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ORIGINAL ARTICLE

Influence of different types of light on the response of the pulp tissue in dental bleaching: a systematic review

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Abstract

Objectives This systematic review (PROSPERO register: CRD42016053140) investigated the influence of different types of light on the pulp tissue during dental bleaching.

Materials and methods Two independent authors conducted a systematic search and risk of bias evaluations. An electronic search was undertaken (PubMed/Medline, Embase, The Cochrane Library, and other databases) until May 2017. The population, intervention, comparison, outcomes (PICO) question was: "Does the light in dental bleaching change the response of the pulp to the bleaching procedure?" The intervention involved pulp tissue/cells after bleaching with light, while the comparison involved pulp tissue/cells after bleaching without light. The primary outcome was the inflammation/cytotoxicity observed in pulp after bleaching.

Results Out of 2210 articles found, 12 articles were included in the review; four were in vivo studies (one study in dogs/others in human), and eight were in vitro studies (cell culture/with artificial pulp chamber or not). The light source used was halogen, light-emitting diode (LED), and laser. Only one in vivo study that used heat to simulate light effects showed significant pulp inflammation. Only two in vitro studies demonstrated that light influenced cell metabolism; one using halogen light indicated negative effects, and the other using laser therapy indicated positive effects. Given that animal and in vitro studies have been identified, there remain some limitations for extrapolation to the human situation. Furthermore, different light parameters were used.

Conclusions The effects of dental bleaching on the pulp are not influenced by different types of light, but different light parameters can influence these properties.

Clinical relevance There is insufficient evidence about the influence of different types of light on inflammation/cytotoxicity of the pulp.

Keywords Dental bleaching · Light activation · Low-level laser therapy · Pulp inflammation · Systematic review

Introduction

Studies have shown that hydrogen peroxide (HP) in bleaching gels can cause morphological alterations in the dental surface, such as the reduction of the enamel hardness and increased roughness [1, 2], in addition to histochemical alterations [3]. Furthermore, bleaching agents release reactive oxygen species (ROS) that reach the pulp tissue and cause cell damage [4, 5]. Histological analyses revealed severe alterations in the mandibular human incisors [6, 7], dog teeth [8], and rat molars [4, 9–12] following treatment with bleaching agents. Cell culture studies demonstrated changes in the pulp's cell morphology and viability [13, 14] as well as enzymatic activity [15]. These alterations were directly linked to tooth sensitivity [16].

Despite these results, dental bleaching remains quite popular among dental treatments, allowing patients with tooth stains to achieve esthetically pleasing smiles. This technique was initiated by Haywood and Heyman [17], when at-home bleaching with 10% carbamide peroxide (CP) was introduced in dentistry. Nonetheless, over time, in-office bleaching with higher concentrations of HP gained preference for promoting

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faster dental bleaching [18]. It is in these cases that major effects on the dental pulp have been reported [4].

In addition, to accelerate the bleaching process, protocols were proposed whereby bleaching was activated by different types of light [19, 20], such as halogen light, light-emitting diodes (LED), or LED/laser [21, 22]. Indeed, the light heats the bleaching gel, which generates a faster dissociation of HP and increases the release and penetration of ROS [21]. However, previous studies reported no difference in the efficacy of dental bleaching activated by light [23] and showed increased dentin sensitivity in patients undergoing this treatment [24]. Thus, there remain doubts regarding the effects of light on the pulp tissue.

One of the main factors that determine the effect of light on tissues is the wavelength of the emitted radiant energy (nm) [21], which differs in the visible spectrum or near the infrared or ultraviolet spectrum [25]. Light with a wavelength of 400–500 nm, previously applied to photo-activated resin composite systems, is also used to activate dental bleaching gels. However, this visible light may cause injury to the tissues due to ROS production via light irradiation [26]. Furthermore, the increase in the pulp temperature was reported after the use of halogen light, LED, or laser [25, 27]. However, lasers at a wavelength ranging from 790 to 980 nm emit a well-defined monochromatic light to reduce overheating [21]. Thus, several laser systems are still used during dental bleaching [28].

However, laser not only activates the bleaching gel but can also be used to reverse the negative effects caused by this esthetic procedure [29]. In these cases, the laser is employed as a therapy through low-intensity laser therapy (LLLT) [30] and is used to induce analgesia, anti-inflammation, and biomodulation [30, 31]. The primary effects of LLLT occur at the cellular and/or molecular level, later generating secondary effects, such as increased cellular metabolism, collagen synthesis, DNA and RNA modifications, local effects on the immune system, and increased angiogenesis [32, 33]. These properties suggest that LLLT could minimize the damage to the pulp resulting from oxidative stress stemming from the bleaching procedure [29].

Nevertheless, no consensus has been reached on whether light can alter the effects of dental bleaching on the pulp. The objective of this systematic review and meta-analysis was to elucidate if light influences the response of the pulp tissue to dental bleaching agents. The null hypothesis was that different types of light do not alter the effects of bleaching gels on the pulp tissue.

Material and methods

Registry protocol

The present study was structured based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist [34] and in accordance with models proposed in the literature [35–37]. Moreover, this study was registered in the international prospective register of systematic reviews (PROSPERO) (CRD42016053140).

Eligibility criteria

The eligible studies presented the following characteristics: (1) studies that compared the effects of the bleaching gel on the pulp tissue with and without the use of light or heat; (2) in vivo and in vitro studies; and (3) studies published in English. The exclusion criteria were (1) studies comparing only the effects of bleaching gel without light or only bleaching gel with light and (2) duplicated studies.

The population, intervention, comparison, outcomes (PICO) approach was used to address the following question: "Can the light (halogen/LED/laser) used in dental bleaching alter the bleaching-induced pulp tissue response?" In this process, the population was the pulp tissue or pulp cells after bleaching. The intervention was the pulp tissue or the cells in the pulp tissue after bleaching with light. The comparison was the pulp tissue or cells in the pulp tissue after bleaching without light. The primary outcome evaluated was the effects on the inflammatory response in the in vivo studies and the cytotoxicity or cell metabolism of the pulp tissue in the in vitro studies. The cell morphology and protein activity were considered secondary outcomes.

Search strategy and information sources

Two independent authors (F.B. and C.A.A.L.) conducted an electronic search until May 2017 based on the title and abstract of the articles according to the eligibility criteria in the following databases: PubMed/MEDLINE, Embase, and Cochrane Library. The search strategy was as follows: "((“dental pulp”[MeSH Terms] OR (“dental”[All Fields] and “pulp”[All Fields]) OR “dental pulp”[All Fields] OR “pulp”[All Fields]) and (“hydrogen peroxide”[MeSH Terms] OR (“hydrogen”[All Fields] and “peroxide”[All Fields]) OR “hydrogen peroxide”[All Fields])) OR ((“tooth bleaching”[MeSH Terms] OR (“tooth”[All Fields] and “bleaching”[All Fields]) OR “tooth bleaching”[All Fields]) and (“light”[MeSH Terms] OR “light”[All Fields]))."

To complement this review, a manual search in area-specific journals was carried out, including the following journals: *Journal of Endodontics*, *International Endodontic Journal*, *Journal of Dentistry*, *Operative Dentistry*, and *Lasers in Medical Science.* Identified studies in the electronic and manual searches were selected based on their titles and abstracts according to the inclusion criteria. In the second stage of the process, the full texts of the selected articles were reviewed. Any disagreements were resolved through discussion, and when necessary, a third reviewer (L.T.A.C.) was consulted.

Data collection and analysis

One author (F.B.) collected the data from the selected articles according to the relevant information and tabulated them for the analysis of results. Subsequently, a second author (M.O.G.) checked all of the collected information.

Quality assessment

Two investigators (F.B. and M.O.G.) independently assessed the methodological quality of the selected studies, according to their levels of evidence as proposed by the methodological index for non-randomized studies (MINORS) scale [38], with some modifications. The items of the MINORS scale were as follows: *clearly stated aim*, *contemporary groups*, *clear bleaching protocol*, *clear light protocol*, *justification of specimen size*, *statistical analysis*, *baseline equivalence of groups*, and *blinded analysis*. The item *baseline equivalence of groups* was considered only for the in vivo studies. The item *blinded analysis* was considered only for a descriptive analysis. Each item was scored using a 3-point scale: 0, content not reported; 1, content reported inadequately; and 2, content sufficiently reported [39]. Doubts and discrepancies between the investigators were discussed to enter consensus, and if not resolved, a third examiner (C.A.A.L.) was consulted.

Additional analysis

The kappa score was used to calculate the inter-reader agreement during the inclusion process for publication-evaluated databases. Any disagreements were resolved by discussion and consensus of all authors.

Results

Selected studies

The article selection process is presented in Fig. 1. During the search process, 2210 articles were found in the previously cited databases. After the first screening consisting of title and abstract evaluations, 14 articles were selected. These articles were subjected to full-text evaluation that resulted in the exclusion of two articles [40, 41]. Finally, 12 articles met the inclusion criteria and were included in this review [8, 13, 15, 19, 20, 22, 29, 42–46].

The assessed Cohen kappa coefficient value for the inter-investigator agreement was equal to 0.86 for PubMed, 0.89 for Embase, and 1.00 for the Cochrane Library search. These values indicate an almost perfect agreement among reviews on the selection of the studies according to the scale of Landis and Koch [47].

Characteristics of the included studies

Twelve studies were included in this systematic review. These studies were categorized into in vivo and in vitro studies (Table 1). A total of four in vivo studies were selected [8, 19, 20, 42]. Of these, one was performed in dog [8], and the others were performed on human premolar teeth. A total of eight in vitro studies were found in a systematic review [13, 15, 22, 29, 43–46] and were based on cell culture designs either associated [13, 22, 43, 44, 46] with an artificial pulp chamber or not [15, 29, 45]. The cell lines used were mostly odontoblast-like MDPC-23 cells [13, 15, 22, 43, 44, 46]. Other studies used the FP5 [29] or pulp incisor bovine cell lineage [45].

Most of the studies used bleaching gel with 35% HP [8, 13, 19, 22, 29, 42–44, 46]. Regarding the light source, the studies used halogen light [13, 20, 22, 43, 44], LED [19, 22], LED/laser [22], only laser [19], or LLLT [15, 29, 46]. The remaining studies used other heat sources [8, 42, 45] and were included in the systematic review for analyzing the effects of dental bleaching on the pulp tissue with heat simulating light-activated bleaching. These heat sources were a water bath at 50 °C [45], a shaped metal tip at 62 °C [8], and a bleaching instrument at 46 to 51 °C (Union Broach-Indiana University) [42].

The characteristics of the light used in the 12 selected studies were also different. The dose of irradiance of the halogen light ranged from 430 to 500 mW/cm^2 [13, 20, 22, 43, 44], while that of the LED light was 500 mW/cm^2 in one study [22], and was not mentioned in the other LED study [19]. In the LED/laser hybrid systems, the range was 120 mW/cm^2 [22]. The fluence of laser used in LLLT ranged from 4 to 15 J/cm^2, during 4 to 1200 s [15, 29, 46]. The wavelength range of the halogen light and the LED light was described in only one study as 450–500 nm and 440–480 nm, respectively [22]. Regarding the laser, the wavelength ranged from 660 to 808 nm in four studies [15, 22, 29, 46] and was not mentioned in one study [19]. Only three studies [13, 22, 44] provided information on the distance of the light source application, which ranged from 5 to 10 mm.

Table 2 summarizes the results of the analysis performed in each study included in this review. The inflammatory response and cell metabolism are described in the following section. The results of other parameters evaluated in the selected studies, such as pulp tissue disorganization, reactionary dentine formation, protein analysis, and cell morphology analysis, can be found in Table 2.

Inflammatory response

The inflammatory response to the bleaching procedure was described in three in vivo studies [8, 20, 42]. In two of these studies, the bleaching gel alone did not cause changes in the pulp tissue [20, 42], while the activation of the bleaching gel

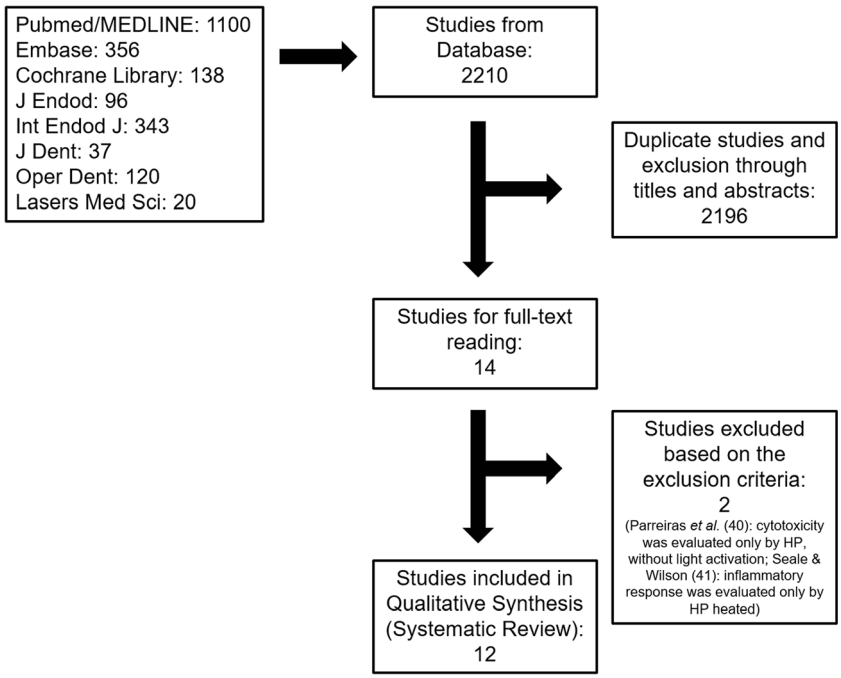

Fig. 1 Flow diagram of the search strategy of the systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines

caused significant alterations in one study [42]. In the third study [8], the bleaching gel generated changes in the pulp which were not intensified by heat.

Cell metabolism

The cell metabolism was described in seven in vitro studies which were categorized according to the aim of the use of light: to activate the bleaching gel [13, 22, 43–45] or as a laser therapy [15, 29, 46]. When used to activate the bleaching gel, cytotoxicity was enhanced by light in one study [44] and was not enhanced in three studies [13, 22, 43]. When used as a laser therapy, the light was incapable of modulating positively the cell metabolism in two studies [15, 46] but was able to compensate for the cytotoxic effects in one study [29].

Quality assessment

Table 3 summarizes the results of the bias risk assessment. None of the studies scored the highest score possible or reported the *justification for sample size*. Among the studies that performed descriptive analysis or reported scores, only one indicated that a blind operator performed the analysis. Three studies did not perform statistical analysis. However, a low risk of bias was found in the *clearly stated aim*, *clear bleaching protocol*, and *clear light protocol* (Fig. 2). The high risk of bias was observed for specific items including the *justification of sample size*, *baseline equivalence of groups*, and *blinded analysis*.

Discussion

To our knowledge, this is the first systematic review that investigated the influence of different types of light on the response of the pulp tissue to dental bleaching. Only studies including direct comparison were selected, which considered the effects of dental bleaching with and without the use of light on the pulp tissue. The aim of this review was to clarify the effects of the different types of light used during dental bleaching on the pulp tissue. The null hypothesis that the different types of light do not alter the effects of bleaching gels on pulp tissue was accepted.

Different light sources have different mechanisms of action that are not yet completely understood. According to Buchalla and Attin [21], the mechanism of action most likely used in the different types of light to activate bleaching gels occurs by thermocatalysis. The increase in temperature causes the release of ROS from HP, thus increasing the speed of action and the effectiveness of the bleaching process [21]; this is because part of the light is absorbed by the bleaching gel and converted to heat [21].

The few in vivo studies presented in this review have used widely different protocols and concentrations of bleaching gels, which made it difficult to discuss them clearly. Two of these studies did not perform any statistical analysis, suggesting a high risk of bias. However, several points can be still considered in the discussion. Two studies showed significant changes in the pulp after dental bleaching, according to the performed analysis, but only one study indicated the influence of light on the bleaching effect. Robertson and Melfi [42], nonetheless, noted a significant response of the pulp tissue

Table 1 Characteristics of the studies included in the review

In vivo studies – activation of bleaching gel

Authors	Experimental model	Dental bleaching protocol	Type of light	Light Protocol	Groups	Analysis period
Kina et al. [20]	Human premolar teeth	38% HP, 3 × 10 min	HL (480 mW/cm^2)	2 × 1.5 min, 2 min interval between applications, to each application of HP (desensitizing gel for 5 min after HP)	G1, HP + HL (n = 10); G2, HP (n = 10); G3: no treatment (control)	(n = variable) 2 at 15 days
Caviedes-Bucheli et al. [19]	Human premolar teeth	38% HP: 15 min; 35% HP: 3 min; 25% HP: 20 min	Infrared laser diode; LED	Infrared laser diode (35% HP), 3 min; LED (25% HP), 20 min	G1, control group; G2, 38% HP; G3, 35% HP + Laser; G4, 25% HP + LED	(n = 10) 10 min after bleaching session
Seale et al. [8]	Dog canine teeth	35% HP, 30 min, 1×/week, 4 week	Heat, shaped metal tip with 62 °C	1 s contact and removed for 3 s/30 min	G1, 35% HP; G2, HP + Heat; G3, Heat; G4, Control Group	(n = 2) 3, 15 and 60 days
Robertson and Melfi [42]	Human premolar teeth	35% HP: 5 min, two appointmentsspaced four days apart	Bleaching instrument (Union Broach-Indiana University) - 46 to 51 °C	5 min, two appointments, spaced 4 days apart	G1, Control group; G2, Heat + 35% HP; G3, Heat + saline solution; G4, 35% HP	(n = 7) 4 days after second appointment

In vitro studies – activation of bleaching gel

Authors	Experimental model	Dental bleaching protocol	Type of light	Light Protocol	Groups	Analysis period
Goncalves et al. [22]	Artificial pulp chambers/bovine incisors/MDP-C-23 odontoblast-like cell line	35% HP/ 3x15min/1× week/ 3 weeks	HL (500 mW/cm^2–450 and 500 nm); LED (500 mW/cm^2–440 and 480 nm); LED/Laser (120 mW/cm^2–470 nm - three infrared lasers - 808 nm - power of 0.2 W)	HL: 20 s at each application, distance of 5 mm from the surface; LED: three applications of 30 s/session, distance of 5 mm; LED/Laser: three applications of 3 min/session	(n value in analysis in Table 2) G1, HP; G2, HP + HL; G3, HP + LED; G4, HP + LED/Laser; G5, Ac + HP; G6, Ac + HP + HL; G7, Ac + HP + LED; G8, Ac + HP + LED/Laser	T0, before bleaching gel; T1, 30 min after the first bleaching session; T2, 30 min after the second bleaching session; T3, 30 min after the third bleaching session
Coldebella et al. [43]	Artificial pulp chambers/bovine incisors/MDP-C-23 odontoblast-like cell line	35% HP/ 5 × 15 min consecutive	HL (power of 430 mW/cm^2)	20 s to each application of HP	(n value in analysis in Table 2) G1, 35% HP; G2, 35% HP + HL; G3, Control (no treatment)	24 h
Dias Ribeiro et al. [44]	Artificial pulp chambers/bovine incisors/MDP-C-23 odontoblast-like cell line	35% HP/ 2 × 15 min consecutive	HL (500 mW/cm^2 - light dose of 10 J/cm^2)	20 s to each application of HP, distance of 10 mm	(n value in analysis in Table 2) G1: 35% HP; G2: 35% HP + HL; G3: HL; and G4: Control (no treatment)	24 h
Trindade et al. [13]	Artificial pulp chambers/bovine incisors/MDP-C-23 odontoblast-like cell line	35% HP/ 3x15min consecutive	HL (power of 430 mW/cm^2)	20 s to each application of HP, distance of 10 mm	(n value in analysis in Table 2) G1, 35% HP; G2, 35% HP + HL; G3, control (no treatment)	24 h
		1.25–15% HP/			(n = variable)	During 1 to 30 min

Table 1 (continued)

Bowles & Thompson [45]	Cell culture, pulp incisors of calves	30 min	Heated by immersing the samples in a water bath at 50 °C	Heat + HP: 2.5% HP- 7.5 min, 7.5% HP - 15 min, and 15% HP- 30 min. Only heat treatment: 1–30 min	8 groups, 1–30 min at 50 °C; 5 groups: 1.25–15% HP; Heat + HP, 2.5% HP - 7.5 min, 7.5% HP - 15 min, and 15% HP - 30 min	

In vitro studies analysis – LLLT

Authors	Experimental model	Dental bleaching protocol	Type of light	Light Protocol	Groups	Analysis period
Lima et al. [15]	Cell culture: MDPC-23 odontoblast-like cell line	10% CP diluted to 0.01% of CP (approximately 2.21 μg of HP) 1 h	LLLT (780 nm - 0.04 W - different energy dose: 4, 10 and 15 J/cm^2)	4 J, 300 s; 10 J, 800 s; 15 J, 1200 s	(n value in analysis in Table 2) G1-Negative control: any treatment; G2-Positive control: HP; G3, LLLT 4 J; G4, LLLT 10 J; G5, LLLT 15 J; G6, HP + LLLT 4 J; G7, HP + LLLT 10 J; G8, HP + LLLT 15 J	24 h after irradiation
Lima et al. [46]	Artificial pulp chambers/bovine incisors/MDP-C-23 odontoblast-like cell line	35% HP/ 3x15min	LLLT (780 nm - 0.025 W - different energy dose: 4, 10 and 15 J/cm^2)	4 J, 300 s; 10 J, 800 s; 15 J, 1200 s	(n value in analysis in Table 2) G1-Negative control: any treatment; G2-Positive control: HP; G3, LLLT 4 J; G4, LLLT 10 J; G5, LLLT 15 J; G6, HP + LLLT 4 J; G7, HP + LLLT 10 J; G8, HP + LLLT 15 J	24 h after irradiation
Dantas et al. [29]	Cell culture, FP5 cell lineage	40 min of dilution of 35% HP (conditioned medium: 0.2 g of 35% HP per 1 mL of culture medium, for 30 min, and diluted to 10^{-3})	LLLT (diode laser, potency 40 mW)	RL1: 660 nm, 4 J/cm^2, 4 s; RL2: 660 nm, 6 J/cm^2, 6 s; RL3: 660 nm, 10 J/cm^2, 10 s; NIR1: 780 nm, 4 J/cm^2, 4 s; NIR2: 780 nm, 6 J/cm^2, 6 s; NIR3: 780 nm, 10 J/cm^2, 10 s	($n = 6$) PC: Cells in fresh medium and non-irradiated. Cells grown in conditioned medium: NC: non-irradiated; RL1; RL2; RL3; NIR1; NIR2; NIR3	0 and 24 h

HP hydrogen peroxide, *HL* halogen light, *LED* light emitter diode, *Ac* 37% phosphoric acid gel, *LLLT* low-level laser therapy, *CP* carbamide peroxide, *PC* positive control, *NC* negative control, *RL* visible red laser, *NIR* near infrared laser

only with the use of heated bleaching gel, which is in contrast to the results of Kina et al. [20] who did not observe any alterations even when using a higher concentration and longer application time of the bleaching gel.

A study demonstrated that raising the temperature by 5 °C is harmful to the pulp [43]. Robertson and Melfi [42] used a bleaching instrument at 46 to 51 °C, which may have raised the temperature to damage the pulp tissue. However, one should take into account the time at which the pulp tissue was analyzed in each study. In the study by Kina et al. [20], the teeth removed at 2 days after treatment presented discrete changes. Therefore, it is possible that if more teeth were extracted in short periods, more significant changes could be observed. In the study with dogs [8], the changes were observed in the HP group with or without heat; they appeared in the initial periods (at 3 days) and were reversible afterwards. Studies on rat molars also demonstrated the reversibility of the severe changes in the pulp after dental bleaching over time [10, 11].

In the in vivo studies, groups that evaluated only the effect of light/heat on the pulp indicated that light or heat by itself does not damage the tissue. Thus, their results suggested that the greatest consequence to the pulp response stems from the presence of HP and not from heat. Interestingly, in the study by Caviedes-Buchelli et al. [19], the bleaching gel did not increase the expression of substance P (SP), a neuropeptide related to the sensory response [48], but SP was significantly increased in the presence of light.

The in vitro studies constituted the bulk of the studies included in this review. In three of four studies that reported cytotoxicity after the activation of dental bleaching, the light source used did not influence the generated damage [13, 22, 43]. In one study [44], light increased cytotoxicity to the pulp cells. In this case, the authors used a halogen light source, similarly to that previously used in Trindade et al. [13]. However, Trindade et al. [13] performed a further application of the bleaching gel. Thus, it can be speculated that the greater damage generated from the bleaching gel outweighed the effects of the light. In the study by Bowles and Thompson [45], which used low concentrations of HP, the heating of the bleaching gel caused a significant reduction of the enzymatic activity in the pulp tissue. Thus, the use of a temperature of 50 °C should be considered.

When analyzing the light parameters that increased the bleaching gel cytotoxicity in the pulp [44], we found that the use of halogen light at 500 mW/cm^2, with a dose of 10 J/cm^2, and two applications of HP 35% for 20 s each was associated with the highest response of the pulp tissue. However, the use of halogen light cannot be generalized as a response enhancer of the pulp tissue to bleaching, because this light type did not intensify the damage to the pulp in other studies [13, 22, 43]. Factors such as wavelength, distance from the bleaching gel, power output at exit window, irradiance, and time of exposure to light might influence the effects of light on the tissues or bleaching gel [21, 49]; however, these parameters were not fully provided in all studies included in this review.

The interaction between the light and the bleaching agent is not only influenced by the light parameters but also by the colorant present in the bleaching gel [50], which hinders the reasonable comparison between the effects of each type of light on the pulp tissue. Therefore, further studies investigating these variables and clarifying the possible harmful effects of light on the pulp tissue are necessary. Moreover, a previous systematic review indicated that the activation of the bleaching gel did not increase its efficiency [51], thus making its use unjustified.

Three in vitro studies evaluated the influence of LLLT. Light at 660 or 780 nm (10 J/cm^2 for 10 s) increased the cell metabolism in only one study [29]. The effects of LLLT were also associated with light-related parameters, including among others the energy, fluence, wavelength, and distance of light source application, which might differently influence the biological reactions [52, 53]. When using a near-infrared laser (780 nm) with 4, 10, and 15 J/cm^2 and for 300, 800, and 1200 s, respectively, Lima et al. [15, 46] did not observe any beneficial effects of LLLT on cell metabolism despite the fact that the alkaline phosphatase activity increased with the use of a lower LLLT intensity (4 J/cm^2) [15]. Moreover, they noted a more significant damage when using 15 J/cm^2 after HP [46], which is supported by a previous study reporting that low-power light seems to generate ROS [54]. High rates of fluency were also related to inhibitory effects on fibroblasts, and the use of low fluency was also indicated [55]. For Moshonov et al. [56], a laser with lower energies should be the choice in clinical practice to obtain more favorable results.

Interestingly, one of the protocols used by Lima et al. [15] was similar to that used in Dantas et al. [29] (4 J/cm^2, 40 W, and 780 nm), except that it had a higher exposure time. A previous study showed that better results on the induction of fibroblast proliferation were obtained with a shorter time of laser application [55], which corroborates the positive results reported by Dantas et al. [29]. Regarding the wavelength, a clinical study demonstrated that irradiation at a wavelength of 810 nm significantly potentiated the ability of LLLT to reduce tooth sensitivity after bleaching than using laser at a wavelength of 660 nm [30]. Thus, the different light parameters used by the studies included in this systematic review have different effects on the pulp tissue. We observed that LLLT, with specific parameters, may have the potential to minimize the pulpal damages caused by bleaching [29]. However, an adequate and safe protocol for the use of LLLT in the clinic has yet to be determined.

The thickness of the teeth is known to be variable in both animals and humans, which may influence the effects of bleaching on the pulp tissue [6, 20]. Likewise, the thickness of the enamel and dentin can also influence the effects of light

Table 2 Summary of results found for each selected study

In vivo studies analysis – activation of bleaching gel					
Authors	Inflammatory cell response	Pulp tissue disorganization	Reactionary dentine formation	Radioimmunoassay	Outcome
Kina et al. [20]	G1, one specimen: some dilated and congested blood vessels, discrete inflammation. G2 and G3: no inflammation	G1 and G2: Two and one specimen showed disorganized odontoblastic layer, but normal pulp core	G1 and G2: one specimen each showed mild hard tissue deposition underneath the region of the buccal tooth surface	NR	38% HP with or without HL: not cause damage to the pulp tissue of sound human premolar teeth
Caviedes-Bucheli et al. [19]	NR	NR	NR	*Substance P - G1: = 756.94; G2: = 760.23; G3: # 1054.66; G4: § 1649.52	Activated tooth-bleaching systems increase significantly SP expression in human dental pulp
Seale et al. [8]	HP and HP + Heat – 3d: dense inflammation, with characteristic of acute inflammation; 15d: marked inflammatory response; 60d: resolution of the inflammation. Heat - 3, 15 and 60d: no changes and comparable with control	HP and HP + Heat - 3d: change of odontoblastic layer, and presence of odontoclastic activity; 15d: flattening and eventual obliteration of the odontoblastic layer, and odontoclastic activity continued; 60d: repair of the areas of internal resorption, odontoblasts had not yet returned to normality, and vascular damage had disappeared. Heat - 3, 15 and 60d: no changes and comparable with control	HP and HP + Heat – 3d: pulp tissue more apical showed calciotraumatic line and poor dentine; 60d: newly formed dentin. Heat - 3, 15 and 60d: no changes and comparable with control	NR	HP: produces severe, but apparently reversible, destructive changes in the pulps of dogs; Heat: no deleterious effect on the pulp of dogs; not intensify the damage caused by the HP
Robertson & Melfi [42]	*G1: = no inflammation; G2: # four specimens - slight inflammation; G3: = five specimens - no inflammation; G4: =# three specimens - inflammation	NR	NR	NR	HP + heat: significant responses in superficial pulp tissues; Heat + saline solution or HP alone: not cause a significant response
In vitro studies analysis – activation of bleaching gel					
Authors	Penetration of HP	Cell Metabolism Analysis	Cell Morphology Analysis	Protein analysis	Outcome
Goncalves et al. [22]	(*n* = 12) *T1, T2, and T3: =; T0: #. Light: G4 - # highest values at T1; G2: # lowest average at T2; G7 and G8: # increased at T1 with respect to those without light. Ac: # increased in T1 in G7, and in T2 in G6	(n = 10) *G4 X G8: # pretreating decreased. Only Ac: = cell metabolism. HP with or without light: # reduction	(*n* = 2) HP with or without light or pre-etching of the enamel: cell death, detachment from the glass substrate, few remaining cells with rounded, thin, and short cytoplasmic extensions	NR	HP + light sources and/or Ac: few significant changes in color, transenamel and transdentinal penetration of HP, or cytotoxicity and cell morphology
Coldebella et al. [43]	NR	(n = 6) **G1: # decreased 62.09%; G2: # decreased 61.83%	(n = 1) G1 and G2: rounded shape and few thin and short cytoplasmic processes, presence of fragments of the cytoplasmic membrane of lethality damaged cells, smaller number of cells	(*n* = 3) **Total protein dosage - G1: # decreased 93.13%; G2: # decreased 91.80%	35% HP, with or without HL, causing toxic effects to the cells
Dias Ribeiro et al. [44]	NR	(n = 7) G1, G2, and G3: decreased 31.7%, 41.6%, and 11.5% (# comparing G2 X G3 as well as G2 X G4)	(n = 3) G1 and G2: presented a smaller number of cells adhered to dentin, of small-sized, rounded morphology and thin or no cytoplasmatic prolongations, large number of membrane cell fragments	NR	HP with light presented cytotoxic effects: direct damage to odontoblasts and decrease of metabolic activity

Table 2 (continued)

Trindade et al. [13]	NR	(n = 7) **G1: # decreased 92.03%, G2: # decreased 82.47%	(n = 3) G1 and G2: smaller number of viable cells remained adhered to the glass substrate, these cells were small-sized and presented rounded morphology and few or no cytoplasmatic prolongations in membrane	NR	35% HP caused toxic effects on cultured odontoblast-like cell MDPC-23; these effects were not increased with HL
Bowles & Thompson [45]	NR	NR	NR	**Heat - ICD: = unaffected. Heat 5 min - G6-PDH: # losing half of activity. Heat 30 min - Aldolase, ALP, MDH, PHI: # 80% of initial activity; SGOT: = retained about 65% of its initial activity; G6-PDH: less than 5% of initial activity. HP - # higher concentrations inhibited all enzymes. 15% HP - PHI: = retained 90% of its initial activity; ALP, MDH: # retained 40% and 30%. HP above 5% - G6-PDH, ICD: # completely destroyed. HP + Heat - 2.5% HP/7.5 min - G6-PDH, ICD: # completely destroyed; = PHI and SGOT retained more than half of initial activity; Others: # severe reduction. 7.5% HP/15 min - # reduced the activity of all enzymes, = except PHI. 15% HP/30 min: # only SGOT and aldolase retained any residual activity	HP inhibited pulpal enzymes, especially when heated
In vitro studies analysis – LLLT					
Authors	Penetration of HP	Cell Metabolism Analysis	Cell Morphology Analysis	Protein analysis	Outcome
Lima et al. [15]	NR	(n = 10) **Bleaching agent: # decreased; Laser irradiation: there was no alteration	NR	(*n* = 10) **ALP activity - Bleaching agent: # reduced; Laser 4 J/cm2: # increased with or without CP	0.01% CP: reductions in odontoblast-like cells metabolism and in ALP activity; LLLT (4, 10, and 15 J/cm^2) is incapable of modulating cell metabolism positively; however, the dose of 4 J/cm^2 increased the ALP activity after dental bleaching
Lima et al. [46]	NR	(n = 10) **HP: # reduction 40–60%; LLLT + HP: # not capable of reversing the cytotoxic effects by HP; *G8: # higher reduction; Groups without HP: similar levels of cell metabolism	NR	(n = 10) **ALP activity - HP with or without laser: # reduction; LLLT: not promoted alteration … (*n* = 6)	HP caused a reduction in cell metabolism, in the activity of ALP, and in the gene expression of COL-I, ALP and FN. LLLT was not capable of influencing the cell metabolism,

Table 2 (continued)

				**qPCR: expression of ALP and COL-I - HP: # reduced; Laser: not modulate the expression of genes. Expression of FN - HP: # negative influence; Laser: # decreased groups without HP, and not reversed the negative effects of HP	ALP activity and gene expression of ALP and COL-I. LLLT promotes an inhibitory effect on FN gene expression on odontoblasts without exposure to bleaching agents, in all doses after 24 h of the irradiation
Dantas et al. [29]	NR	PC X NC: # PC higher. 0 h: RL = NC, except for the RL3 that was similar to PC. **24 h: all groups: # increased; RL: # higher NC; however not reach the values of PC. NIR: NIR1 = NC; NIR2 and NIR3 = NC at 0 h, and # higher in 24 h; NIR3 = PC in 24 h	NR	NR	35% HP is cytotoxic to human cultured fibroblasts; LLLT emitting in the visible red (660 nm) was able to compensate the cytotoxic effects of substances released by 35% HP; LLLT emitting in the near infrared (780 nm) was able to compensate the cytotoxic effects of 35% HP

NR not related, *HP* hydrogen peroxide, *HL* halogen light, *Ac* 37% phosphoric acid gel, *ICD* isocitrate dehydrogenase, *G6-PDH* glucose 6-phosphate dehydrogenase, *ALP* alkaline phosphatase, *MDH* malate dehydrogenase, *PHI* phosphohexose isomerase, *SGOT* serum glutamic-oxaloacetic transaminase, *LLLT* low-level laser therapy, *CP* carbamide peroxide, *qPCR* real-time polymerase chain reaction, *COL-I* type I collagen, *FN* fibronectin, *PC* positive control, *NC* negative control, *RL* visible red laser, *NIR* near infrared laser

*The symbols =, #, and § indicates statistical difference among groups

**The symbol # indicates statistical difference when compared with control

Table 3 Quality assessment of included studies based on adapted methodological index for nonrandomized studies (MINORS)

Quality criteria	Kina et al. (20)	Caviedes-Bucheli et al. (19)	Seale et al. (8)	Robertson and Melfi (42)	Gonçalves et al. (22)	Coldebella et al. (43)	Dias Ribeiro et al. (44)	Trindade et al. (13)	Bowles and Tompson (45)	Lima et al. (15)	Lima et al. (46)	Dantas et al. (29)
Clearly stated aim	2	2	2	2	2	1	2	1	2	2	2	2
Contemporary groups	0	0	2	0	2	2	2	2	1	2	2	2
Clear bleaching protocol	2	2	2	1	2	2	2	2	2	2	2	2
Clear light protocol	2	1	2	1	2	2	2	2	2	2	2	2
Justification of sample size	0	0	0	0	0	0	0	0	0	0	0	0
Statistical analysis	0	2	0	1	1	1	2	2	0	2	2	2
Baseline equivalence of groups	0	0	0	0	–	–	–	–	–	–	–	–
Blinded analysis	2	–	0	0	0	0	0	0	–	–	–	–
Total score	8	7	8	5	9	8	10	9	7	10	10	10

0, not reported; *1*, reported but inadequate; *2*, reported and adequate

on the pulp tissue. For example, a smaller thickness provides less protection to the pulp tissue from the heating caused by light in animals [21], while a greater thickness of the teeth necessitates a larger wavelength of light in the LLLT in order for the treatment to reach the target tissue effectively [21]. Moreover, most of the studies included in this systematic review were in vitro studies, and used bovine teeth, which, even if prepared at a similar thickness of human teeth [13, 22, 43, 44, 46], would still lack vital components such as dentinal fluid and cytoplasmic extensions that can influence the pulp response to bleaching [13, 20]. Thus, as animal/in vitro studies are identified, the findings of the present systematic review cannot be extrapolated to the human situation.

The primary outcome of this review was the effect of light on the inflammation or cytotoxicity of the pulp as a result of bleaching [4–13, 15, 22, 57]. However, the secondary outcomes indicated that other factors were also affected by light associated with bleaching, even in studies where no inflammation/cytotoxicity was reported or analyzed [15, 19, 45, 46]. However, given that the effects of bleaching on the pulp tissue are still poorly understood, the secondary outcomes of this review indicated that further studies involving pulp alterations other than the inflammatory response or cellular metabolism are still warranted.

In summary, few studies have previously evaluated the effects of bleaching gel associated with light, particularly laser

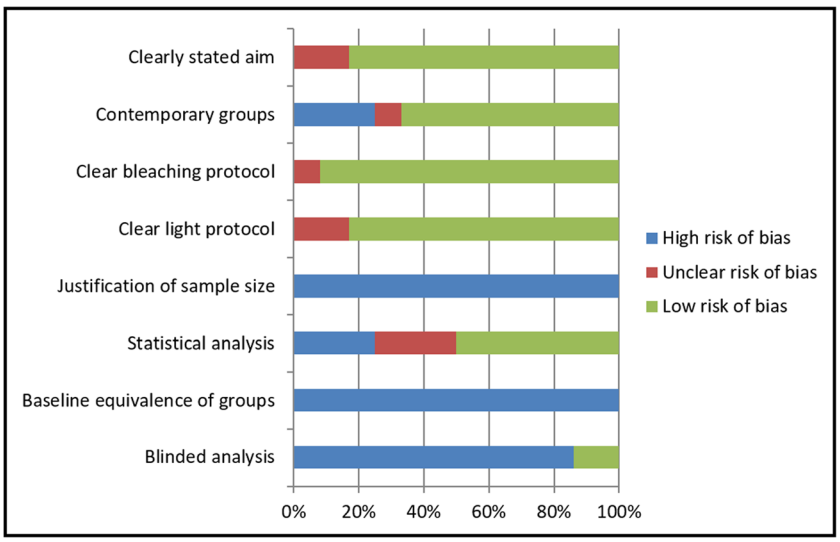

Fig. 2 Assessing the risk of bias in the included studies according to the modified methodological index for non-randomized studies (MINORS), by the percentage of the scores attributed to each evaluated study

therapy, on pulp tissue. Although this review included 12 articles, these had tremendous variations in relation to the bleaching gel and light source used. Thus, further studies should be performed, especially in vivo, to examine more clearly the influence of light during the dental bleaching procedure. Moreover, in order to obtain acceptable clinical protocols, future studies must take into consideration the importance of providing all details on the light parameters used.

Conclusion

Limited evidence suggests that the different parameters of light can influence its effects on the pulp tissue. However, in general, the parameters of different lights do not influence the effects of dental bleaching on pulp inflammation or cytotoxicity.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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