Otosporin reduces pulp inflammatory reactions after dental bleaching of rat molars

Luciana Louzada **FERREIRA**[1]
Francine **BENETTI**[1,2]
Larissa **ÁLAMO**[1]
Ana Caroline **BOSISIO**[1]
Ariane Santana de **PROENÇA**[1]
Vanessa **RAHAL**[3]
Carla Renata **SIPERT**[4]
André Luiz Fraga **BRISO**[3]
Luciano Tavares Angelo **CINTRA**[1]

DOI: https://doi.org/10.14436/2358-2545.10.1.054-061.oar

ABSTRACT

Introduction: Patients undergoing dental bleaching relate to postoperative sensitivity, that is linked to hydrogen peroxide (H_2O_2) penetrating on the dental pulp. This study evaluated the anti-inflammatory effect of ibuprofen, Otosporin®, and curcumin gel on the pulp of the rats' teeth after bleaching. **Methods:** Fifty rats were divided into CG: control-placebo gel; BLE: bleached (35% H2O2, 30 minutes); BLE-I: bleached and ibuprofen oral administration (twice every 12 hours in 2 successive days); BLE-O: bleached followed by Otosporin® application in the molar surfaces (10 minutes); and BLE-C: bleaching session followed curcumin gel (10 minutes). After two days, the rats were killed for histological analysis. Statistical tests were performed (P<.05). **Results:** BLE, BLE-I, and BLE-C had severe inflammation or necrosis in the occlusal third of coronal pulp (P>.05); BLE-O had mild inflammation and was similar from CG (P>.05) and different from other groups (P<.05). In the middle third, BLE-O group had lower inflammatory infiltration and remained different from BLE group (P<.05); BLE, BLE-I, and BLE-C were similar (P>.05). In the cervical third, BLE, BLE-I, and BLE-C had a reduction of inflammation, without difference between bleached groups (**P**>.05). **Conclusions:** Otosporin® can reduce the inflammation in the pulp after dental bleaching; this result was not observed using ibuprofen or curcumin gel. Therefore, this study shows a new teeth bleaching post-treatment possibility using Otosporin®, which minimizes the inflammation generated to the pulp tissue by the bleaching gel. This could consequently minimize the postoperative sensitivity.

Keywords: Anti-Inflammatory Agents. Hydrogen Peroxide. Dental Pulp. Tooth Bleaching

[1] Universidade Estadual Paulista, Faculdade de Odontologia de Araçatuba, Departamento de Endodontia (Araçatuba/SP, Brazil).

[2] Universidade Federal de Minas Gerais, Faculdade de Odontologia, Departamento de Odontologia Restauradora, Endodontia (Belo Horizonte/MG, Brazil).

[3] Universidade Estadual Paulista, Faculdade de Odontologia de Araçatuba, Departamento de Odontologia Restauradora (Araçatuba/SP, Brazil).

[4] Universidade de São Paulo, Faculdade de Odontologia, Departamento de Endodontia (São Paulo/SP, Brazil).

How to cite: Ferreira LL, Benetti F, Álamo L, Bosisio AC, Proença AS, Rahal V, Sipert CR, Briso ALF, Cintra LTA. Otosporin reduces pulp inflammatory reactions after dental bleaching of rat molars. Dental Press Endod. 2020 Jan-Apr;10(1):54-61. DOI: https://doi.org/10.14436/2358-2545.10.1.054-061.oar

» The authors report no commercial, proprietary or financial interest in the products or companies described in this article.

Introduction

Dental bleaching has become popular in recent years due to the esthetic appeal of a white smile.[1] There are two types of bleaching for vital teeth: at-home bleaching, using carbamide peroxide or low hydrogen peroxide (H_2O_2) concentrations associated with acetate trays; and in-office bleaching, using high H_2O_2 concentrations.[2] In-office bleaching is for attending to patients who do not tolerate the use of the tray for a long time in order to achieve immediate results[3]. They include major complications of the use of bleaching agents on the pulp.[4]

Most patients undergoing dental bleaching relate to postoperative sensitivity,[3] which can occur even in healthy teeth, contrary to common tooth sensitivity, when pain occurs due to the exposed dentin. This is directly linked to H_2O_2 penetrating the hard tooth tissues reaching the pulp-dentin complex.[4]

Though the mechanisms of tooth sensitivity after the dental bleaching have not been fully determined, it is believed that inflammatory mediators may play an important role.[5] The inflammatory reaction is a complex process that involves vascular and neuronal reactions.[6] The increase of substance-P in the pulp of bleached teeth was reported, and is related to enhance of pulpal blood flow and a rapid increase of inflammatory cells at the site of the inflammation.[2] The presence of severe inflammation or necrosis was also observed in the pulp after bleaching.[4,7-10,11,12]

Considering the inflammatory process generated in the pulp tissue by dental bleaching gels, anti-inflammatory substances could be used to minimize the damage[5]. The use of ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID), has been widely studied for decreasing the tooth sensitivity after bleaching.[1,5] This drug may reduce the tooth intensity during[5] or up to one hour after the bleaching session[1]. Still, though ibuprofen has shown some ability to minimize tooth sensitivity, it does not reduce the absolute risk of sensitivity.[1] In addition, there is still insufficient evidence regarding the use of NSAIDs to prevent tooth sensitivity caused by in-office bleaching.[13]

The use of topical medications with anti-inflammatory potential in dental tissue after the bleaching procedure may be a promising alternative to minimizing the pulp damage. The Otosporin® (Farmoquímica-S/A, Rio de Janeiro, RJ, Brazil), a neomycin/polymyxin B/hydrocortisone association, is commonly used in endodontic procedures[14-16] and presents anti-inflammatory, immunosuppressive and vasoconstrictor effects.[14,15] It is recommended for treatment in deep cavities to prevent or alleviate dentinal and pulpal pain and hypersensitivity due the diffusion ability in the dentin, and it is capable of reducing the intrapulpal pressure.[17,18] It is also used during the treatment of pulp capping and pulpotomy.[19]

The bleaching gel increases in quantity the depth the microcracks presented in dental enamel[20] and facilitates the penetration of topical medications in the pulp. Thus, Otosporin® and other topical medications may be effective in the treatment of pulp inflammation caused by the bleaching.

The curcumin extracted from Curcuma longa roots (turmeric) rhizome has immunomodulatory and anti-inflammatory antioxidant properties,[21] which would minimize the damage in the pulp tissue. Still, it has an anti-fibrotic effect[22] and can reduce the maturation of collagen fibers of dental pulp that occurs after a bleaching procedure.[8]

Therefore, in the search of an alternative treatment for patients who want to whiten their teeth without negative consequences, we compared the anti-inflammatory potential of ibuprofen -a drug used by clinicians- with the topical medications proposed in this study, Otosporin® and curcumin gel, on the rat pulp tissue after bleaching. The null hypothesis of the study is that anti-inflammatory drugs are not able to minimize pulp inflammation caused by dental bleaching.

Materials and Methods

A total of 50 male Wistar albino rats (approximately 200g each) were used. The rats were housed in a temperature-controlled environment (22°C±1°C) on a standard light/dark schedule with food and water ad libitum. The experimental protocol was approved by the Institutional Ethics Committee of São Paulo State University (CEUA-00885) of the local and conducted in accordance with relevant guidelines.

Tooth Bleaching

The rats were anesthetized by intramuscular injections of Ketamine 10% (87mg/kg, União Química Farmacêutica-S/A, Embu-Guaçu, SP, Brazil) and Xy-

lazine (13 mg/kg, Syntec Brasil LTDA, Cotia, SP, Brazil). Their upper first molars were randomly divided into (n=10): CG: control group-placebo gel; BLE: one bleaching session; BLE-I: one bleaching session and ibuprofen oral administration; BLE-O: one bleaching session followed by Otosporin® application; and BLE-C: one bleaching session followed by curcumin gel application.

The bleaching was performed with 0.01mL of 35% H2O2 gel (Whiteness HP-Maxx; FGM Dental-Products, Joinville, SC, Brazil) in a single application of 30 minutes7,23; the CG received a placebo gel. After the bleaching, the teeth were washed and dried. The ibuprofen (Medley-Farmacêutica LTDA, Campinas, SP, Brazil), was administrated via gavage (50mg/kg body weight)24 as the animals recovered from the anesthesia twice every 12 hours in successive 2 days. The 0.01mL of Otosporin® or curcumin gel (2% curcumin, 2% carbopol and 30% ethanol, Aphoticário, Araçatuba, SP, Brazil)25 were applied to the surface of the upper bleached molars for 10 minutes (Table 1).

Histological Analysis

After two days, the animals were killed by overdose of the anesthetic solution (240mg/Kg, Thiopentax; Cristália-Produtos Químicos-Farmacêuticos LTDA, Itapira, SP, Brazil). The right and left maxillae from the rats were fixed in 10% buffered formalin (24 hours), decalcified in a 10% ethylenediaminetetraacetic acid solution (three months) and dehydrated in a graded ethanol series, and then it was clarified and embedded in paraffin.

Six-micron sections were cut in the vestibular-lingual plane and stained with hematoxylin-eosin. The serial histological sections were selected from the point where the mesial root of the first molar was seen in all its longitudinal extension.[4,9]

To histological analysis, the pulp chamber of the first molar was divided into thirds (occlusal, middle, and cervical)9. The inflammation was scored according to the approximate average number of inflammatory cells in each third of the same specimen (Table 2). The histological analysis was performed by a single calibrated operator in a blinded manner under light microscopy (400x, DM 4000 B; Leica-Microsystems, Wetzlar, Germany).

Data were collected and submitted to Kruskal-Wallis and Dunn statistical tests; the significance level was 5%.

Results

The pulp tissue of the control group showed histological characteristics of healthy pulp tissue: well-defined odontoblastic layer and even distribution of

Table 1. Distribution of experimental groups according to the treatment.

Groups	Session Bleaching	Post-bleaching treatment
CG	_ _ _ _ _ _ _	_ _ _ _ _ _ _
BLE	1 application of bleaching gel for 30 min	_ _ _ _ _ _ _
BLE-I	1 application of bleaching gel for 30 min	Oral Ibuprofen for 2 days, 12/12 hours
BLE-O	1 application of bleaching gel for 30 min	1 topical application of Otosporin for 10 min
BLE-C	1 application of bleaching gel for 30 min	1 topical application of Curcumin gel for 10 min

CG: control group; BLE: dental bleaching; I: ibuprofen administration; O: Otosporin application; C: Curcumin application.

Table 2. Scores attributed to the intensity of inflammatory cell infiltration

Score	Pulpal tissue condition
1	Inflammatory cells absent or negligible in number
2	Mild inflammatory infiltrate (<25 cells per field)
3	Moderate inflammatory infiltrate (between 25 and 125 cells per field)
4	Severe inflammatory infiltrate (>125 cells per field) or necrosis

blood vessels in intact extracellular matrix, with absence of inflammation (Fig 1A e B). Most specimens of the BLE group showed severe inflammation, with lymphocytes, macrophages, and plasmocytes or necrosis in the occlusal third; the middle third had moderate inflammation; mild inflammation could still be found in the cervical third of the coronal pulp (Fig 1C e D).

The BLE-I group had severe inflammation or necrosis in the region of pulp horns; in the middle third, it showed mild or moderate inflammation and inflammatory cells in negligible numbers or mild inflammation in the cervical third (Fig 1E e F). The BLE-O group showed mild inflammation in the occlusal third of the coronal pulp with cellular disorganization in the pulp horn region and inflammatory cells in negligible numbers; in the middle and cervical thirds, most of the specimens presented no inflammation with an intact pulp (Fig 1G e H). The BLE-C group showed from moderate inflammation to necrosis in the occlusal third, and mild to moderate inflammation in the middle third; the cervical thirds showed tissue disorganization and mild inflammation (Fig 1I e J). The inflammatory cells observed characterized a chronic inflammatory infiltrate .

Comparison among the Groups

The scores attributed to each third are presented in Table 3; The inflammation was observed in bleached groups with disorganization of the odontoblastic, congested blood vessels and alteration of the loose connective tissue of the central pulp. The CG and the BLE-O group did not present any statistical difference when comparing all thirds (P>.05). There was a significant difference in the occlusal third between the BLE-O with the BLE, BLE-C, and BLE-I groups (P<.05). Similar histological findings were still observed in the middle third of the pulp between the BLE, BLE-C, and BLE-I groups (P>.05) that presented moderate inflammation; no difference was found between the bleached groups that received the medications (P>.05); however, there was a significant difference between the BLE-O compared to the BLE group (P<.05) and between BLE-I and BLE-C with the CG (P<.05). In the cervi-

Table 3. Scores observed for inflammatory cell response according to the groups.

Thirds of coronal pulp	Score 2 days	Groups					p
		CG	BLE	BLE-I	BLE-O	BLE-C	
Occlusal	1	10/10	0/10	0/10	4/10	0/10	< 0,001
	2	0/10	0/10	0/10	5/10	0/10	
	3	0/10	4/10	4/10	1/10	5/10	
	4	0/10	6/10	6/10	0/10	5/10	
	Median*	1[a]	4[b]	4[b]	2[a]	4[b]	
Middle	1	10/10	0/10	0/10	5/10	0/10	< 0,001
	2	0/10	3/10	5/10	4/10	4/10	
	3	0/10	6/10	5/10	1/10	5/10	
	4	0/10	1/10	0/10	0/10	1/10	
	Median*	1[a]	3[b]	3[bc]	1[ac]	3[bc]	
Cervical	1	10/10	2/10	6/10	9/10	3/10	< 0,001
	2	0/10	7/10	4/10	1/10	6/10	
	3	0/10	1/10	0/10	0/10	1/10	
	4	0/10	0/10	0/10	0/10	0/10	
	Median*	1[a]	2[b]	1[ab]	1[ab]	2[ab]	

*Same letters on the line indicate no statistical difference among the groups (P>.05).

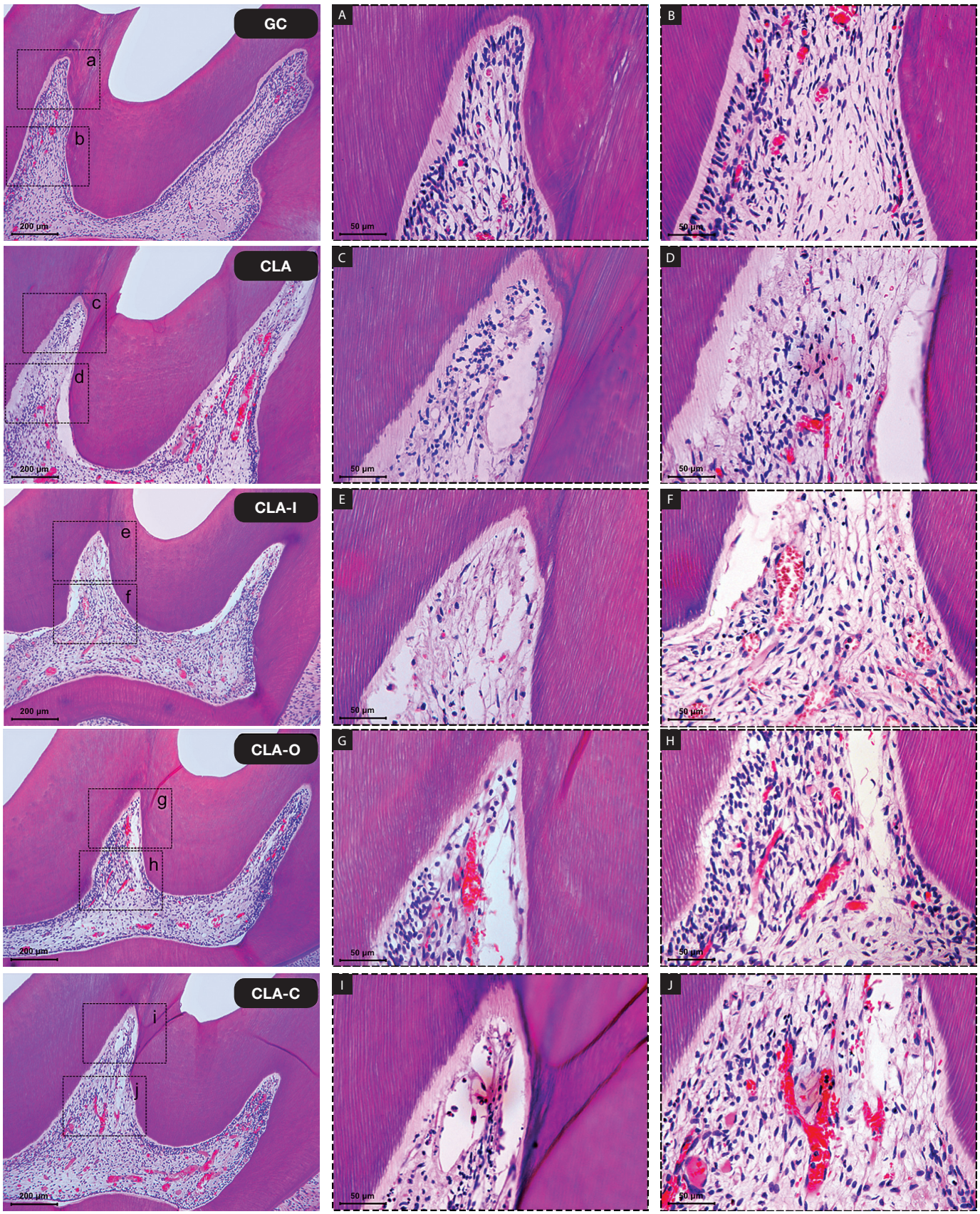

Figure 1. Representative images of coronal pulp tissue of the control group and the experimental groups: CG (**A, B**); BLE (**c, d**); BLE-I (**E, F**); BLE-O (**G, H**); and BLE-C (**I, J**) (100x magnification). Panels a-j are magnified images of insets, indicating the occlusal (**A, C, E, G, I**) and middle thirds (**B, D, F, H, J**) of the pulp tissue (400x magnification). [Hematoxylin-eosin staining]

cal third, the bleached groups had a reduction in the inflammation and there was no difference between them ($P>.05$); nevertheless, a difference was present between BLE and the CG ($P<.05$).

Discussion

This study compared the anti-inflammatory potential of ibuprofen, Otosporin® and curcumin gel on the pulp of rat teeth after bleaching, and the null hypothesis was in part supported: out of the tested drugs, only Otosporin® was capable of reducing the inflammation in the pulp tissue. Previous studies showed that the H_2O_2 and the products of its degradation, such as reactive oxygen species (ROS),[20] caused alterations on teeth structures.[9,20] As ROS molecules have low molecular weight, they can penetrate the pulp, resulting in damage as necrosis.[4,7,9,10,12]

The tooth sensibility after bleaching may be related to the release of ROS in the pulp, promoting the presence of chemical mediators, such as prostaglandins, that activates nociceptors and results in pain.[5,6] This justifies the use of NSAIDs, such as ibuprofen. This drug has a high analgesic and anti-inflammatory action and acts by inhibiting cyclooxygenases, preventing the activation of prostaglandins.[6]

This medication has been used in endodontic cases to relieve moderate to severe pain[1]. Clinical studies showed that ibuprofen reduced tooth sensitivity caused by dental bleaching[1,5], but is not completely effective[1]. The current study showed that, in the used dosage, the ibuprofen did not present an anti-inflammatory effect on the pulp tissue. It is suggested that prostaglandin's expression may occur in the first hour after bleaching and then other pro-inflammatory mediators may be expressed, triggering tooth sensitivity.[1] The neuropeptides that increase after dental bleaching[2] are known for being involved in pulp pain and inflammation,[2,26] and ibuprofen is not able to prevent their production.[1]

The main question is: can topical medications act in the inflammation of the dentin-pulp complex? The answer is based on the diffusion of the medication through the micropore or cracks present in teeth enamel.[20] Still, the bleaching agents, when applied to the enamel, increase the pores due to the disruption of matrix proteins[20], allowing the medication to penetrate through the enamel and dentin, reaching the pulp.

Otosporin® is commonly used as intracanal medication[14,15] or in pulp capping and pulpotomy.[16] A study in animals showed that Otosporin®, used as intracanal medication, preserves the integrity of the pulp stump and improves its healing after over-instrumentation.[14] The positive effects of Otosporin® are related to its intimate interaction with the vehicle and the elevated penetration potential in tissues[14]. For this reason, it is also widely used in direct contact with the pulp, promoting its corticosteroid action, which can minimize the dilation of blood vessels and the inflammatory process[27]. Its penetration in dentin is also well documented[18] as being used to reduce sensitivity after the preparation of deep cavities in the tooth with excellent clinical and histological results[18].

Therefore, we believe Otosporin® has potential in minimizing the pulp damage caused by the bleaching. Knowing that tooth sensibility is related to the inflammation on the pulp caused by dental bleaching agents,[3] we observed that the group BLE-O presented better-defined cellular organization and a milder inflammation when compared to other bleached groups. This result helps to illuminate the properties of this medication's effectiveness against the bleaching agent consequences.

The other medication used was the curcumin gel. It has been studied regarding a number of human diseases,[28] but its action on the pulp tissue is not known. A previous study showed that curcumin could down-regulate the expression of TNF-a in all the diseases for which TNF blockers are currently being used.[1] However, the present study observed that the protocol of the curcumin application did not act as anti-inflammatory agent. This result might be related to curcumin insolubility, resulting in a poor bioavailability and a slow cellular uptake, meaning repetitive doses are necessary to achieve significant concentrations for an anti-inflammatory effect.[21] Our study applied the curcumin gel only once, which might have contributed to the non-effective anti-inflammatory effect on the pulp.

Despite studies evaluating the effects of medications and their interaction with the pulp,[1,5,14-16] just few evaluated its effects with regards to adverse bleaching effects.[1,5,29] One of these studies observed that pulp tissue from ascorbic acid-treated rats featured faster regenerative potential over time, but a slight reduc-

tion in initial pulp damage during post-bleaching was promoted by this medication.[29] Despite this favorable response, in another study from a randomized clinical trial, oral administration of 500mg ascorbic acid in human subjects one hour prior to in-office bleaching and up to 48 hours post-bleaching, showed no significant difference for the risk and intensity of tooth sensitivity in patients with or without ascorbic acid administration.[30]

Regardless of the study limitations, the methodology used may be useful for further investigations, especially for the assessment of products to reduce the undesirable effects of bleaching, such as pulp inflammation. Considering the enamel and dentin thickness, rat molar teeth were used to simulate the events commonly found in human mandibular incisors.[9,10] Furthermore, this study can start to deeper studies of a future alteration in the clinical protocol of dental bleaching: as severe damage was shown in the pulp of the teeth after bleaching, Otosporin® could be used to minimize this damage and, consequently, tooth sensitivity. Nevertheless, as it is a bleaching procedure, it is also necessary to verify if the use of topical anti-inflammatories may impair the whitening effect of this procedure.

Conclusion

Otosporin® applied topically after dental bleaching was able to minimize the cytotoxic effect of the bleaching, reducing the inflammation in the pulp. This result was not observed using ibuprofen or curcumin gel.

References

1. Paula E, Kossatz S, Fernandes D, Loguercio A, Reis A. The effect of perioperative ibuprofen use on tooth sensitivity caused by in-office bleaching. Oper Dent. 2013;38(6):601-8.
2. Caviedes-Bucheli J, Ariza-García G, Restrepo-Méndez S, Ríos-Osorio N, Lombana N, Muñoz HR. The Effect of tooth bleaching on substance P expression in human dental pulp. J Endod. 2008 Dec;34(12):1462-5.
3. Reis A, Kossatz S, Martins GC, Loguercio AD. Efficacy of and effect on tooth sensitivity of in-office bleaching gel concentrations: A randomized clinical trial. Oper Dent. 2013 July-Aug;38(4):386-93.
4. Cintra LT, Benetti F, Ferreira LL, Gomes-Filho JE, Ervolino E, Gallinari MO, et al. Penetration capacity, color alteration and biological response of two in-office bleaching protocols. Braz Dent J. 2016 Mar-Apr;27(2):169-75.
5. Charakorn P, Cabanilla LL, Wagner WC, Foong WC, Shaheen J, Pregitzer R, et al. The effect of preoperative ibuprofen on tooth sensitivity caused by in-office bleaching. Oper Dent. 2009 Mar-Apr;34(2):131-5.
6. Nakanishi T, Shimizu H, Hosokawa Y, Matsuo T. An immunohistological study on cyclooxygenase-2 in human dental pulp. J Endod. 2001 June;27(6):385-8.
7. Cintra LT, Benetti F, Ferreira LL, Rahal V, Ervolino E, Jacinto RC, et al. Evaluation of an experimental rat model for comparative studies of bleaching agents. J Appl Oral Sci. 2016 Jan-Feb; 24(1):95-104.
8. Cintra LT, Ferreira LL, Benetti F, Gastélum AA, Gomes-Filho JE, Ervolino E, et al. The effect of dental bleaching on pulpal tissue response in a diabetic animal model. Int Endod J 2017;50:790-8.
9. Cintra LTA, Benetti F, Silva-Facundo AC, Ferreira LL, Gomes-Filho JE, Ervolino E, et al. The number of bleaching sessions influences pulp tissue damage in rat teeth. J Endod. 2013 Dec;39(12):1576-80.
10. Costa CAS, Riehl H, Kina JF, Sacono NT, Hebling J. Human pulp responses to in-office tooth bleaching. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010 Apr;109(4):e59-64.

11. Ferreira LL, Gomes-Filho JE, Benetti F, Carminatti M, Ervolino E, Briso ALF, et al. The effect of dental bleaching on pulpal tissue response in a diabetic animal model: Immunoregulatory cytokines study. Int Endod J. 2018 Mar;51(3):347-356.
12. Seale NS, Wilson CFG. Pulpal response of bleaching of teeth in dogs. Pediatr Dent 1985;7:209-14.
13. Faria-e-Silva AL, Nahsan FP, Fernandes MT, Martins-Filho PR. Effect of preventive use of nonsteroidal anti-inflammatory drugs on sensitivity after dental bleaching: a systematic review and meta-analysis. J Am Dent Assoc. 2015 Feb;146(2):87-93.e1.
14. Holland R, Otoboni-Filho JA, Souza V, Nery MJ, Bernabé PF, Dezan-Júnior E. Calcium hydroxide and a corticosteroid-antibiotic association as dressings in cases of biopulpectomy. A comparative study in dogs' teeth. Braz Dent J. 1998;9(2):67-76.
15. Panzarini SR, Trevisan CL, Brandini DA, Poi WR, Sonoda CK, Luvizuto ER, et al. Intracanal dressing and root canal filling materials in tooth replantation: a literature review. Dent Traumatol. 2012 Feb;28(1):42-8.
16. Percinoto C, De Castro AM, Pinto LM. Clinical and radiographic evaluation of pulpotomies employing calcium hydroxide and trioxide mineral aggregate. Gen Dent. 2006 July-Aug;54(4):258-61.
17. Fry AE, Watkins R, Phatak NM. Topical use of corticosteroids for the relief of pain sensitivity of dentine and pulp. Oral Surg Oral Med Oral Pathol. 1960;13(5):594-7.
18. Holland R, Okabe JN, Souza V, Saliba O. Diffusion of corticosteroid-antibiotic solutions through human dentine. Rev Odont UNESP. 1991;20:17-23.
19. Mello W, Holland R, Berbert A. Estudo histopatológico da polpa dental inflamada de dentes de cães após pulpotomia ou curetagem pulpar e proteção com hidróxido de cálcio. Efeito de um agente antiflogístico. Rev Odont UNESP. 1983;12:7-19.
20. Kawamoto K, Tsujimoto Y. Effects of the hydroxyl radical and hydrogen peroxide on tooth bleaching. J Endod 2004;30:45-50.
21. Srivastava RM, Singh S, Dubey SK, Misra K, Khar A. Immunomodulatory and therapeutic activity of curcumin. Int Immunopharmacol 2011;11(3):331-41.
22. Zhang D, Huang C, Yang C, Liu RJ, Wang J, Niu J, et al. Antifibrotic effects of curcumin are associated with over expression of cathepsins K and L in bleomycin treated mice and human fibroblasts. Respir Res. 2011;12(1):154.
23. Benetti F, Gomes-Filho JE, Ferreira LL, Ervolino E, Briso ALF, Sivieri-Araújo G, et al. Hydrogen peroxide induces cell proliferation and apoptosis in pulp of rats after dental bleaching in vivo. Arch Oral Biol. 2017 Sept;81:103-9.
24. Shah A, Jung D. Dose-dependent pharmacokinetics of ibuprofen in the rat. Drug Metab Dispos. 1987;15:151-4.
25. Patel NA, Patel NJ, Patel RP. Formulation and evaluation of curcumin gel for topical application. Pharm Dev Technol. 2009;14(1):80-9.
26. Lepinski AM, Hargreaves KM, Goodis HE, Bowles WR. Bradykinin levels in dental pulp by microdialysis. J Endod. 2000 Dec;26(12):744-7.
27. Fava LRG. Human pulpectomy: incidence of postoperative pain using two different intracanal dressings. Int Endod J. 1992 Sept;25(5):257-60.
28. Aggarwal Bb, Gupta Sc, Sung B. Curcumin: an orally bioavailable blocker of TNF and other pro-inflammatory biomarkers. Br J Pharmacol 2013;169(8):1672-92.
29. Lima AF, Marques MR, Soares DG, Hebling J, Marchi GM, Costa CAS. Antioxidant therapy enhances pulpal healing in bleached teeth. Restor Dent Endod. 2016 Feb;41(1):44-54.
30. De-Paula EA, Kossatz S, Fernandes D, Loguercio AD, Reis A. Administration of ascorbic acid to prevent bleaching-induced tooth sensitivity: a randomized triple-blind clinical trial. Oper Dent. 2014 Mar-Apr;39(2):128-35.