or delaying root resorption after late reimplantation (10–19). Within this context, for ethical reasons and due to the difficult in standardizing dental trauma conditions in clinical studies, animal models have been widely used to investigate new treatment alternatives for delayed replantation (20-21).

Photobiomodulation of biological tissues, also known as Low-Level Light Therapy (LLLT) (22), has been widely investigated over the last few years and used in Medicine in different clinical situations (23). Dentistry already has protocols with promising results for the treatment of mucositis, recurrent labial herpes, recurrent aphthous stomatitis, soft tissue trauma, among others (22, 24-26). The cellular effects of photobiomodulation are proliferation, migration, adhesion and prevention of cell apoptosis (22,27-28). An *in vivo* study by Matos *et al*. showed that photobiomodulation was able to promote angiogenesis in the periodontium of rat teeth that were later reimplanted (20). Other investigations revealed that photobiomodulation promote inflammation modulation, tissue repair and analgesia (23,21,29), being also capable to increase cementum thickness (30) Given the exposed, the use of photobiomodulation as an adjuvant therapy in cases of delayed reimplantation of avulsed teeth is a promising alternative for mitigate or delay root resorption.

However, there is no consensus amongst the available studies on its histological effects in cases of delayed tooth reimplantation. Therefore, this systematic review evaluated preclinical studies to verify if photobiomodulation presents a more favorable histological response than other treatments prior to delayed replantation of avulsed teeth, aiming to support future clinical studies in the area.

MATERIALS AND METHODS

Protocol and Registration

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Page et al. 2020). It was registered in the International Prospective Register of Ongoing Systematic Reviews (PROSPERO) under the registration number CRD42021268870 entitled “Histological effects of photobiomodulation on delayed tooth replantation: a systematic review”.

Focused Question

The clinical question was formulated and organized using the Population, Intervention, Comparison, Outcome and Study (PICOS) strategy. The review question was as follows: Does photobiomodulation used in delayed dental replantation in in vivo studies in animal models provide a more favorable histological response than other treatments without photobiomodulation?

Study Selection Criteria

The inclusion criteria were as follows:

1. Studies from the inception of the databases to July 29, 2021.

2. *In vivo* studies in animal model which simulate tooth avulsion and delayed reimplantation.
3. The study must have a control group and at least one group with photobiomodulation performed in the periodontal ligament and / or in the dental socket as an adjunct therapy to delayed dental replantation.
4. The study must present histological evaluation of the results.

Exclusion Criteria

The exclusion criteria were as follows:

1. *In vivo* studies that do not involve animal's delayed tooth replantation and histological evaluation;
2. Studies that do not present comparison groups and do not include laser photobiomodulation as one of the groups.
3. Studies with no access to complete text.

Search Strategies

The search was conducted independently by two reviewers (B.T. and L.Z). The following electronic databases were searched from their inception to July 29, 2021: PubMed, Embase, Scopus and Web of Science. No language restrictions were applied. The search strategy adapted terms for each database and followed their syntax rules (Table 1). After identification in the database, the studies were imported into the EndNote Web software® (http://www.myendnoteweb.com), and duplicates were removed. Articles that resulted from the search strategy were first screened based on the title and abstract. In the second screening, full-text articles were analyzed and included in the review if they met inclusion criteria. A manual search of the reference list of the selected studies was also conducted. In case of disagreement at any stage of the search, the reviewers met for discussion and a consensus was defined by two senior investigators (R.S. and P.K.).

Data Extraction and Data Synthesis

Data were independently extracted by two reviewers (B.T. and L.Z.) into a standardized data spreadsheet in Microsoft Office Excel® 2016 (Microsoft Corporation, Redmond, WA). The information was organized as follows: authors, publication year, species, number of animals, number and type of teeth, groups evaluated, extra-alveolar time, parameters for laser and other study groups, presence and characteristics of containment, observation time points, evaluation methods, characteristics evaluated and significant results.

Methodological Quality and Risk of Bias (RoB) Assessment

The two independent reviewers (B.T. and L.Z.), previously calibrated by discussing each checklist item, evaluated the methodological quality and the RoB of the studies included. Any disagreement after the evaluation of methodological quality and RoB was decided as described above. Methodological quality was evaluated using the 21-item checklist of the Animal Research: Reporting of In Vivo Experiments (ARRIVE) 2.0 guidelines: (1) study design, (2) sample size, (3) inclusion and exclusion criteria, (4) randomization, (5) blinding, (6) outcomes measure, (7) statistical methods, (8) experimental animals, (9) experimental procedures, (10) results, (11) abstract, (12) background, (13) objectives, (14) ethical statement, (15) housing and husbandry, (16) animal care and monitoring, (17) interpretation/scientific implications, (18) generalizability/translation, (19) protocol registration, (20) data access and (21) declaration of interests (31).

A pre-defined grading system described by Schwarz et al. (2012) and adapted for the ARRIVE 2.0 guidelines was used to assign scores to each item, as following: items 1 to 12, 14 to 18 and 21 received a score ranging from 0 to 2: 0 = clearly inaccurate or not reported; 1 = possibly accurate, unclear, or incomplete; 2 = clearly accurate. The other items (13, 19, and 20) received a score of 0 or 1: 0 = inaccurate, not concise, or not reported; 1 = accurate, concise, or reported. Differences between ARRIVE (Kilkenny et al. 2010) and ARRIVE 2.0 guidelines were discussed by two reviewers, who then assigned scores to the modified items. The sum of the scores ranged from zero to 39 points (32).

Maximum scores by column were added up to obtain quality scores by category (Delgado-Ruiz et al. 2014), and the result of the division of quality score by maximum score generated three possible quality coefficients: 0.8–1, excellent; 0.5–0.8, average and <0.5, poor (33).

Bias was evaluated using the RoB tool for animal studies of the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) (34). This tool, based on the Cochrane RoB tool, assesses RoB for 10 types of bias/domains: (1)

selection bias/sequence generation; (2) selection bias/baseline characteristics; (3) selection bias/allocation concealment; (4) performance bias/random housing; (5) performance bias/blinding; (6) detection bias/random outcome assessment; (7) detection bias/blinding; (8) attrition bias/incomplete outcome data; (9) reporting bias/selective outcome reporting; and (10) other sources of bias. RoB for each item in the selected studies was classified as low, high, or unclear using the RevMan 5.4 software (The Cochrane Collaboration, Denmark). If no checklist item had a RoB, the study was classified as having a low RoB; if RoB was unclear for any item, the RoB of the study was unclear; and if any item had a high Rob, Rob was classified as high for that study.

RESULTS

Study Selection

Screening in all databases returned 1898 articles: 64 in PubMed, 1513 in Embase, 257 in Scopus and 64 in Web of Science. After removing duplicates, 1657 studies were eligible for title and abstract reading, and, after that, 7 were selected for full-text assessment. Two studies were excluded: one because it did not perform photobiomodulation in the evaluated groups (Hamaoka *et al.* 2009) and another because it was the same study of other already included in this review, but with another title (de Carvalho et al. 2014). One study was added after reference screening (Pereira *et al.* 2019). Finally, 6 studies were included in the qualitative synthesis (Figure 1).

Characteristics of the studies included

The summary of characteristics and results of the included studies are described in Table 2, 3 and 4. Publication dates ranged from 2011 to 2019. All studies used rats as the animal model. The type of tooth evaluated in all studies was the maxillary incisors. The sample size ranged from 20 to 72 animals. Although in all studies there was at least one experimental group using LLLT and a control group with no laser treatment, different storage media were employed. Extra-alveolar time ranged from 4 to 60 minutes. In all included studies the application sites of LLLT were root surface and alveolus. All studies performed LLLT prior replantation, and three of them further used LLLT after replantation (#3, #4 and #5). The wavelength for LLLT ranged from 660 nm to 830 nm. Several laser parameters data were not reported by the authors.

The staining used for histologic evaluation was hematoxylin-eosin in all studies. One study (#4) also used sirius red staining to visualize type I and III collagen fibers. Only one study conducted immunohistochemical analysis (#1). The characteristics evaluated more frequently in the included studies were replacement and inflammatory root resorption (n = 5) and ankylosis (n = 4). Other characteristics evaluated were: inflammatory cells, necrotic areas, disorganization of odontoblasts cell layer and degenerating odontoblasts, osteoclasts, periodontal repair and angiogenesis. Qualitative, semi-quantitative or quantitative methods were used to evaluate these characteristics. All studies used statistical methods to analyze data. However, one study did not show statistical methods for all the outcomes proposed (#2).

Results of the studies included

A meta-analysis was not conducted because data on the mean and standard deviation of some of the evaluated studies was not available. Therefore, study results were analyzed qualitatively (Table 2, 3 and 4).

Root resorption (RR) was the most evaluated outcome in these studies. Some studies divided results in IRR and RRR. Although one study did not show statistically significant differences between all groups regarding RR (#1), three studies revealed that LLLT seems to decrease the occurrence of RR (#2, #3 and #4). One study demonstrate that RR was higher in LLLT group than in the other evaluated groups, except in comparison with delayed replantation control group (#6).

Regarding ankylosis, two studies indicated that groups in which LLLT was used, ankylosis was more frequent (#1 and #6). However, another two studies observed a positive impact of LLLT in this outcome (#3 and #4): Carvalho *et al.* (2016) demonstrated absence of ankylosis in LLLT group prior replantation in all observation time points; Matos and colleagues (#4) showed no ankylosis in 15 days for all groups. In 30 days, all groups without irradiation and only one group which used LLLT presented ankylosis.

With respect to inflammatory response, two studies evaluated this outcome (#2 and #3). Vilella *et al.* (2012) measured the degree of inflammatory cells and used descriptive analysis for results: after 15 days, inflammatory cells and blood clot were present in control and LLLT groups; after 30 and 60 days, control group was classified as intense for inflammatory cells, and LLLT group was classified as slight and moderate, respectively. Carvalho *et al.* (2016) used a semi-quantitative method to analyze inflammation. LLLT group with laser irradiation only on root surfaces and in alveolus prior replantation showed the best results for inflammation: in 15 days, inflammation was classified as discrete, in 30 days as absent and in 60 days as discrete.

One study assessed angiogenesis by counting the number of blood vessels (#5). In this study, LLLT groups presented significant increase of angiogenesis when comparing with control groups. Two studies evaluated periodontal repair (#4 and #6). Matos *et al.* (2016) showed that LLLT increased the perimeter of periodontal repair in all groups at 30 days. Pereira *et al.* (2019) assessed periodontal repair regarding two characteristics: connective tissue formed and reinsertion of periodontal fibers. For both characteristics, immediate replantation control group presented better results. All experimental groups presented mean scores similar to delayed replantation control group.

Only one study performed immunohistochemical analysis of OPG, RANK, RANKL and TRAP immunostaining intensity (#6). OPG immunostaining was significantly greater in L4; RANK immunostaining was greater in C30 and C45; RANKL immunostaining was similar in all groups at the three extra-alveolar times; TRAP immunostaining was greater in L4 and L30. RANKL immunostaining predominated over RANK and OPG in both groups with immediate tooth replantation (4 min extra-alveolar time); For the 30-min extra-alveolar time, there was a balance in proteins immunostaining; For the 45-min extra-alveolar time, there was greater evidence of RANK over RANKL immunostaining for both control and laser-treated groups.

Carvalho *et al.* (2016) measured the presence of osteoclasts, showing that LLLT groups prior and after replantation did not present this type of cells or were classified as discrete (#3). Matos *et al.* (2016) assessed areas of type I and III collagen deposition and concluded there was higher collagen deposition in the irradiated groups in all observation time points (#4).

Methodological Quality

Tables 5 and 6 show the scores and the percentages of studies according to the different reporting categories of the ARRIVE 2.0 checklist. Studies were scored as described above.

No study had a protocol registration (item 19) or provided data access (item 20). Blinding (item 5) was not reported in any study. Most studies received a score of 1 for sample size (83%), inclusion and exclusion criteria (100%), randomization (100%), experimental animals (100%), results (67%), background (100%), objectives (100%) and animal care and monitoring (100%). For item 7 (statistical methods), half of the studies scored 1 and the other half scored the maximum grade. The percentages of studies that received a score of 2 for checklist items were study design (100%), outcome measure (100%), experimental procedures (100%), abstract (83%), ethical statement (100%), housing and husbandry (67%), interpretation/scientific implications (100%), generalizability/translation (100%) and declaration of interests (67%).

Nine categories received excellent scores and achieved coefficients of 0.8–1: (1) study design, (6) outcome measure, (9) experimental procedures, (11) abstract, (13) objectives, (14) ethical statement, (15) housing and husbandry, (17) interpretation/scientific implications and (18) generalizability/translation. Nine categories had intermediate grades, with coefficients of 0.5–0.8: (2) sample size, (3) inclusion and exclusion criteria, (4) randomization, (7) statistical methods, (8) experimental animals, (10) results, (12) background, (16) animal care and monitoring and (21) declaration of interests. Finally, three categories had scores that indicated a poor quality, with coefficients <0.5: (5) blinding, (19) protocol registration and (20) data access.

Risk of Bias

The results of RoB assessment according to the SYRCLE RoB tool (Hoojimans et al. 2014) are showed in Figure 2. Four studies had a high RoB for “selective reporting”. Almost all studies did not report detailed information. Therefore, RoB was defined as unclear for most studies. RoB was low for “blinding of outcome data” in all studies, for “blinding of participants and personel” in two studies and for “selective reporting” in only one study.

DISCUSSION

This systematic review was conducted to verify if photobiomodulation presents a more favorable histological response than other treatments prior to delayed replantation of avulsed teeth. Four of the included studies concluded that LLLT could bring benefits in replanted teeth cases (#1, #2, #3, #6). The other two studies (#4, #5) were not favorable for LLLT. In general, the treatments compared between the experimental groups of the included studies were the application or not of LLLT. The type of storage medium and the extra-alveolar time before replantation were also factors that varied between the study groups.

Several studies have recommended the use of photobiomodulation on traumatized tissue due to its properties of cell bio stimulation and acceleration of the healing process, in addition to its anti-inflammatory and analgesic effects (24,35-36). Matos *et al.* (2016) was the only included study in this review that evaluated type I and III collagen deposition and demonstrated that in all groups in which LLLT was performed greater collagen deposition was observed. This same study assessed the perimeter of periodontal repair and observed that, in general, when the perimeter of periodontal repair was greater, there was also the presence of greater collagen deposition. Another study by Matos *et al*. (2018) included in this review analyzed angiogenesis as an outcome and showed that photobiomodulation was able to promote angiogenesis in the periodontal tissue after delayed tooth replantation in rats (20). This result corroborates a study showing that the stimulation of blood vessel formation is related to faster and greater tissue repair (37). Considering the results of these studies one may infer that LLLT accelerate and improve the periodontal repair of replanted teeth. On the other hand, Pereira *et al.* did not notice a benefice using photobiomodulation for this outcome, which may be explained by two factors: first, the aggression to dental support tissues in cases of avulsion is severe and there is a shortage of PL cells, possible impairing photobiomodulation to improve periodontal tissues repair through cellular stimulation; second, the use of different methodologies such as laser parameters, extra-alveolar time and storage medium may have contributed to the divergent results amongst studies.

Previous studies stated that photobiomodulation is capable to modulate inflammation (23). Carvalho *et al.* and Vilela *et al.* were the only two included studies that evaluated the degree of inflammation and concluded that LLLT could mitigate inflammation in cases of delayed tooth replantation. These results corroborate a recent *in vitro* study which simulated damaged PL of avulsed teeth and observed that photobiomodulation of 808 nm laser was able to reduce inflammation and also improve proliferation, migration and osteogeneses of normal, starved and inflamed PL cells (38). Moreover, inflammation promotes the presence of clastic cells and, thus, stimulates resorption. This was supported in Carvalho *et al.* study who assessed osteoclasts as an outcome and observed that when inflammation was scored as moderate and intense there was also the presence of osteoclastic cells and external inflammatory root resorption. Conversely, groups that were classified as absent or discrete did not presented osteoclasts or root resorption. Therefore, the use of LLLT to mitigate inflammation appears to be rational and effective to prevent root resorption in replanted teeth.

In this systematic review, studies included were, in general, showed a favorable effect of LLLT in reducing root resorption. Groups in which LLLT was not performed usually presented greater resorption than LLLT groups. In contrast, two included studies did not observed benefits regarding root resorption using photobiomodulation. Saito *et al.* did not find significant statistical difference concern IRR or RRR between irradiated and non-irradiated groups. Pereira et al. compared high power laser, photobiomodulation and also the association between both types of lasers, concluding that high power laser groups presented less root resorption than control and irradiated groups. These results may be explained by the use of different methodologies such as laser parameters and extra-alveolar time.

The RANK-RANKL-OPG system plays an important role in bone metabolism and researchers seek to better understand how this system works in the root resorption process (39). In a brief explanation, RANK is a receptor of osteoclastic cells, and when activated by its ligand, RANKL, bone resorption initiates. To cease bone resorption, osteoblasts release a cytokine called OPG (40). In this systematic review, only the study by Saito *et al*. performed immunohistochemistry as a tool to complement the histomorphometrical analysis. They observed and equivalence for RANK and OPG immunostaining in irradiated and non-irradiated groups in all extra-alveolar times. This result is in accordance with histomorphometrical analysis that did not show significant differences between irradiated and non-irradiated groups regarding IRR and RRR. TRAP, a marker of the enzyme that demonstrates the osteoclastic activity, was also assessed. The results showed that TRAP and RANKL had similar behavior, which confirms the hypothesis that RANKL signalizes and initiate bone resorption and TRAP confirms resorption.

Ankylosis is a common outcome after delayed tooth replantation (8). Carvalho *et al.* and Matos *et al.* (2016) did not observe statistically significant differences for ankylosis using LLLT in 30 days. On the contrary, Saito *et al.* revealed that LLLT group replanted after 30 minutes presented greater ankylosis perimeter than its control group, probably due to viable PL cells reduction and greater stimulation of bone cells by photobiomodulation.

Systematic reviews of preclinical studies have become more common in the last few years and are relevant to identify which therapy has the most promising results to support future clinical studies in the area (41). Despite the possibility of translating the knowledge generated by preclinical studies to the development of clinical trials and studies in humans, researchers must be cautious. Further improvements in animal research are needed to maximize its contribution to evidence-based translational research (42). The low number of studies assessing protocols for delayed tooth replantation and the heterogeneity of methodology difficult comparison between studies. Standardization regarding laser parameters and extra alveolar time is necessary. Laser parameters such as wavelength, output power, dose, energy, time of irradiation, emission mode, number of applications and application mode plays a fundamental role in LLLT outcomes. Preclinical studies can serve to identify the best values for each of these parameters and for each of the desired effects on dental tissues.

The ARRIVE guidelines aim to help researchers to improve the rigor and transparency of reporting of study methods, findings and reproducibility (31). The SYRCLE RoB tool is bases on the Cochrane RoB tool and has been adapted for use in animal intervention studies and seek to avoid discrepancies in assessing the methodological quality of studies (34). In the present systematic review, ARRIVE item 10 and SYRCEL RoB item 9, regarding reported results, were classified as average and high, respectively. Vilela *et al.* performed statistical analysis for only one of the outcomes (root resorption). Other outcomes were measured using a semiquantitative scoring system. Statistical analysis could also have been done for the other results to allow a better comparison between groups. Carvalho *et al.* also measures the results using a semi-quantitative criterion. Despite performing statistical analysis, it only shows the percentage of the highest frequency score in each of the groups for each observed time. It would be interesting to bring the percentage of each score to enable a comparison with other studies. Matos *et al.* 2016 did not show the standard deviation of all outcomes, missing the results for ankylosis. In addition, despite the study showing the averages of ankylosis in 30 days, it did not show if there was a statistically significant difference. Ultimately, Pereira *et al.* showed mean scores for all outcomes, but did not show standard deviation. Failure to adequately report the results did not allow conducting a meta-analysis.

In general, the included studies presented high methodological heterogeneity, intermediate reporting quality and high RoB. In addition, inherent limitations of preclinical studies must be considered and, thus, the knowledge generated by this systematic review should be translated cautiously. Despite these limitations, this review shows that methodological changes in the design of preclinical studies are needed. It is strongly suggested that standardized protocols and reporting guidelines be used for preclinical studies in this field, increasing reporting quality and decreasing RoB.

CONCLUSION

Despite the limitations regarding methodological quality and RoB of the included studies in this systematic review, the histological response of photobiomodulation after delayed tooth reimplantation was more favorable when compared to its non-use. Preclinical studies supported by guidelines should be encouraged to identify the best values for each of the laser parameters and for each of the intended effects on dental tissues. These studies should be the base for future clinical studies aiming to assess the advantages and limitations of using photobiomodulation for cases of delayed tooth replantation.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Brenda Ai Refosco Takagi: Main researcher. Contributed to carrying out the investigation, analyzed and interpreted the data, drafted the article, and approved the final version. **Luciéli Zajkowski:** Reviewer. Contributed to carrying out the investigation, analyzed and interpreted the data. **Patrícia Maria Poli Kopper:** Contributed to the conception and design of the manuscript, carried out the investigation, analyzed the data, and revised and approved the final version. **Roberta Kochenborger Scarparo:** Study supervisor. Contributed to the conception and design of the manuscript, carried out the investigation, analyzed and interpreted the data, and revised and approved the final version.

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Figure 1 PRISMA flow diagram of screening and selection processes.

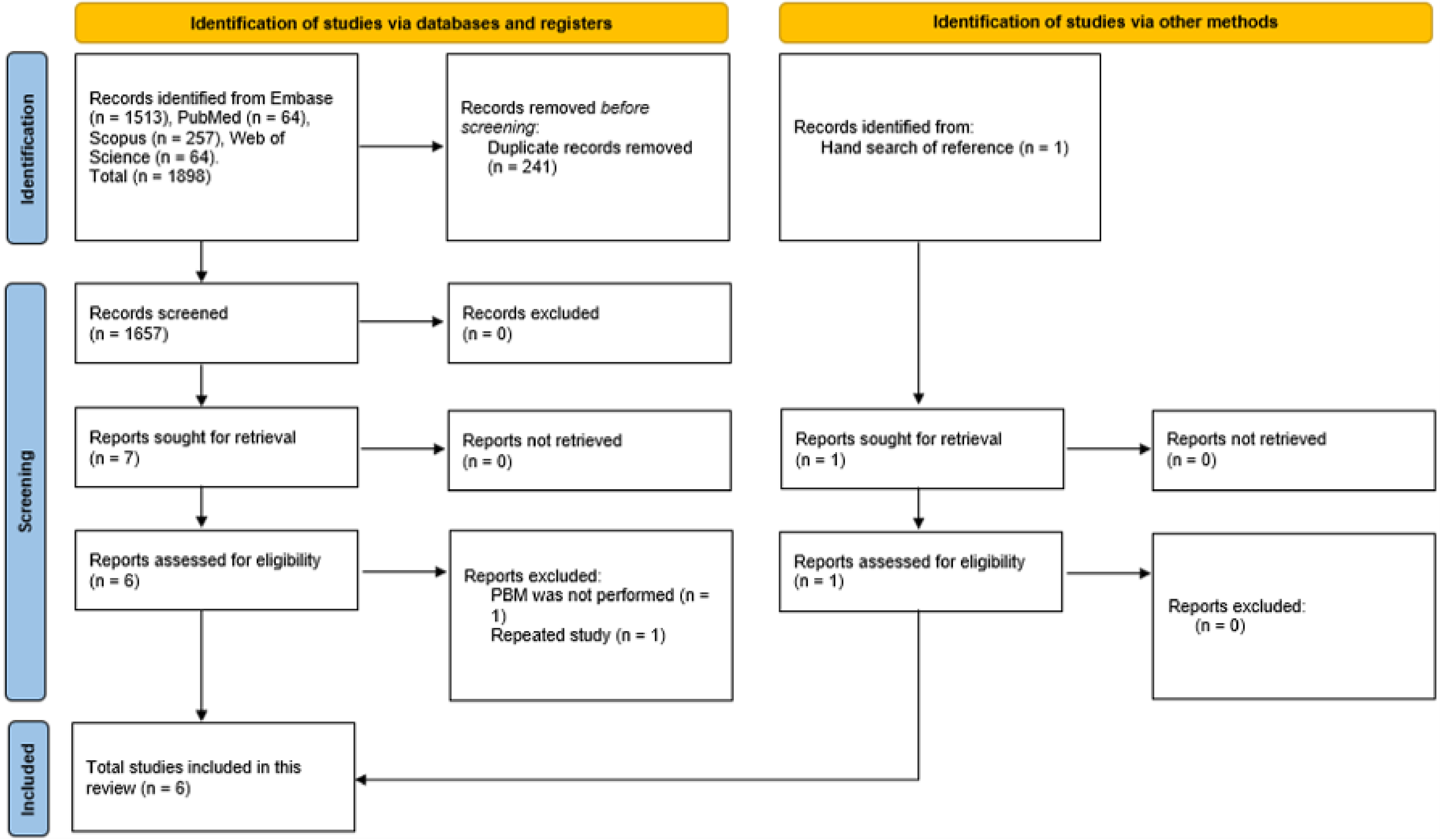

Figure 2 Risk of bias according to categories: evaluation by review author described as percentages across all studies and for each study included.

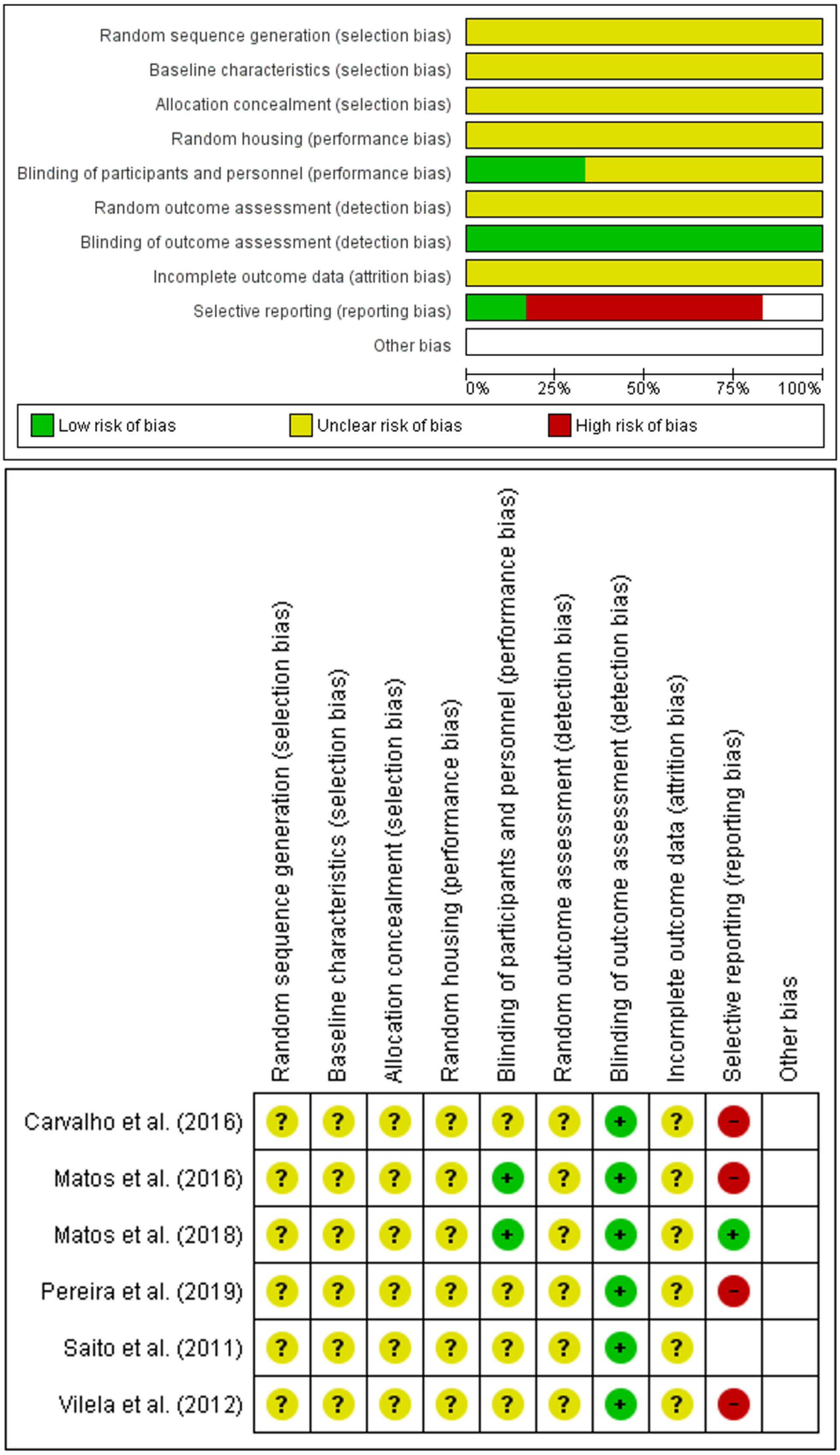

Table 1 Search strategy used and results for each electronic database (Embase, PubMed, Scopus, Web of Science).

Databases	Search	Query	Items found
Embase	#1	'tooth injury' OR 'avulsion, tooth' OR 'dental injury' OR 'dental trauma' OR 'dental traumata' OR 'injury, dental' OR 'injury, tooth' OR 'tooth avulsion' OR 'tooth damage' OR 'tooth injuries' OR 'tooth trauma' OR 'trauma, dental' OR 'trauma, tooth'	13,759
	#2	'tooth replantation' OR 'dental reimplantation' OR 'dental reinclusion' OR 'dental replantation' OR 'tooth reimplantation' OR 'tooth reinclusion'	525
	#3	'tooth disease'/exp OR 'tooth resorption' OR 'tooth root resorption' OR 'dental root resorption'	257,906
	#4	'periapical tissue'	481
	#5	'tooth periapical disease'	7,076
	#6	'low level laser therapy'/exp OR 'laser biostimulation' OR 'laser therapy' OR 'laser therapy, low-level' OR 'laser treatment' OR 'low energy laser therapy' OR 'low energy laser treatment' OR 'low intensity laser therapy' OR 'low intensity laser treatment' OR 'low level laser treatment' OR 'low level light therapy' OR 'low power laser therapy' OR 'low power laser treatment' OR 'low-level laser therapy' OR 'low-level light therapy' OR 'photobiomodulation'	40,561
	#7	#1 OR #2 OR #3 OR #4 OR #5 AND #6	1,506
PubMed	#1	(Tooth Avulsion) OR (Avulsion, Tooth) OR (Avulsions, Tooth) OR (Tooth Avulsions) OR (Avulsed Tooth) OR (Tooth, Avulsed) OR (Dislocation, Tooth) OR (Dislocations, Tooth) OR (Tooth Dislocation) OR (Tooth Dislocations)	3,300
	#2	(Tooth replantation) OR (Replantation, Tooth) OR (Replantations, Tooth) OR (Tooth Replantations) OR (Reimplantation, Tooth) OR (Reimplantations, Tooth) OR (Tooth Reimplantations) OR (Tooth Reimplantation)	2,394
	#3	(Root Resorption) OR (Resorption, Root) OR (Resorptions, Root) OR (Root Resorptions)	6,578
	#4	(Periapical Tissue) OR (Periapical Tissues) OR (Tissue, Periapical) OR (Tissues, Periapical) OR (Periodontium, Apical) OR (Apical Periodontium) OR (Apical Periodontiums) OR (Periodontiums, Apical)	3,901
	#5	(Periapical Diseases) OR (Disease, Periapical) OR (Diseases, Periapical) OR (Periapical Disease)	9,169
	#6	(Low-Level Light Therapy) OR (Light Therapies, Low-Level) OR (Light Therapy, Low-Level) OR (Low Level Light Therapy) OR (Low-Level Light Therapies) OR (Therapies, Low-Level Light) OR (Therapy, Low-Level Light) OR (Photobiomodulation Therapy) OR (Photobiomodulation Therapies) OR (Therapies, Photobiomodulation) OR (Therapy, Photobiomodulation) OR (LLLT) OR (Laser Therapy, Low-Level) OR (Laser Therapies, Low-Level) OR (Laser Therapy, Low Level) OR (Low-Level Laser Therapies) OR (Laser Irradiation, Low-Power) OR (Irradiation, Low-Power Laser) OR (Laser Irradiation, Low Power) OR (Low-Power Laser Therapy) OR (Low Power Laser Therapy) OR (Laser Therapy, Low-Power) OR (Laser Therapies, Low-Power) OR (Laser Therapy, Low Power) OR (Low-Power Laser Therapies) OR (Low-Level Laser Therapy) OR (Low Level Laser Therapy) OR (Low-Power Laser Irradiation) OR (Low Power Laser Irradiation) OR (Laser Biostimulation) OR (Biostimulation, Laser) OR (Laser Phototherapy) OR (Phototherapy, Laser) OR (Photobiomodulation)	13,222
	#7	#1 OR #2 OR #3 OR #4 OR #5 AND #6	64
Scopus	#1	TITLE-ABS-KEY("tooth avulsion" OR "avulsed tooth" OR "tooth dislocation" OR "tooth avulsions" OR "tooth dislocations" OR "avulsion, tooth" OR "avulsions, tooth" OR "tooth, avulsed" OR "dislocation, tooth" OR "dislocations, tooth" OR "tooth injury" OR "dental injury" OR "dental trauma" OR "dental traumata" OR "injury, tooth" OR "tooth damage" OR "tooth injuries" OR "tooth trauma" OR "trauma, dental" OR "trauma, tooth")	8,969
	#2	TITLE-ABS-KEY("tooth replantation" OR "replantation, tooth" OR "replantations, tooth" OR "tooth replantations" OR "reimplantation, tooth" OR "reimplantations, tooth" OR "tooth reimplantations" OR "tooth reimplantation" OR "tooth replantation" OR "dental reimplantation" OR "dental reinclusion" OR "dental replantation" OR "tooth reinclusion")	2,176
	#3	TITLE-ABS-KEY("root resorption" OR "resorption, root" OR "resorptions, root" OR "root resorptions" OR "tooth disease" OR "tooth resorption" OR "tooth root resorption" OR	43,113

		"dental root resorption")	
	#4	TITLE-ABS-KEY("periapical tissue" OR "periapical tissues" OR "tissue, periapical" OR "tissues, periapical" OR "periodontium, apical" OR "apical periodontium" OR "apical periodontiums" OR "periodontiums, apical")	1,879
	#5	TITLE-ABS-KEY("periapical diseases" OR "disease, periapical" OR "diseases, periapical" OR "periapical disease" OR "tooth periapical disease")	6,859
	#6	TITLE-ABS-KEY("low-level light therapy" OR "light therapies, low-level" OR "light therapy, low-level" OR "low level light therapy" OR "low-level light therapies" OR "therapies, low-level light" OR "therapy, low-level light" OR "photobiomodulation therapy" OR "photobiomodulation therapies" OR "therapies, photobiomodulation" OR "therapy, photobiomodulation" OR "lllt" OR "laser therapy, low-level" OR "laser therapies, low-level" OR "laser therapy, low level" OR "low-level laser therapies" OR "laser irradiation, low-power" OR "irradiation, low-power laser" OR "laser irradiation, low power" OR "low-power laser therapy" OR "low power laser therapy" OR "laser therapy, low-power" OR "laser therapies, low-power" OR "laser therapy, low power" OR "low-power laser therapies" OR "low-level laser therapy" OR "low level laser therapy" OR "low-power laser irradiation" OR "low power laser irradiation" OR "low intensity laser therapy" OR "low intensity laser treatment" OR "laser biostimulation" OR "biostimulation, laser" OR "low energy laser therapy" OR "low energy laser treatment" OR "laser phototherapy" OR "phototherapy, laser" OR "laser therapy" OR "photobiomodulation")	38,121
	#7	#1 OR #2 OR #3 OR #4 OR #5 AND #6	257
Web of Science	#1	TS=("tooth avulsion" OR "avulsed tooth" OR "tooth dislocation" OR "tooth avulsions" OR "tooth dislocations" OR "avulsion, tooth" OR "avulsions, tooth" OR "tooth, avulsed" OR "dislocation, tooth" OR "dislocations, tooth" OR "tooth injury" OR "dental injury" OR "dental trauma" OR "dental traumata" OR "injury, tooth" OR "tooth damage" OR "tooth injuries" OR "tooth trauma" OR "trauma, dental" OR "trauma, tooth")	2,784
	#2	TS=("tooth replantation" OR "replantation, tooth" OR "replantations, tooth" OR "tooth replantations" OR "reimplantation, tooth" OR "reimplantations, tooth" OR "tooth reimplantations" OR "tooth reimplantation" OR "tooth replantation" OR "dental reimplantation" OR "dental reinclusion" OR "dental replantation" OR "tooth reinclusion")	312
	#3	TS=("root resorption" OR "resorption, root" OR "resorptions, root" OR "root resorptions" OR "tooth disease" OR "tooth resorption" OR "tooth root resorption" OR "dental root resorption")	9,183
	#4	TS=("periapical tissue" OR "periapical tissues" OR "tissue, periapical" OR "tissues, periapical" OR "periodontium, apical" OR "apical periodontium" OR "apical periodontiums" OR "periodontiums, apical")	621
	#5	TS=("periapical diseases" OR "disease, periapical" OR "diseases, periapical" OR "periapical disease" OR "tooth periapical disease")	337
	#6	TS=("low-level light therapy" OR "light therapies, low-level" OR "light therapy, low-level" OR "low level light therapy" OR "low-level light therapies" OR "therapies, low-level light" OR "therapy, low-level light" OR "photobiomodulation therapy" OR "photobiomodulation therapies" OR "therapies, photobiomodulation" OR "therapy, photobiomodulation" OR "lllt" OR "laser therapy, low-level" OR "laser therapies, low-level" OR "laser therapy, low level" OR "low-level laser therapies" OR "laser irradiation, low-power" OR "irradiation, low-power laser" OR "laser irradiation, low power" OR "low-power laser therapy" OR "low power laser therapy" OR "laser therapy, low-power" OR "laser therapies, low-power" OR "laser therapy, low power" OR "low-power laser therapies" OR "low-level laser therapy" OR "low level laser therapy" OR "low-power laser irradiation" OR "low power laser irradiation" OR "low intensity laser therapy" OR "low intensity laser treatment" OR "laser biostimulation" OR "biostimulation, laser" OR "low energy laser therapy" OR "low energy laser treatment" OR "laser phototherapy" OR "phototherapy, laser" OR "laser therapy" OR "photobiomodulation")	13,691
	#7	#1 OR #2 OR #3 OR #4 OR #5 AND #6	59

Table 2 Summary of the included studies characteristics.

#	Authors/Year	Animal number/Specie	Number/Type of evaluated teeth	Groups evaluated	Extra-alveolar time (min)	Containment characteristics	Observation time point (days)
1	Carvalho et al (2016)	60 Wistar rats	60 MI	• NSM • Milk • Milk + LLLT 1* • Milk + LLLT 2**	40	Absent	15, 30 and 60
2	Matos *et al.* (2016)	60 Wistar rats	60 MI	• PN • PNL • WM • WML • SM • SML	45	Absent	15 and 30
3	Matos *et al.* (2018)	20 Wistar rats	20 MI	• PN • PNL • WM • WML	45	NR	15
4	Pereira *et al.* (2019)	50 Wistar rats	50 MI	• IR • DR • HPL • LLLT • HPL + LLLT	0 60 60 60 60	Absent	60
5	Saito *et al* (2011)	60 Wistar rats	60 MI	• IR • DR 30 • DR 45 • IR + LLLT • DR 30 + LLLT • DR 45 + LLLT	4 30 45 4 30 45	NR	60
6	Vilela *et al.* (2012)	72 Wistar rats	72 MI	• NSM • LLLT	15	Semi-rigid	15, 30 and 60

MI, maxillary incisors. NR, not reported. NSM, no storage medium. LLLT, low-level laser therapy. PN, paper napkin storage medium. PNL, paper napkin laser. WM, whole milk storage medium. WML, whole milk laser. SM, soy milk storage medium. SML, soy milk laser. IR, immediate replantation. DR, delayed replantation. HPL, high power laser. *, LLLT on root surfaces and at the entrance of alveolus before replantation. **, LLLT on root surfaces and at the entrance of alveolus before replantation + on buccal and palatal alveolar mucosa after replantation.

Table 3 Summary of laser parameters of the included studies.

				Clinical parameters							Physical parameters		
#	Application site	Dose (J/cm^2)	Irradiation time (s)	Intensity	Irradiation method	Mode of application	Time of laser application	Laser equipment	Wavelength (nm)	Type of emission	Output power	Beam diameter (mm)	Irradiated area (cm^2)
1	RS + Alveolus Alveolar mucosa[1]	16.8, 4.2 and 8.4[2]	320, 60 and 120[3]	NR	Non-contact (RS) / NR (alveolus and alveolar mucosa)	NR	PR and AR[4]	GaAlAs	780	Continuous	70 mW	2.2	0.04
2	RS + Alveolus Alveolar mucosa[5]	61	119 PR / 34 AR	3.6 W/cm^2	Contact	Punctual	PR and AR	GaAlAs PR / InGaAIP AR	808 PR / 660 AF	Continuous	100 mW	1.9	0.028
3	RS + Alveolus Alveolar mucosa[5]	61	119 PR / 34 AR	3.6 W/cm^2	Contact	Punctual	PR and AR	GaAlAs PR / InGaAIP AR	808 PR / 660 AF	Continuous	100 mW	1.9	0.028
4	RS + Alveolus[6]	90 RS / 60 Alveolus	30, 60 and 180[7]	NR, 40 mW/cm^2 and 30 mW/cm^2[8]	Contact	Scanning and punctual[9]	PR	HP and LP	810, 780 and 660[10]	Continuous	1.5 W HP / NR LP	NR	NR
5	RS + Alveolus[11]	57.14	133 (RS) / 100 (alveolus)	NR	NR (RS) / Contact (alveolus)	Scanning (RS) / Punctual (alveolus)	PR	GaAlAs	660 and 830[12]	Continuous	30 mW (RS) / 40 mW (alveolus)	3	0.07
6	RS + Alveolus Alveolar mucosa[5]	50	NR	2.5 W/cm^2	Non-contact	Scanning	PR and AR	InGaAIP	685	Continuous	40 mW	1.6	0.02

RS, root surface. NR, not reported. PR, prior replantation. AR, after replantation. HP, high power diode laser. LP, low power diode laser. [1], RS + at the entrance of alveolus for both LLLT groups PR and in alveolar mucosa of the alveolus only in Milk + LLLT 2 group AR. [2], RS (16.8), alveolus (4.2), alveolar mucosa (8.4). [3], RS (320 s), alveolus (60 s), alveolar mucosa (120 s). [4], PR for both LLLT groups and AR only in Milk + LLLT 2 group. [5], RS + inside of the alveolus PR and in alveolar mucosa of the alveolus AR. [6], only on RS for DR + HPL group, RS + alveolus for DR + LLT and DR + HPL + LLLT groups. [7], RS high power laser (30 s), alveolus (60 s), RS LLLT (180 s). [8], RS high power laser (NR), alveolus (40 mW/cm^2), RS LLLT (30 mW/cm^2). [9], RS high power laser (scanning), alveolus (punctual) RS LLLT (scanning + punctual). [10], RS high power laser (810), alveolus (780) RS LLLT (660). [11], palatal RS and middle third of the palatal surface of the alveolar wound. [12], 660 (RS) and 830 (alveolus).

Table 4 Summary of characteristics and results of the included studies showing significant differences between evaluated groups.

#	Evaluation methods	Evaluated characteristics	Significant results (time points – days)
1	Histological: H&E	External inflammatory root resorption	
		• Degree: absent, discrete (<25%), moderate (25-50%), intense (50-100%)	Milk + LLLT 1 < other groups (15, 30, 60)
		Ankylosis	
		• Degree: absent, discrete (<25%), moderate (25-50%), intense (50-100%)	NSD
		Inflammation	
		• Degree: absent, discrete (<25%), moderate (25-50%), intense (50-100%)	Milk + LLLT 2 > NSM, Milk (15); Milk + LLLT 1 < NSM, Milk, Milk + LLLT 2 (30); LLLT 1 < NSM
		Osteoclasts	
		• Degree: absent, discrete (<25%), moderate (25-50%), intense (50-100%)	Milk + LLLT 2 < Milk, Milk + LLLT 1 (15); Milk + LLLT 2 < other groups (30); Milk + LLLT 1 < other groups (60)
2	Histological: H&E and SR	Root resorption	
		• Area	PN > PNL, WM = WML, SM = SML; PN > other groups (15, 30)
		Replacement root resorption	
		• Area	NO (15); NSD (30)
		Ankylosis	
		• Perimeter	NO (15); NSD (30)
		Periodontal repair	
		• Perimeter	PNL > PN, WML = WM, SML > SM (15); PNL, WML, SML > PN, WM, SM (15, 30)
		Type I and III collagen deposition	
		• Area	PNL, WML, SML > PN, WM, SM (15, 30)
3	Histological: H&E	Angiogenesis	
		• Count the number of blood vessels	PNL, WML > PN, WM
4	Histological: H&E	Inflammatory root resorption	
		• Severity (scores): (0) none, (1) mild, (2) moderate, (3) severe	HPL, HPL + LLLT < DR, LLLT
		Replacement root resorption	
		• Severity (scores): (0) none, (1) mild, (2) moderate, (3) severe	HPL, HPL + LLLT < DR, LLLT
		Ankylosis	
		• Severity (scores): (0) none, (1) mild, (2) moderate, (3) severe	HPL, HPL + LLLT < DR, LLLT

		Periodontal repair	
		• Characteristics of the connective tissue (scores): (0) absence, (1) thin/disorganized tissue, (2) thick/organized tissue	HPL, LLLT, HPL + LLLT < IR and = DR
		• Reinsertion of periodontal fibers (scores): (0) absence, (1) fibers not inserted in cementum, (2) fibers inserted in cementum	HPL, LLLT, HPL + LLLT < IR and = DR
5	Histological: H&E Immunohistochemical: OPG, RANK, RANKL, TRAP	Replacement resorption	
		• Area (scores): (1) no resorption, (2) 0.1 to 50% of the area with resorption, (3) 51 - 99% of the area with resorption, (4) 100% of the area with resorption	NSD
		Inflammatory resorption	
		• Area (scores): (1) no resorption, (2) 0.1 to 50% of the area with resorption, (3) 51 - 99% of the area with resorption, (4) 100% of the area with resorption	NSD
		Ankylosis	
		• Perimeter (scores): (1) absence of ankylosis, (2) 0.1 to 50% of the perimeter with ankylosis, (3) 51 to 99% of the perimeter with ankylosis, (4) 100% of the perimeter with ankylosis	DR 30 + LLLT > DR 30
		Bone metabolism	
		• Immunostaining intensity (scores): (1) absent/negligible, (2) weak, (3) moderate, (4) strong	OPG: IR + LLLT > IR; RANK: DR 30, DR 45 > DR 30 + LLLT, DR 45 + LLLT; TRAP: IR + LLLT, DR 30 + LLLT > IR, DR 30 RANKL > RANK, OPG for both IR groups; OPG = RANK = RANKL for both DR 30 groups; RANK > RANKL for both DR 45 groups
6	Histological: H&E	Root resorption	
		• Area (%)	NSM > LLLT (15, 30, 60)
		Inflammatory cells	
		• Degree: slight (<20%), moderate (20-40%), intense (>40%)	Inflammatory cells and blood clot were present in both groups (15); NSM > LLLT (30, 60)
		Disorganization of odontoblasts cell layer and degenerating odontoblasts	
		• Degree: slight (<20%), moderate (20-40%), intense (>40%)	NSM > LLLT (15, 30); NR (60)
		Necrotic areas	
		• Degree: slight (<20%), moderate (20-40%), intense (>40%)	NR (15); NSM > LLLT (30, 60)

NO, not observed. NA, information not available. NSD, no statistical difference. H&E, hematoxylin and eosin. SR, Sirius red. OPG. RANK. RANKL. TRAP, tartrate-resistant acid phosphatase.

Table 5 The scores of quality assessment according to Animal Research Reporting In Vivo Experiment (ARRIVE 2.0) guidelines of the included studies.

#	Author/year	Itens																					
		Essential-10										Recommended Set											
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	T
1	Saito *et al.* (2011)	2	1	1	1	0	2	1	1	2	2	2	1	1	2	1	1	2	2	0	0	0	25
2	Vilela *et al.* (2012)	2	1	1	1	0	2	2	1	2	1	1	1	1	2	2	1	2	2	0	0	0	25
3	Carvalho *et al.* (2016)	2	1	1	1	0	2	1	1	2	1	2	1	1	2	1	1	2	2	0	0	2	27
4	Matos *et al.* (2016)	2	1	1	1	0	2	1	1	2	1	2	1	1	2	2	1	2	2	0	0	2	28
5	Matos *et al.* (2018)	2	1	1	1	0	2	2	1	2	2	2	1	1	2	2	1	2	2	0	0	2	29
6	Pereira *et al.* (2019)	2	2	1	1	0	2	2	1	2	1	2	1	1	2	2	1	2	2	0	0	2	29
	Category Score	12	7	6	6	0	12	9	6	12	8	11	6	6	12	10	6	12	12	0	0	8	
	Maximum Score Expected	12	12	12	12	12	12	12	12	12	12	12	12	6	12	12	12	12	12	6	6	12	
	Ratio Quality Score	1,00	0,58	0,50	0,50	0,00	1,00	0,75	0,50	1,00	0,67	0,92	0,50	1,00	1,00	0,83	0,50	1,00	1,00	0,00	0,00	0,67	

(1) study design, (2) sample size, (3) inclusion and exclusion criteria, (4) randomization, (5) blinding, (6) outcomes measure, (7) statistical methods, (8) experimental animals, (9) experimental procedures, (10) results, (11) abstract, (12) background, (13) objectives, (14) ethical statement, (15) housing and husbandry, (16) animal care and monitoring, (17) interpretation/scientific implications, (18) generalisability/translation, (19) protocol registration, (20) data access and (21) declaration of interests. (T) Total: represents total score obtained by each study out of a maximum of 39 points.

Table 6 Percentage publications (n = 6) in different categories per ARRIVE 2.2 checklist item.

	Grading		
Item	0 (%)	1 (%)	2 (%)
1	0	0	100
2	0	83	17
3	0	100	0
4	0	100	0
5	100	0	0
6	0	0	100
7	0	50	50
8	0	100	0
9	0	0	100
10	0	67	33
11	0	17	83
12	0	100	0
13	0	100	-
14	0	0	100
15	0	33	67
16	0	100	0
17	0	0	100
18	0	0	100
19	100	0	-
20	100	0	-
21	33	0	67

(0) Clearly inaccurate or not reported, (1) possibly accurate, unclear or incomplete, (2) clearly accurate

3 CONSIDERAÇÕES FINAIS

Apesar das limitações quanto à qualidade metodológica e ao risco de viés dos estudos incluídos nesta revisão sistemática, a resposta histológica da fotobiomodulação foi mais favorável quando comparada ao seu não uso. Estudos pré-clínicos apoiados em diretrizes devem ser incentivados a fim de identificar os melhores valores para cada um dos parâmetros do laser e para cada um dos efeitos pretendidos nos tecidos dentais. Este é o primeiro passo para que, no futuro, possam ser realizados ensaios clínicos que avaliem qual terapia deve ser recomendada na prática clínica para os casos de reimplante dentário tardio.

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