Review Article

Preemptive and Preventive Systemic Anti-Inflammatory Drugs for Dental Sensitivity Control in-Office Bleaching

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Abstract

Dental sensitivity after in-office bleaching is the most common adverse effect produced by the hydrogen peroxide (H2O2) bleaching agents. Inflammatory processes induced by chemical mediators and direct activation of ion channels by H2O2 and oxidative products have been related to this side effect. However, current data suggest that production and release of inflammatory mediators may not play an important role in the development of tooth sensitivity induced by bleaching. Possible mechanisms of dental sensibility after in-office whitening are discussed in this literature review.

ABBREVIATIONS

TRPA1: The Action Potential Transient Receptor; TNF-A: Tumor Necrosis Factor-Alfa; ATP: Adenosine Triphosphate; COX-2: Cycloxygenase-2; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

INTRODUCTION

Treatment of discolored vital teeth using peroxide bleaching agents have a high success rate [1] and can be performed following either at-home or in-office bleaching protocol [2]. Although the at-home bleaching treatment is the most popular one, many patients do not want to use a bleaching tray or do not want to wait several weeks to achieve the results [3,4] In this scenario, the in-office bleaching procedure is frequently request.

The in-office bleaching allows the control by the professional, avoids the exposition of soft tissues, reduces the risk material ingestion, reduces the incidence of gingival irritation and it has the best potential for immediate results [5,6]. However, some adverse effects have been widely reported in the literature, such as the sensitivity induced by in-office protocol [7-12]. In certain cases, the tooth sensitivity is so severe that some patients discontinue the treatment [13]. In attempt to explain this clinical situation, some current studies in molecular biology, have been carried out to elucidate this adverse event.

SENSITIVITY TO THE TOOTH BLEACHING

Sensitivity to the bleaching procedure seems to be the result

from the facilitated passage of H_2O_2 through enamel and dentin toward the pulp tissue [14] causing an inflammation process in this connective tissue [1]. Although the discomfort could be intense and responsible for the withdrawal of treatment in some cases, [15] this pain is usually mild and disappears within 48 hours after the bleaching treatment [10,15-17].A systematic review by Kielbassa et al., 2015 [18] about tooth sensitivity during and after vital tooth bleaching shows that tooth bleaching sensitivity continues to be an unsolved phenomenon that needs further follow-up with high quality studies. Despite this, some events that occur during and immediately after the procedure can clarify this side effect.

Free radicals, oxidation and sensitization of the dentin-pulp complex

H_2O_2 is a free-radical derived from oxygen, thermally unstable, often found within the cells due intracellular reactions in some organelles, mainly mitochondria [19]. This chemical agent exhibit oxidative properties, [20-22] and in high concentrations have been used for treating discolored teeth [23].The main mechanisms responsible for the toxicity of peroxide compounds is associated with oxidative reactions and the consequent cellular damage caused by free-radicals [24]. Despite the well-known ability of free radicals to degrade the complex organic molecules that are responsible for tooth staining, [22] the exact mechanisms by which the teeth are whitened are not fully understood.

Besides, it has been reported that low molecular weight molecules of H_2O_2 are capable of diffusing through the enamel

and dentin and reach the pulp tissue [19]. Consequently, the H_2O_2 and their degradation products can cause damage to pulp cells, especially in the odontoblast layer underlying the dentin [25]. According to Wataha et al., [26] the risk caused by dental materials on the dentin-pulp complex depends on the ability of the components to diffuse through enamel and dentin, reaching the dental pulp. Several studies have shown the diffusion process, [27,28] which is facilitated by their low molecular weight as well as its ability to denature tissue proteins [29]. Moreover, high concentrations of free-radicals in the bleaching gels increase the diffusion of H_2O_2 through the enamel and dentin [24].

Ion channels and pulp sensitivity

Odontoblasts can act as sensory cells that modulate nociceptive transduction in dental pulpal nerve fibers. For instance, odontoblasts layer express mechanosensitive, [30] acid-sensitive, [31] and thermosensitive transient receptor potential [32-34] ion channels. When opening of these cation-permeable ion channels cause a membrane potential producing inward currents. Odontoblasts also express voltage-gated Na+ channels [35]. However, the role of odontoblasts in dental sensitivity and the underlying cellular and molecular mechanisms for dental nociception initiation and transduction have not been fully established.

According to Markowitz et al., [15] dental sensitivity induced by bleaching gels can result from a direct activation of neuronal receptors by H_2O_2. The action potential transient receptor (TRPA1) could be the responsible for the pain induced by H_2O_2. Peroxides and other oxidizing agents can oxidize cysteine residues in TRPA1 ion channel, resulting on the receptor activation [36], and triggering pain. Besides, the intracellular reaction between peroxide and iron ions, producing oxygen radicals by the Fenton reaction, could also contribute to the activation of the cysteine residues into TRPA1 channel [37]. In fact, a long-term treatment with the tumor necrosis factor-alfa (TNF-α) used as an hypotonicity-inductor membrane stretch, resulted in up-regulation of TRPA1 expression in human odontoblast-like cells, [38] indicating that this ion channel could be activated by a variety of inflammatory cytokines, making it a gatekeeper of inflammation [39].

Furthermore, it has been demonstrated that adenosine triphosphate (ATP) is released from the dental pulp upon external cold or mechanical dentin stimulation [40]. Moreover, odontoblasts may mediate nociceptive signaling via ATP release through the connexin [41,42] and pannexin channels [40,43]. ATP in turns can activate inotropic purinergic P2X3 receptors expressed in dental pulpal nerve fibers [44] and intercellular odontoblast neuron communication [45]. These findings support the importance of ATP signaling in mediating dentin hypersensitivity and dental pain [46].

Pulp swelling and necrosis

Pain is the result of activation of sensory structures called nociceptors [47,48]. Most of the nociceptors involved in the inflammatory pain process are polymodal (sensitive to different kind of stimuli) with a high excitability threshold. The ability to distinguish pain sensations resulting from pressure, heat or cold must involve decoding of noxious signals within the central nervous system [49].

It is believed that pain of dental pulp is a consequence of the inflammatory response [50,51] due to tissue damage [52]. Hence, vasodilation and increased vascular permeability occurs, resulting in edema formation and increased internal pressure. This stimulates nociceptors, which in turn triggers the pain [53]. It has been reported that the use of H_2O_2 produce a transient inflammatory reaction in the pulp tissue14 and, as a consequence, the release of bradykinin [54] and substance P [55]. These two substances are known to be involved in pain and inflammation processes of dental pulp [55,56]. Moreover, some biological active mediators derived from the arachidonic acid could contribute to this process, since the cycloxygenase-2 (COX-2), an important enzyme in the inflammatory pathway, is up-regulated in inflamed tissues [57,58], and it has been shown to play important roles in human pulpal inflammation pathogenesis [59,60].

In fact, some studies have demonstrated that H_2O_2 bleaching gel induces an inflammatory infiltrate and necrosis [61,62], and the number of bleaching sessions influences on the extent of damage in the pulp tissue directly [62].

SENSITIVITY CONTROL AFTER IN-OFFICE BLEACHING

Local control using topical agents

The dental sensitivity is the most common adverse reaction right after bleaching procedure, especially in anterior teeth [63], and it is mandatory to establish a protocol to prevent or treat the teeth sensitivity. The most successful approaches to reduce dental sensitivity after bleaching are achieved by topical application of a gel based on potassium nitrate and sodium fluoride [16,51], and by a product containing 2 – 8% glutaraldehyde and 25% - 50% 2-hydroxyethyl methacrylate (GLUMA) [10].The use of these local measures has been suggested as effective methods for controlling dental sensitivity after bleaching.

Systemic anti-inflammatory drugs

Preoperative and perioperative therapeutic schemes are currently proposed using systemic glucocorticoids [64] and non-steroidal anti-inflammatory drugs (NSAIDs) [8,9,65] aiming to control the post procedure tooth sensitivity. Table 1 provides details regarding these studies. These therapeutic protocols have been justified by the inhibition of the pro-inflammatory mediators for long time, as central sensitization may not be prevented if the treatment is discontinued during the acute phase of inflammation [66].

Thus, drugs that prevent and treat the inflammatory process would be useful to control tooth sensitivity after bleaching process. However, dexamethasone, even at high daily doses, administered before and after of in-office tooth bleaching failed to prevent pain during and after bleaching. These findings suggest that production and release of inflammatory mediators could have a minor or no role at all in the development of tooth sensitivity induced by bleaching and, therefore, other mechanisms must be involved [64].

These outcomes are supported further by other studies

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Table 1: Summary of clinical researches uning anti-inflammatory drugs to control sensivity after in-office bleaching.					
Reference	Number of patients	Bleaching agent and protocol	Anti-inflammatory and protocol	Tooth sensitivity intensity mean Visual Scale Analogue (standard deviation)		Side effects
Paula *et al.*, 2013[8]	Placebo: 15 Experimental: 15	35% H_2O_2 (Whiteness HP Maxx, FGM -Joinville, SC, Brazil) 15min + 15min + 15min Two sessions with one week interval	Ibuprofen 400mg 1h before bleaching, and continue for every 8h for 48h.	Up to 1h	*†Placebo: 3.8 (± 3.25) *†Experimental: 1.5 (± 2.2)	Not reported
				1h to 24h	*†Placebo: 3,05 (± 2.75) *†Experimental: 3.1 (± 2.9)	
				24h to 48h	*†Placebo: 0.0 (± 0.0) *†Experimental: 0.0 (± 0.0)	
Paula *et al.*, 2013[9]	Placebo: 15 Experimental: 15	35% H_2O_2 (Whiteness HP Maxx, FGM - Joinville, SC, Brazil) 15min + 15min + 15min Two sessions with one week interval	Etoricoxib 60mg 1h before bleaching, and a second dose after 24h.	Up to 1h	†Placebo: 3.3 (± 2.9) †Experimental: 2.6 (± 2.4)	One patient from the placebo group received an extra analgesic drug due to severe tooth sensitivity.
				1h to 24h	†Placebo: 2.4 (± 2.7) †Experimental: 2.2 (±2.8)	
				24h to 48h	†Placebo: 0.0 (± 0.0) †Experimental: 0.1 (± 0.4)	
Rezende *et al.*, 2016[63]	Placebo: 30 Experimental: 33	35% H_2O_2 (Whiteness HP Maxx, FGM -Joinville, SC, Brazil) 15min + 15min + 15min Two sessions with one week interval	Dexamethasone 8mg 1h before procedure, and 4mg every 6h for 48h	During	†Placebo: 2.7 (± 2.3) †Experimental: 3.2 (± 2.7)	7 patients from the experimental group (21.2%) had allergic reactions to dexamethasone. 9 patients have to take an extra different painkiller due to severe tooth sensitivity.
				Up to 1h	†Placebo: 3.5 (± 2.9) †Experimental: 3.5 (± 2.7)	
				1h to 24h	†Placebo: 2.2 (±2.8) †Experimental: 1.9 (± 2.6)	
				24h to 48h	†Placebo: 0.4 (± 1.7) †Experimental: 0.2 (±0.8)	
Charako-rn*et al.*, 2009[64]	Placebo: 16 Experimental: 15	38% H_2O_2 (Opalescence Xtra Boost, Ultradent Products, Inc, South Jordan, UT, USA) 20 min + 20 min	Ibuprofen 600mg One single dose 30 min before bleaching	Immedi-ate	‡Placebo: 26.6 (± 31.0) ‡Experimental: 5.0 (± 9.9)	Not reported.
				Up to 1h	‡Placebo: 30.9 (± 30.5) ‡Experimental: 31.5 (± 32.1)	
				1h to 24 h	‡Placebo: 31.1 (32.6) ‡Experimental: 25.8 (± 30.8)	
*Average of values measured for maxillary and mandibular arches. *† Visual ScaleAnalogue (0 – 10).* *‡ Visual ScaleAnalogue (0 – 100).*						

where neither the 400mg ibuprofen8 nor 60mg etoricoxib9 administered in the perioperative managed to reduce sensitivity during and after tooth whitening, suggesting that prostaglandins blocking by the cyclooxygenase inhibition is not the main mechanism involved. However, the 600mg ibuprofen preoperative single dose was able to reduce sensitivity during but not after treatment [65]. This dose-depend response could be explained by the prostaglandins dependent analgesic effect of this agent, since ibuprofen can interact with sodium channels(Nav 1.7 and 1.8) reducing neuron hyperexcitability [67,68]; also inhibiting leukotrienes and other products from activated polymorph-nuclear leucocytes [69]; increasing the

production of the endocannabinoid anandamide [70,71]; and affecting serotoninergic and noradrenergic pathways on the dorsal horn [72,73].

DISCUSSION

Although the mechanism of tooth sensitivity induced by bleaching is not well understood, the transient activation of some odontoblast and/or neuronal ion channels in the odontoblast layer by the H_2O_2 could help to explain this phenomenon. Since local application of 5% potassium nitrate and 2% sodium fluoride gel [74] and GLUMA10 has been shown good clinical results with lower systemic risk, these effective methods should be appropriately used in order to reduce the risk of dental sensitivity after bleaching. Besides, this local application before dental bleaching did not affect the efficacy of H_2O_2 bleaching agents [74].

There is a lack of clinical evidence to support the use of systemic anti-inflammatory drugs to control tooth sensitivity. In fact, the use of NSAIDs for reducing sensitivity after dental bleaching did not show any significant effect of preventive analgesia [75], maybe due to the lack of COX-2 expression on dental pulp after this procedure [9]. Furthermore, inflammatory mediators may not play an important role in the development of tooth sensitivity induced by H_2O_2. Nevertheless, since a preoperative single dose of 600mg ibuprofen was able to prevent the sensitivity during the in-office dental bleaching, it could be useful in special selected patients with a high sensibility risk predictor, as tooth sensitivity and surface loss [76]. Although ibuprofen is a nonprescription over-the-counter drug, it must be carefully indicated, especially in some medically compromised patients [73].

CONCLUSION

There is not enough clinical evidence to indicate systemic anti-inflammatory drugs to control tooth sensitivity after dental bleaching. Further studies are necessary to clarify the mechanism and systemic control of this tooth whitening side effect.

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