



# Alternative to Avoid Tooth Discoloration after Regenerative Endodontic Procedure: A Systematic Review

Luciane Geanini Pena dos Santos<sup>1</sup>, Luiz Alexandre Chisini<sup>1</sup>, Camila Guerner Springmann<sup>2</sup>, Beatriz Dulcinea Mendes de Souza<sup>2</sup>, Fernanda Geraldo Pappen<sup>1</sup>, Flávio Fernando Demarco<sup>1</sup>, Mara Cristina Santos Felipe<sup>2</sup>, Wilson Tadeu Felipe<sup>2</sup>

<sup>1</sup>Graduate Program in Dentistry, UFPel - Universidade Federal de Pelotas, Pelotas, RS, Brazil  
<sup>2</sup>Department of Dentistry, UFSC - Universidade Federal de Santa Catarina, Florianópolis, SC, Brazil

Correspondence: Flávio Fernando Demarco, Rua Gonçalves Chaves, 457, 5<sup>o</sup> andar, CEP 96015-560 Pelotas, RS, Brazil. Tel.: +55-53-3222-6690. e-mail: [ffdemarco@gmail.com](mailto:ffdemarco@gmail.com)

This systematic review aimed to evaluate whether alternative materials to conventional triple antibiotic paste (TAP - metronidazole, ciprofloxacin, and minocycline) and grey mineral trioxide aggregate (GMTA) could avoid tooth discoloration in teeth submitted to Regenerative Endodontic Procedure (REP). It was also investigated if dental bleaching is able to reverse the color of darkened teeth due to REP. The search was conducted in four databases (Medline via PubMed, Scopus, ISI Web of Science and BVS - Virtual health library), following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. The retrieved papers were uploaded in the software EndNote™ and two reviewers independently selected the studies and extracted the data. Only studies in humans (case reports, case series, clinical trials) were included in the review. From 1,122 potentially eligible studies, 83 were selected for full-text analysis, and 38 were included in the review. The included studies were mainly case reports (76.3 %). The studies described a total of 189 teeth submitted to REP. From these, about 54% of teeth presented some degree of discoloration. Most teeth presenting color alteration were treated with TAP, especially when combined with GMTA. Only three studies performed dental bleaching to restore the color of teeth and neither bleaching technique was able to restore the original color of the crowns. The use of alternative materials to TAP and GMTA, such as double antibiotic paste or Ca(OH)<sub>2</sub> pastes and white mineral trioxide aggregate or Biodentine™, reduces the occurrence of tooth discoloration.

**Key Words:** dental pulp, disinfection, regenerative endodontics, tooth discoloration, triple antibiotic paste.

## Introduction

Regenerative endodontic procedure (REP) has been proposed as a treatment option for necrotic immature permanent teeth (NIPT) in detriment to apexogenesis with calcium hydroxide (CaOH<sub>2</sub>) and apexification with trioxide mineral aggregate (MTA) (1). REP is based on the formation of blood clot into the root canal space creating a natural scaffold that serves as anchorage site for cells from apical papilla and periodontal tissues. Additionally, blood supplies growth factors that act along with those from dentin matrix, contributing to the formation of a new tissue into the pulp cavity and to the resumption of root development (1,2). Therefore, REP seems to provide an increase in root lengthening and thickening, as well as a remission of the signs and symptoms of apical periodontitis (2).

In the Clinical Considerations for a Regenerative Procedure, the American Association of Endodontists (AAE) (3) recommends for root canal disinfection the use of CaOH<sub>2</sub> or triple antibiotic paste (TAP - metronidazole, ciprofloxacin and minocycline), for a short period (3). Probably, the presence of minocycline, an antibiotic of tetracycline family, in TAP composition plays an important

role in tooth discoloration (4,5). Minocycline binds to the calcium ions present in the dentin by means of chelation, being incorporated into the dentin matrix and inducing a change in the color of the dental structure (4). To avoid crown discoloration, it was proposed to seal the coronal dentinal tubules with bonding agent prior to the use of TAP as intracanal medication (6) as well as the replacement or eliminating minocycline from TAP composition. The alternatives to minocycline report in the literature are performed mainly with cefaclor (7), amoxicillin (8) or clindamicine (9). Some studies have adopted only the elimination of minocycline of conventional TAP, so called Double antibiotic paste (DAP - metronidazole, ciprofloxacin) (10,11).

Moreover, the blood clotted inside of the root canal must be protected in its cervical portion by a sealing material, conventionally the MTA (2). However, MTA also can lead to a change in the tooth color due to presence of minerals as bismuth oxide, its radiopacifier component (12). Although the AAE recommends the use of glass ionomer cement (GIC) to avoid the discoloration in areas where esthetic is primordial (3), several studies have performed the seal with

white MTA (WMTA) due to less amount of metallic ions (7,13,14), which could reduce tooth crown discoloration.

Therefore, although satisfactory biological results are achieved after REP (1,2,15), several case reports have indicated color change, especially in those cases treated with TAP (16-18). A recent literature review (19) has also shown that TAP is the main reason to tooth discoloration in REP, although did not directly compare the possible reduction of tooth discoloration when alternatives materials (to TAP and gray MTA) are employed. Thus, it suggest that the use of pastes alternative to TAP and the replacement of grey MTA (GMTA) could decrease the percentage of tooth discoloration (5,20,21). Moreover, in cases of discoloration, dental bleaching can be performed aiming to minimize esthetic damages. However, the ability of dental bleaching in restore the original color of teeth did not was aim of systematic reviews. Similarly, little is investigated to ability of alternatives materials to TAP and GMTA to avoid the tooth discoloration in REP. Thus, the aim of this study was to review the literature systematically and evaluate whether alternatives to conventional TAP and GMTA could avoid tooth discoloration in teeth submitted to revascularization and investigate if dental bleaching is able to reverse the color of discolored teeth due to REP.

## Material and Methods

This systematic review was carried out according to the guidelines of Cochrane Handbook for Systematic Reviews of Interventions, following the four-phase flow diagram of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (22). This report is based on the PRISMA Statement. The question of research was adapted from the PICO framework; Population – human immature permanent teeth; Intervention and Comparison – use of TAP and GMTA in regenerative endodontic procedures vs. alternative materials; Outcome – tooth discoloration.

A structured research was carried in Pubmed/Medline, Scopus, ISI Web of Science and BVS - *Virtual health library*. Date limit was set up to March 2017, with no language restriction. The search and the combinations of syntaxes are described in Table 1. The references of all eligible papers were also hand-searched. A wide search strategy was used to avoid missing information. Duplicated studies were removed by using EndNote™ X7 software (Thomson Reuters, Rochester, New York, NY, USA). The inclusion criteria were *in vivo* original studies (prospective, retrospective, clinical cases, case series, clinical trials) in which regenerative procedures were performed in immature permanent teeth, and which color maintenance or the tooth discoloration, as an outcome or not, were described. Studies were included independently of their follow-up intervals. The exclusion criteria were: reviews, *in vitro* studies, studies in animals,

or studies that did not report the color maintenance or tooth discoloration.

Two independent reviewers (L. A. C. and C. G. S.) initially screened the titles of all identified studies. If the title indicated possible inclusion, the abstract was carefully appraised, and the manuscripts considered eligible for the review (or in case of doubt) were selected for full-text reading. Discrepancies were resolved by discussion with a third reviewer (L. G. P.) Standardized outline was used for data extraction of the studies that met the inclusion criteria. Due to the high heterogeneity of included studies, evaluation of risk of bias and meta-analysis could not be performed. Consequently, the characteristics of studies were summarized descriptively.

## Results

### Studies selection

The flowchart of the systematic review is shown in Figure 1. A total of 1,122 records were identified and 843 remained after duplicated studies removal. After title and abstract evaluation, 83 papers were selected for full-text assessment. From these, 38 studies met the inclusion criteria of the present study. Forty-five studies were excluded after full-text reading once they did not report the color maintenance or the tooth discoloration (23-62), or since the tooth discoloration described had occurred prior to revascularization procedure (63-68).

### Studies Characteristics

Most included papers were case reports (76.3%) followed by case series (15.8%). Few clinical trials were included (69,70). The first published study included in this review was issued in 2009 (71). The studies were conducted in 14 different countries; most of them were carried out in the United States of America (29%) followed by Turkey (13%) (Table 2). The included studies described

Table 1. Structured search strategy carried out in MEDLINE/PubMed database\*

Search Syntaxes	
#1	((clinical trials) OR (random allocation) OR (Longitudinal Studies) OR (Longitudinal Study) OR (Retrospective Studies) OR (Clinical Evaluation) OR (Case Study) OR (Case Studies) OR (Case Histories) OR (Case-Control Study) OR (case reports) OR (Follow-up))
#2	((Immature Permanent Teeth) OR (Immature Permanent Tooth) OR (Young Permanent Teeth) OR (Young Permanent Tooth))
#3	((Root Canal Revascularization) OR (Revascularization OR Maturogenesis))

\* Searches in SciVerse Scopus® (SS), ISI web of a science® and Cochrane library® were adapted according to the database. In ISI web of a science®, the search #5 was included also keyword: (AND Dentistry)

the regenerative procedures performed in a total of 189 teeth. From these, 81% (n=153) were incisors, 17% (n=33) premolar, 1% molars (n=2), and 0.5% (n=1) canine.

Triple antibiotic paste (TAP) in different concentrations were used as intracanal medication in 23.3% of the teeth (n=44). Alternative pastes to TAP, were used in 65.6% of teeth (n=124). From these, minocycline were replaced by cefaclor in 72 cases (6, 7,70,72,73), amoxicillin in 18 (8,74), clindamicine in 31 teeth (9), and tetracycline in one (75). Double antibiotic paste (DAP - metronidazole, ciprofloxacin) were used in two cases (10, 11). In 10.6% of the teeth (n=20), Ca(OH)<sub>2</sub> was used as intracanal medication (14,69,76-81), and in 0.5% of the teeth (n=01) no medication was applied (13).

Regarding the cervical sealing material, grey MTA (GMTA) was employed in 50.8% of the teeth (n=96) (4,8-11,16,71,73-75,80-86), white MTA (6,7,13,14,18,69,70,76-78,87-95) in 46.0% (n=87), Biodentine (72) in 2,1% (n=04) and Calcium-enriched mixture (CEM) (79) cement in 1% (n=02). Although, it was not a goal of this study to review the means by which dental color was taken, it

was noticed that in all the included studies teeth color analysis was performed only by means of visual parameters. Spectrophotometers or colorimeters were not used for this propose in the included studies.

### Synthesis of Results

Considering the 189 teeth evaluated, 54% (n=102) presented some degree of discoloration. Tooth color assessment was performed at the end of REP, therefore the evaluated teeth had already suffered the possible effects of intracanal medication as well as cervical sealing material. Thus, the results of the present review are described according the association of these factors: (1) TAP/GMTA, (2) TAP/alternative materials (AM) to GMTA (WMTA, Biodentine, and CEM), (3) AM to TAP/GMTA, and (4) AM to TAP/ AM to GMTA.

From the 14 teeth treated with TAP/GMTA association, 13 (92.9%) showed tooth discoloration (4,16,71,82-86); while, from de 30 teeth treated with TAP/AM to GMTA, 21 (70.0%) presented crown discoloration (18, 69,87-95). When AM to TAP were associated with GMTA, 45 teeth (54.9%)

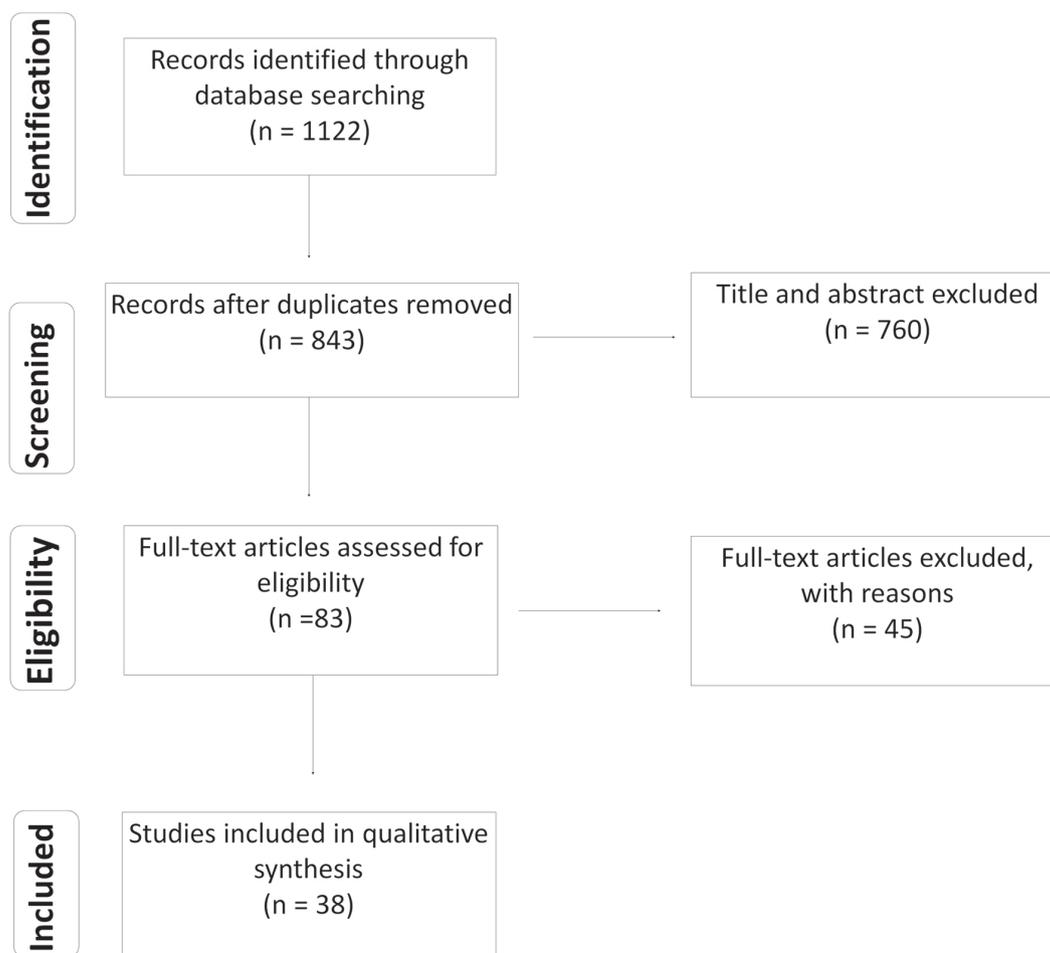


Figure 1. Flow diagram.

Table 2. Summary of descriptive characteristics of included studies

Author (years)	Country	Number of teeth (dental group)	Follow-up Time	Intracanal medication	Cervical Plug	Bleaching Method	Color Analysis
Reynolds et al. (71)	USA	2 (premolar) Only one tooth shown a little discoloration in the region of cervical of crown	18 months	TAP	GMTA	-	Visual
Kim et al. (4)	Korea	1 (incisor) After the use of intracanal medication was observed discoloration. Dental bleaching result in an improve of color, but not returned to original color	8 months	TAP	GMTA	Sodium perborate	Visual
Petrino et al. (88)	USA	4 (incisor) 2 (premolar) Was observed discoloration in one tooth (after 10 days of treatment)	11 months	TAP	WMTA	-	Visual
Torbinejad et al. (17)	USA	1 (premolar) Crown of revascularized tooth presented discoloration	5.5 months	TAP	GMTA	-	Visual
Cehrelli et al. (77)	Turkey	2 (incisor) Did not observe tooth discoloration after 18 months; Dental necrosis was caused due trauma.	18 months	Ca(OH) <sub>2</sub>	GMTA	-	visual
Dabbagh et al. (7)	Canada	18 (incisor and premolar) Was observed color alterations in one tooth	24 months	TAP TAP/cefactor	WMTA	-	Visual
Gelman et al. (89)	USA	1 (central incisor) Grayish discoloration was observed two weeks after the start of triple antibiotic past use	11 months	TAP	WMTA	-	Visual
Narayana et al. (91)	USA	1 (NR) Discoloration did not observe in the period of follow-up	12 months	TAP	WMTA	-	Visual
Nosrat et al. (82)	USA	2 (incisor) The crowns showed moderate discoloration in the final of treatment	72 months	TAP	GMTA	-	Visual
Miller et al. (87)	USA	1 (incisor) Little change color were observed in the cervical crown	18 months	TAP	WMTA	-	Visual
Beccera et al. (92)	Colombia	1 (premolar) Discoloration was observed	24 months	TAP	WMTA	-	Visual
Kottoor et al. (90)	India	1 ( incisor) Discoloration was not observed; the authors attributing it due the use of white MTA	5 years	TAP	WMTA	-	visual
McTigue et al. (9)	USA	29 (incisor) 3 (premolar) In 14 teeth were observed tooth discoloration during the treatment. Dental bleaching was able to whiten the teeth satisfactory	51 months	TAP TAP/ clind.	GMTA and WMTA	Bleaching with sodium perborate and hydrogen peroxide 10%	Visual
Nosrat et al. (83)	USA	1 (incisor) Gradual discoloration was observed at the end of treatment	31 months	TAP	WMTA	Bleaching with sodium perborate	Visual
Wang et al. (18)	China	2 (premolar) Both teeth presented discoloration	18 vmonths	TAP	WMTA	-	Visual
Bezgin et al. (6)	Turkey	2 (premolar) No discoloration was observed. Teeth were sealed with dentin bonding	12 months	TAP / Cefactor	WMTA	-	Visual
Guyen Polat et al. (75)	Turkey	1 (premolar) Did not observe tooth discoloration	24 months	TAP / tetra	GMTA	-	Visual
Kahler et al. (8)	Australia	16 (incisor and premolar) 18 months or more	18 months or more	TAP / Amox.	GMTA	-	Visual
Kaya-Buyukbayram et al. (85)	Turkey	1 (Incisor) Ten of 16 teeth presented discoloration Authors reported discoloration due to MTA and TAP	20 months	Ca(OH) <sub>2</sub> and TAP	GMTA	-	Visual

Lin <i>et al.</i> (86)	Italy	1 (incisor)	16 months MTA caused crown discoloration	TAP	GMTA	-	Visual
Nagata <i>et al.</i> (69)	Brazil	23 (incisor)	15 months	TAP or Ca(OH) <sub>2</sub> + Chlorhexidine 2%	WMTA	-	Visual
Bezgin <i>et al.</i> (70)	Turkey	20 (premolar and incisor) Tooth discoloration was observed in 10 of 12 teeth treated with TAP and in 3 of 11 treated with Ca(OH) <sub>2</sub> Authors related that discoloration was not due antibiotic, but by MTA. 12 cases from 20 presented teeth discoloration; The author report perform the seal of dentinal walls with bonding agent to avoid the discoloration	18 months	TAP / CEF	WMTA	-	Visual
Park <i>et al.</i> (74)	Korea	2 (premolar)	-	TAP/amox.	GMTA	-	Visual
Nagata <i>et al.</i> (78)	Brazil	1 (incisor)	After 12 months of treatment the teeth presented crown discoloration 16	Ca(OH) <sub>2</sub>	WMTA	-	Visual
Sachdeva <i>et al.</i> (93)	India	1 (incisor)	36 months Tooth discoloration did not observed in the follow-ups	TAP	WMTA	-	Visual
Santiago <i>et al.</i> (16)	Brazil	5 (incisor)	15 months The tooth presented further discoloration after intracanal medications	TAP	GMTA	-	Visual
Silva <i>et al.</i> (76)	USA	1 (incisor)	36 months All teeth presented color changes in different levels	Ca(OH) <sub>2</sub>	WMTA	-	Visual
Wang <i>et al.</i> (95)	China	2 (premolar)	30 The teeth presented little discoloration Authors reported sings of tooth discoloration	TAP	WMTA	-	Visual
Asgary <i>et al.</i> (79)	Iran	2 (Incisor)	36 months Calcium hydroxide / TAP	Calcium- enriched mixture	Calcium- enriched mixture	-	Visual
Chamiotis (13)	Greece	1 (incisor)	24 months No discoloration was observed in both teeth treated with calcium hydroxide or TAP Crown discoloration was observed	-	WMTA	-	Visual
Cho <i>et al.</i> (11)	Korea	1 (canine)	24 months DAP / ciprofloxacin and metronidazole	DAP / ciprofloxacin and metronidazole	GMTA	-	Visual
Plascencia <i>et al.</i> (14)	Mexico	1 (Incisor)	32 Months Bluish-gray discolorations was observed after the application of paste Mild discoloration was observed	Ca(OH) <sub>2</sub>	WMTA	-	Visual
Ray <i>et al.</i> (10)	USA	1 (incisor)	36 months DAP ciprofloxacin and metronidazole	DAP ciprofloxacin and metronidazole	GMTA	-	visual
She <i>et al.</i> (80)	China	1 (premolar)	66 Months The tooth presented discoloration	Ca(OH) <sub>2</sub>	GMTA	-	Visual
Wang <i>et al.</i> (94)	China	2 (premolar)	17/18 months It was observed discoloration in cervical region It was observed discoloration	TAP	WMTA	-	visual
Bakhtiar <i>et al.</i> (72)	UK	4 (incisor)	18 months Discoloration was observed in 4 of 4 cases. Besides, Dentin walls of the pulp chamber were sealed with bonding.	TAP/cefclor	Biodentine	-	Visual
Chan <i>et al.</i> (73)	Canada	28(Main incisor)	30 months Discoloration was observed in 16 of 28 teeth evaluated. Also, the discoloration occurs only in teeth with traumatized previously.	TAP/cefclor	GMTA	-	Visual
Timmerman <i>et al.</i> (81)	Australia	1 (incisor)	36 months The tooth did not presented discoloration	Ca(OH) <sub>2</sub>	GMTA	-	Visual

TAP: ciprofloxacin, metronidazol e amoxicilina; TAP/cefclor: ciprofloxacin, metronidazol e cefaclor; TAP/clind.: ciprofloxacin, metronidazol e clindamicina; TAP / tetra ciprofloxacin, metronidazole, and tetracycline; GMTA: grey mineral trioxide aggregate; WMTA: white mineral trioxide aggregate

presented color change (8–11,73–75,80,81). Considering the 63 teeth treated with AM to TAP/AM to GMTA, 21 (33.3%) presented crown discoloration (6,7,13,14,69,70,72,76–79). Thus, a tendency to avoid dental color alterations in studies that employed alternative materials (to TAP and GMTA) is observed in the Figure 2.

Moreover, we observed few studies that followed the strategy advised by AAE for avoid discoloration, sealing pulp chamber walls with dentin bonding agent. Bezgin et al. (6) applying this strategy observed no dentin discoloration in both two revascularized teeth; while, Bakhtiar et al. (72) observed minimal discoloration in all teeth sealed with dentin bonding.

In three studies dental bleaching was performed in 16 teeth (4,9,83) to restore the natural dental color. Internal bleaching technique applying sodium perborate as whitening agent was employed in two studies (2 teeth). The third study, associated 10% hydrogen peroxide to the sodium perborate (83). In studies in which only sodium perborate was used, authors described an improvement in the color of the teeth, but teeth do not return to the original shade. Satisfactory results were reported for 11 of the 14 teeth treated with sodium perborate associated with hydrogen peroxide.

## Discussion

The regeneration of NIPT is a recent approach presenting promissory results (1,2). However, the risk of tooth discoloration, observed in several cases (10,16,18,69,87,89,92,94), can compromise esthetic results and even the quality of life of the individuals (96). In the present study, the literature was systematically reviewed to assess whether alternative materials to conventional

TAP and GMTA could avoid tooth discoloration after pulp revascularization. The included studies showed that there is great potential for tooth discoloration after REP. More than 50% of the revascularized teeth presented some color alteration, mainly when TAP was used as intracanal medication and GMTA as cervical sealing material.

TAP is the most used intracanal medication in revascularization (2), presenting biocompatibility (97) and adequate antimicrobial capacity, being able to perform root canal system disinfection (98–100). According to the American Association of Endodontics (AAE) antibiotic pastes should be used at concentrations ranging from 0.1 mg/mL to 1 mg/mL, which promote low cytotoxicity to stem cells from apical papilla (3), maintaining its disinfection ability (101). However, even nowadays, authors have still employed pastes at different concentrations higher than that recommended. A recent case series study reported the use of 1g/mL on detriment to recommended due to clinical difficulties of applying pastes in low concentrations (72). Hence, crown discoloration has been more frequently reported after the use of 1g/mL TAP in root canal treatment. Some studies reports a rapid tooth discoloration after TAP application (89,93). The main reason for tooth staining (69), has been advocated to minocycline, a tetracycline derivate, present in TAP composition (102). Discoloration induced by minocycline normally occurs in the first 24 hours after its use, promoting a bluish-grey staining, clinically perceivable (11). Usually, this alteration is more evident in tooth crown, and in the cervical third of the root (102). Therefore, modifications to the original TAP (98) have been proposed, with the aim at avoiding discoloration, by the use of cefaclor (6,7,70,72,73), amoxicillin (8,74) and clindamicine instead of minocycline (9) Nevertheless,

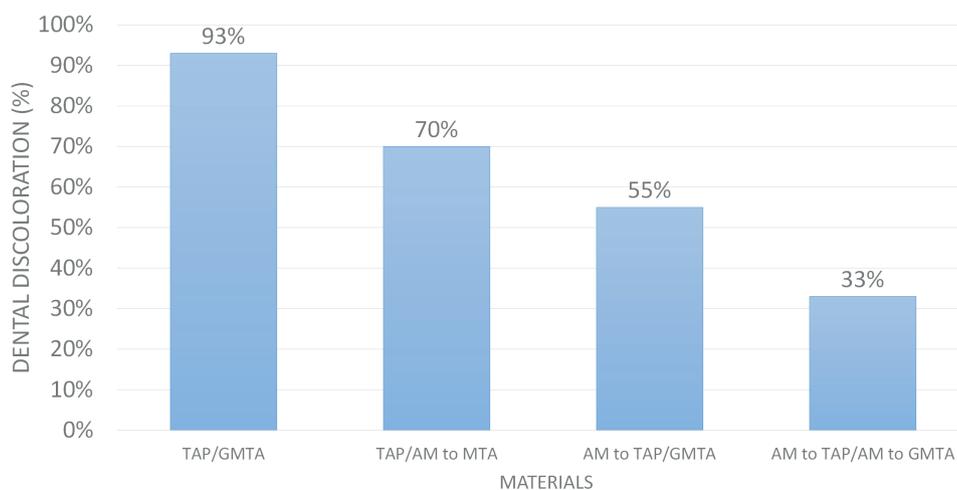


Figure 2. Tooth discoloration according with materials used to regenerative endodontic treatment.

some degree of discoloration has been still observed after the use these alternative medications. Dabbagh et al. (7) associating WMTA to TAP/cefaclor observed discoloration in only one of the 18 revascularized teeth. An *in vitro* study showed that TAP with minocycline promoted higher discoloration than TAP with amoxicillin, doxycycline, or cefaclor (102). It was also observed that TAP induced a severe color change in the first day of the assessment, while the use of amoxicillin showed similar discoloration only after one week. On the other hand, double antibiotic paste (DAB - metronidazole and ciprofloxacin) and  $\text{Ca}(\text{OH})_2$  did not produced color alterations (102). Another *in vitro* study showed similar discolorations induced by these pastes, while the most esthetic outcomes were found when alternatives to minocycline were used (5).

A reduced number of cases reporting discoloration were observed when  $\text{Ca}(\text{OH})_2$  was applied as intracanal medication, however, from 20 teeth revascularized with  $\text{Ca}(\text{OH})_2$  six presented some color change (14,69,76-81). This may be explained by the fact that the materials used in the cervical plug can also promote discoloration, especially GMTA (80,81). Although in some cases is difficult to define if the color change was promote by antibiotic paste.

GMTA has been extensively used as cervical sealing material, being applied above the blood clot in resvascularized teeth (2). However, GMTA presents high levels of iron, magnesium, aluminum, as well as bismuth oxides as radiopacifier, which can oxidize promoting tooth discoloration (12). Staining due to MTA can occur immediately after the first day of application and increase over the time (21). Aiming to avoid tooth discoloration, WMTA was developed, with significant reduction of minerals in its composition. Despite this, *in vitro* studies have shown that WMTA also could promote some degree of discoloration (20,21).

Only one study included in this review used Biodentine™ as cervical plug. As a result, all teeth treated showed minimal discoloration (72). In these cases, the color alteration probably can be attributed to the biochemical interaction between Biodentine™ and platelet-rich fibrin (PRF), mixed to the blood clot, since Biodentine presents zirconium oxide as radiopacifier instead of bismuth oxide (20,21). Biodentine™ was recently developed tricalcium silicate-based material, which presents high biocompatibility and mechanical resistance (103). Recently, in order to avoid the negative effect of the Portland cement-based materials on tooth color, AAE (3) recommends the use of glass ionomer cement in the cervical sealing, especially for the anterior teeth, in which esthetics assumes an important role. No study included in this review used GIC for this purpose.

Another reported way to minimize the risks of tooth discoloration is sealing dentinal tubules of the pulp

chamber with adhesive agent prior to the use of TAP (3). However, more studies are necessary to confirm the role of adhesive agents in prevent color alterations following REP. In the present review, three studies performed this preventive technique (6,70,72). Bezgin et al. (6) applying adhesive agent previously intracanal medication with TAP/cefaclor, followed by WMTA as cervical sealing material. No discoloration was observed in both two evaluated teeth. However, in a study performed in 20 cases of revascularization, the application of an adhesive agent before TAP/cefaclor, did not prevent discoloration in 12 teeth. Nevertheless, the staining was attributed to the GMTA, used as cervical sealing material (70). Finally, Bakhtiar et al. (72) also sealed coronal dentinal tubules prior to treat root canal with TAP/cefaclor; however, as cervical sealing material Biodentine™ was used rather MTA. Discoloration occurred in all the four revascularized teeth. Authors attributed the staining to the interaction between Biodentine and PRF. Confirming the results of those studies, an *in vitro* (4) one observed that the use of the adhesive (self-etching, 2-component adhesive dentin bonding system) reduced, but did not prevent staining. The samples became yellow, reproducing the color of minocycline. The explanation for this was probably due the use of a clear bonding agent, without the ability of completely blocking the yellowish color of the antibiotic. Besides, it is important highlight that the REP *per se* can promote some degree of discoloration. An recent *in vitro* study that evaluate by spectrophotometry the change color in teeth submitted to REP observed a low discoloration in the control group – no antibiotic pastes treatment (5).

Aiming restore tooth color, some studies reported perform dental bleaching. The crowns were treated by the internal bleaching technique with sodium perborate or sodium perborate associated to hydrogen peroxide (4, 9, 83). However, neither technique was able to restore the original color of the crowns. These results did not corroborate with a study that used spectrophotometer, before and after the use of materials commonly applied in REP, to investigate the efficacy of dental bleaching on the color of bovine teeth. The results showed that only one application of 10% carbamide peroxide, inside the pulp chamber and on the outer surface of the crown, was enough to make the color of the teeth similar to the original one (5).

In all the studies included in this review, the visual method of analysis was used to evaluate the color change. However, this method results in a subjective evaluation, which can be affected by factors such as the experience and the chromatic perception of the evaluator, the illumination of the environment (104). In order to avoid biases resulting from the evaluation of the human eye, spectrophotometers should be used instead. Spectrophotometer devices

determine the color of the tooth from numerical values that represent light and hue, being considered reliable methods for color reading (105). However, these devices are not yet widely used in the clinical routine.

It is important to highlight that reports of tooth discoloration was found predominantly in cases treated with TAP and GMTA. Although the high amount of studies found at the initial search, many studies did not fulfill inclusion criteria of this review. Therefore, the present results should be interpreted with caution. Since the main outcome assessed in included studies was the survival of the teeth, dental color was mostly reported as secondary data. Therefore, tooth discoloration might had been underestimate, being reported only in those cases in which a major color change was noticed. Moreover, the lonely effect of the different materials involved in REP on tooth discoloration is a very hard task, since intracanal medication and cervical sealing are applied sequentially, and both have potential to induce tooth color alteration. The conduction of randomized clinical trials evaluating tooth color on each phase of regenerative endodontics is highly recommended to better understand the role of each material in tooth discoloration.

Alternatives to conventional Triple Antibiotic Pastes and Gray MTA avoid tooth discoloration in teeth submitted to revascularization. The association of alternatives to Triple Antibiotic Paste and alternatives to Gray MTA resulted in minor discoloration. Dental bleaching is able to reverse partially the color of discolored teeth due to REP. Minocycline seems to be the main responsible for discoloration induced by TAP.

## Resumo

Esta revisão sistemática teve como objetivo avaliar se materiais alternativos à pasta tri-antibiótica convencional (TAP, em Inglês - metronidazol, ciprofloxacina e minociclina) e ao agregado trióxido mineral cinza (MTA cinza) poderiam evitar a descoloração dentária em dentes submetidos ao procedimento endodôntico regenerativo (REP, em Inglês). Também foi investigado se o clareamento dental é capaz de reverter a cor dos dentes escurecidos devido ao REP. A busca foi realizada em quatro bases de dados (Medline via PubMed, Scopus, ISI Web of Science e BVS - Biblioteca Virtual de Saúde), seguindo os Principais Itens para Relatar Revisões Sistemáticas e Meta-análises. Os artigos obtidos foram carregados no software EndNote™ e dois revisores independentes selecionaram os estudos e extraíram os dados. Apenas estudos em humanos (relatos de casos, séries de casos, ensaios clínicos) foram incluídos na revisão. De 1.122 estudos potencialmente elegíveis, 83 foram selecionados para análise do artigo completo, e 38 foram incluídos na revisão. Os estudos incluídos foram principalmente relatos de casos (76,3%). Os estudos descreveram um total de 189 dentes submetidos ao REP. Destes, cerca de 54% dos dentes apresentaram algum grau de descoloração. A maioria dos dentes com alteração de cor foi tratada com TAP, principalmente quando combinada com MTA-cinza. Apenas três estudos realizaram o clareamento dental para restaurar a cor dos dentes e nem a técnica de clareamento conseguiu restaurar a cor original das coroas. O uso de materiais alternativos à TAP e ao MTA cinza, como a pasta bi-antibiótica, pasta de Ca(OH)<sub>2</sub> e MTA branco ou Biodentine™, reduz a ocorrência de descoloração dentária.

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