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Comparison of Antibiotic Pastes for Tooth Discoloration and Internal Bleaching: An *in vitro* Study

Antibiyotikli Patların Dişlerdeki Renk Değişikliği ve İnternal Beyazlatma Açısından Karşılaştırılması: *in vitro* Çalışma

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This study was presented as an oral presentation at 1st International Dental Research and Health Sciences Congress, May 20-22, 2021, Online.

ABSTRACT Objective: The goal of this research was to examine the color changes that occurred after using various versions of triple antibiotic pastes (TAP) and the teeth-whitening effects of sodium perborate on these colored teeth. **Material and Methods:** The endodontic access cavities of thirty extracted bovine incisors were prepared and then the root canals were enlarged to mimic the immature teeth. The samples were separated into three groups based on the intracanal antibiotic paste placement, TAP-D: mix of metronidazole, ciprofloxacin, and doxycycline, TAP-C: mix of cefaclor, metronidazole, and ciprofloxacin, and TAP-A: mix of amoxicillin+clavulonic acid, metronidazole, and ciprofloxacin. The pastes were inserted into the root canals. After 3 weeks, the pastes were removed. Sodium perborate was placed into the access cavities for bleaching and replaced every week for 3 weeks. Spectrophotometric measurements were obtained at baseline and every week for six weeks. The ΔE value was calculated and analyzed using a two-way analysis of variance and post-hoc Tukey's test (p=0.05). **Results:** Color changes in the TAP-A were statistically significantly higher than the values obtained with TAP-C (p<0.001), and TAP-D (p<0.001). There was no statistically significant difference between TAP-C and TAP-D (p>0.05). For every group, the agent's bleaching impact was statistically similar (p>0.05). **Conclusion:** Mix of amoxicillin+clavulonic acid, metronidazole, and ciprofloxacin caused more discoloration than the other pastes. Sodium perborate provided same bleaching effect on all types of paste groups.

Keywords: Amoxicillin-clavulanic acid combination; cefaclor; regenerative endodontics; tooth bleaching; tooth discoloration

ÖZET Amaç: Bu çalışmanın amacı, çeşitli kombinasyonlardaki üçlü antibiyotikli patların (ÜAP) kullanımı sonrasında oluşan renk değişikliklerini ve sodyum perboratın renklenmiş dişler üzerindeki beyazlatma etkinliklerini incelemektir. **Gereç ve Yöntemler:** Otuz adet çekilmiş sığır keser dişin endodontik giriş kavitelerinin preparasyonu yapıldı ve daha sonra kök kanalları olgunlaşmamış dişleri taklit edecek şekilde genişletildi. Örnekler kanal içi antibiyotik pat yerleşimine göre ÜAP-D: Metronidazol, siprofloksasin ve doksisiklin karışımı, ÜAP-S: Sefaklor, metronidazol ve siprofloksasin karışımı ve ÜAP-A: Amoksisilin+klavulanik asit, metronidazol ve siprofloksasin karışımı olmak üzere 3 gruba ayrıldı. Patlar kök kanallarına yerleştirildi. Üç hafta sonra patlar uzaklaştırıldı. Giriş kavitelerine beyazlatma amacıyla sodyum perborat yerleştirildi ve 3 hafta boyunca her hafta değiştirildi. Spektrofotometrik ölçümler başlangıçta ve 6 hafta boyunca her hafta yapıldı. ΔE değeri, iki yönlü varyans analizi ve "post hoc" Tukey testi kullanılarak hesaplandı ve analiz edildi (p=0,05). **Bulgular:** ÜAP-A grubundaki renk değişikliği, ÜAP-S ve ÜAP-D ile elde edilen değerlerden istatistiksel olarak anlamlı derecede yüksekti (p<0,001). ÜAP-S ve ÜAP-D arasında istatistiksel olarak anlamlı seviyede fark yoktu (p>0,05). Her grup için ajanın ağartma etkisi istatistiksel olarak benzerdi. (p>0,05). **Sonuç:** Amoksisilin+klavulanik asit, metronidazol ve siprofloksasin karışımı, diğer patlara kıyasla daha fazla renk değişikliğine neden oldu. Sodyum perborat tüm pat gruplarında aynı ağartma etkisini sağladı.

Anahtar Kelimeler: Amoksisilin-klavulanik asit kombinasyonu; sefaklor; rejeneratif endodonti; diş beyazlatma; dişte renk değişikliği

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Regenerative endodontic treatment (RET) is an alternative to conventional endodontic treatment for immature and necrotic permanent teeth. RET procedure aims to provide root maturation and apical closure. The main steps of RET are as following: (i) minimal/no instrumentation of the root canal walls, (ii) disinfection with irrigation (iii) intracanal medicament usage, (iv) blood clot formation into the root canal, (v) cervical sealing, and (vi) coronal restoration.[1]

The disinfection of the canal system is traditionally provided with chemical irrigation solutions and mechanical instrumentation. However, in RET procedure instrumentation is not recommended to weaken the thin root canals of an immature tooth.[2,3] The higher concentration of sodium hypochlorite (NaOCl) irrigation is not recommended to prevent the damage of the stem cells in RET procedure.[3] Therefore, the essential disinfection method in RET is intracanal medicament application. A mix of metronidazole, ciprofloxacin, and minocycline [triple antibiotic paste (TAP)] is most used antibiotic paste for RET procedures. Although TAP can achieve a satisfactory antimicrobial effect, minocycline was found associated with crown discoloration.[4] Modified forms of TAPs containing various antibiotics instead of minocycline (doxycycline, cefaclor, amoxicillin+clavulonic acid etc.) were developed to eliminate the discoloration effect of antibiotic pastes.[5-7] The amoxicillin+clavulanic acid, cefaclor and doxycycline had been successfully used in RET procedures.[8-10]

Teeth discoloration induced by intracanal antibiotic pastes can be whitened by intracoronal oxidizing agents as it is a reliable choice that needs less treatment time.[11] Sodium perborate, hydrogen peroxide, and carbamide peroxide had been previously used for whitening of the discolored immature teeth that were treated with RET procedures.[12-15] Sodium perborate is a common bleaching agent, which is less hazardous and easier to manage than concentrated hydrogen peroxide solutions.[16] The mix of sodium perborate and distilled water decomposes into sodium metaborate, hydrogen peroxide, and oxygen and behaves as an oxidizing agent.[17] Discoloration can be determined with a variety of techniques such as color scales, colorimeters, spectrophotometers, and digital photography. Spectrophotometers are widely used method in dentistry as they are dependable for detecting tooth color shade. VITA Easyshade® spectrophotometer was claimed to be a reliable and accurate device.[18]

Tooth staining after intracanal antibiotic paste placement is an unfavorable outcome especially in anterior region, although it can be reversed by intracoronal bleaching agents. This *in vitro* study aimed to evaluate the discoloration effects of the antibiotic pastes used in RET procedures [TAP with amoxicillin+clavulanic acid (TAP-A), TAP with cefaclor (TAP-C) and TAP with doxycycline (TAP-D)] and to examine whether discoloration can be reversed by sodium perborate by using VITA Easyshade® spectrophotometer. The null hypothesizes of this study were that (I) there would be no difference among the antibiotic pastes for tooth discoloration and (II) there would be no difference for the bleaching effect of sodium perborate on the paste groups.

MATERIAL AND METHODS

As a result of the power analysis performed with the G-Power program (Version 3.1, Heinrich Heine Universitat, Düsseldorf, Germany), the number of samples was determined as 30 samples for 3 groups, 10 per group (effect size=0.25, α=0.05, power=0.95, number of measurements=6, correlation among repeated measures=0.5, nonsphericity correction ε=1). The endodontic access cavities of thirty extracted bovine incisors were prepared. To ensure that the root lengths were uniformly 12 mm from the apical foramen to the cementoenamel junction, the apical portions of each tooth were sectioned separately. Hand files up to a #80 K-file and #1-6 peeso-reamer drills were used to instrument the root canals. Two milliliters (mL) of 1.5% NaOCl were used for irrigation with every instrument change. For the final irrigation regimen, 20 mL of 1.5% NaOCl (5 min), 5 mL of distilled water, and 20 mL of 17% ethylenediaminetetraacetic (EDTA) were used. After that, paper points were used to dry the root canals. The samples were randomly separated into three groups based on the intracanal antibiotic paste placement, as shown below:

TAP-D group: The paste contains of equal portions of metronidazole (Sanofi, İstanbul, Türkiye), ciprofloxacin (Biofarma, İstanbul, Türkiye), and doxycycline (Deva, İstanbul, Türkiye).

TAP-C group: The antibiotic paste consists of equal portions of cefaclor (Sanovel, İstanbul, Türkiye), metronidazole, and ciprofloxacin.

TAP-A group: The antibiotic paste consists of equal portions of amoxicillin+clavulonic acid (GlaxoSmithKline, İstanbul, Türkiye), metronidazole, and ciprofloxacin.

The pastes were prepared by mixing the powder with distilled water with a powder/liquid ratio of 1 mg/1 mL, and then inserted into the root canals with a lentulo spiral. The apical openings of the canals were sealed with a composite resin, and the access cavities were temporarily filled (Cavit G; 3M ESPE, Seefeld, Germany). The teeth were kept in storage at 100% humidity and 37 °C. Following a 21-day period, 17% EDTA (20 mL, 4 min) and distilled water (5 mL, 1 min) were used to remove the antibiotic pastes.

Following the removal of the antibiotic paste, a 2 mm thick glass ionomer cement was applied 1 mm below the cement-enamel junction. A plastic tool was utilized to, sodium perborate powder was diluted with distilled water in a 2:1 ratio and then inserted into the pulp chamber using a plastic tool. The access cavities were then temporarily closed (Cavit G; 3M ESPE, Seefeld, Germany). The bleaching agent in the access cavity was replaced every week for 3 weeks. Color measurements on teeth were performed at the following times: Beginning (T0), every week during the time that the antibiotic paste waits in the root canal (T1-T2-T3), and every week that the bleaching agent is replaced after the removal of the antibiotic pastes (T4-T5-T6) (Figure 1).

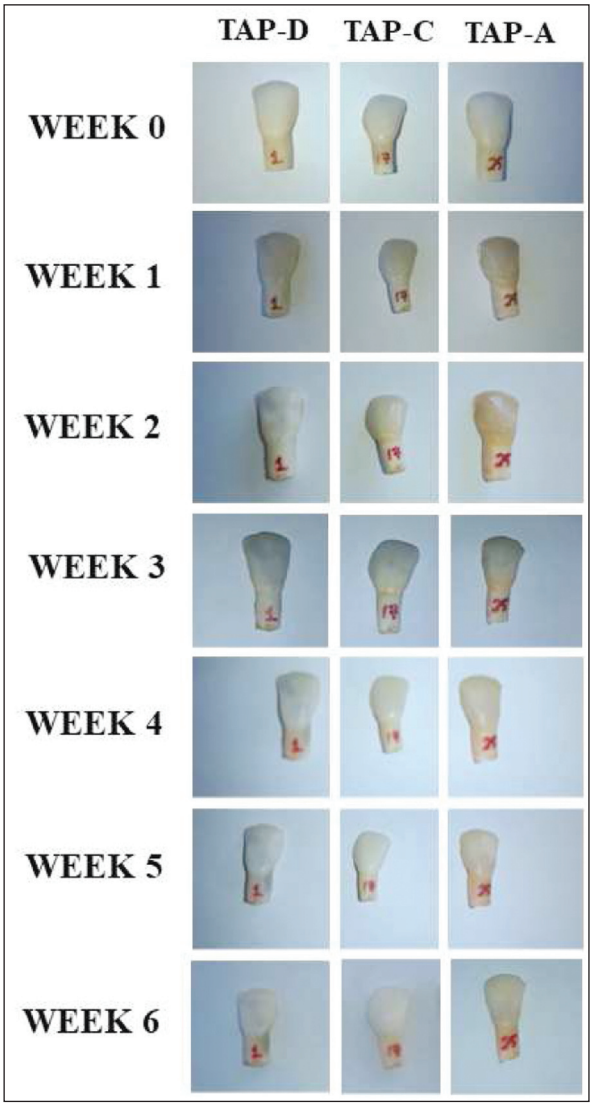

FIGURE 1: Representative images obtained in discoloration and bleaching periods for three groups.
TAP: Triple antibiotic paste; TAP-D: TAP with doxycycline; TAP-C: TAP with cefaclor; TAP-A: TAP with amoxicillin+clavulanic acid.

Every week on the same day, at the same time, measurements were made from the middle third of the buccal surface of each tooth, in the day light. The specimens were dried using a blower for three seconds prior to measurement. The spectrophotometer was calibrated prior to each measurement, and each was performed three times. Vita EasyShade 5 spectrophotometer (VITA Easyshade Compact 5.0, VITA Zahnfabrik, Bad Säckingen, Germany) device was used for color measurement. This device makes the measurements with system called CIE Lab (L * a * b *) that means:

L = color lightness and values change on this scale, from 0 for black to 100 for white,

a = red (positive values) to green (negative values),

b = yellow (positive values) to blue (negative values) color components.

The formula below is utilized to determine the ΔE value of the color difference between two colors:

$\Delta E = [(\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2]^{½}$. The spectrophotometer device was calibrated before measurement procedure as the manufacturer's instructions.

Statistical analyses were performed using SPSS 21.0 software (SPSS Inc., Chicago, IL, USA). ΔE values were calculated and statistical analysis was performed using two-way analysis of variance and post-hoc Tukey test. Statistical significance level was determined as $p<0.05$. The threshold for human detectability was set at 3.7 units to identify the clinically noticeable differences between measurements.[6]

RESULTS

For every group, the ΔE value indicated a color difference over all time units (ΔE>3.7). Color changes after intracanal antibiotic paste placement were shown in Table 1 and Figure 2. Color changes in the TAP-A group were statistically significantly higher than the values obtained with TAP-C (p=0.000), and TAP-D (p=0.000). There was no statistically significant difference between TAP-C and TAP-D groups (Figure 1) (p=0.138). Following the administration of the antibiotic paste, the color change observed at weeks two and three (T2 and T3) was statistically similar (p=1) and both were greater than that observed in the first week (T1) (p=0.000 for both weeks).

Color differences obtained after intracoronal bleaching agent were shown in Table 1 and Figure 2. For every group, the agent's bleaching impact was statistically comparable (p>0.216). The ΔE value achieved at 2nd week after intracoronal bleaching agent placement (T5) was statistically significantly higher than that was provided at 1st week (T4)

TABLE 1: Mean ΔE values obtained after intracanal antibiotic paste placement (T1, T2 and T3) and after intracoronal bleaching agent placement (T4, T5 and T6).

	Discoloration with antibiotic paste (X̄±SD)			Whitening with bleaching agent (X̄±SD)		
	T1	T2	T3	T4	T5	T6
TAP-D	5.65±3.23	9.87±4.55	10.71±4.72	10.83±3.32	13.88±5.60	13.88±5.61
TAP-C	5.74±3.71	13.29±4.12	13.87±4.22	12.18±3.97	18.63±3.26	12.18±3.97
TAP-A	19.62±3.28	28.76±5.20	24.27±5.00	10.27±5.38	12.98±3.18	11.18±5.07

SD: Standard deviation; TAP: Triple antibiotic paste; TAP-D: TAP with doxycycline; TAP-C: TAP with cefaclor; TAP-A: TAP with amoxicillin+clavulanic acid.

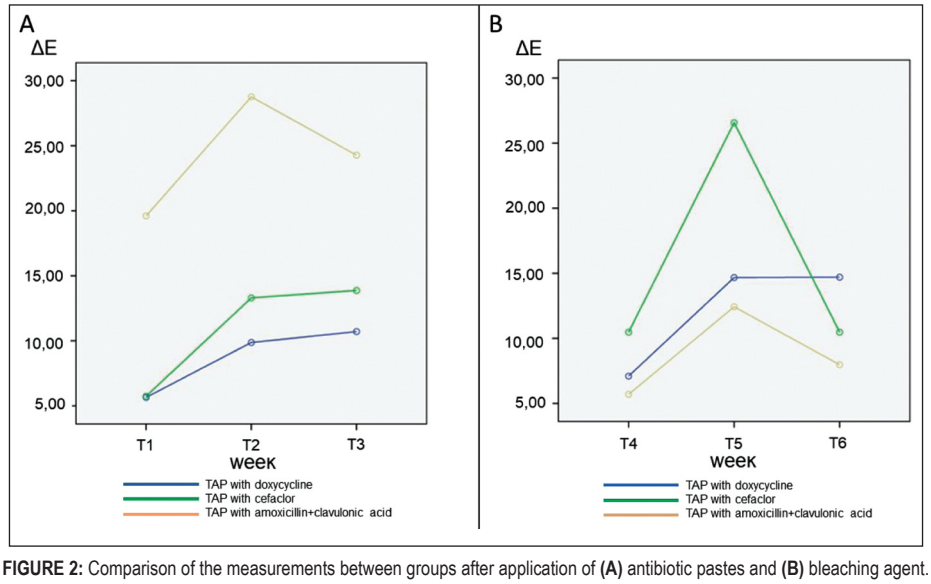

FIGURE 2: Comparison of the measurements between groups after application of **(A)** antibiotic pastes and **(B)** bleaching agent. TAP: Triple antibiotic paste.

(p=0.02). There was no statistically significantly difference between T5 and T6 (p=0.059), and T4 and T6 (p=0.772).

DISCUSSION

The purpose of the current study was to compare color changes that occurred following the application of various antibiotic pastes and the bleaching effects of sodium perborate on stained teeth. TAP-A produced more discoloration than TAP-C and TAP-D. The color changes in TAP-C and TAP-D were comparable. For all pastes, sodium perborate had a similar bleaching effect. Thus, the null hypothesis (I) was rejected, and the null hypothesis (II) was accepted.

The American Association of Endodontists has advised using TAP with minocycline in RET procedures.[19] TAP is mostly used in RET because of its capacity to remove microorganisms from dentinal tubules.[20] As a component of an intracanal medicament, minocycline has been proven to have a considerable tooth staining impact.[21,22] Thus, many antibiotics have been used instead of minocycline to address aesthetic problems. Alternatives to TAP with minocycline include modified antibiotic pastes that use amoxicillin, clindamycin, or cefaclor instead of the minocycline, as well as double antibiotic pastes made of ciprofloxacin and metronidazole.[23,24]

According to the CIE L*a*b* system, ΔE values under 3.7 indicate a clinically apparent difference.[6] According to the results of this study, the ΔE values obtained after intracanal antibiotic paste placements were over 3.7. All the pastes used in this study provided visible color changes.

Previously, it was shown that TAP with minocycline caused the most discoloration, followed by TAP-D, TAP-A and the TAP-C, all of which caused less discoloration.[5-7] However, in this study, TAP-A produced greater discoloration than TAP-C and TAP-D. Fundaoğlu Küçükekenci et al. used the antibiotic pastes at a concentration of 0.1 mg/ 1 mL, and the other studies recorded the final paste concentration as 3:1 powder/liquid ratio.[5-7] In this investigation, all antibiotic pastes were utilized at a dosage of 1 mg/1 mL. The variations in concentration between the studies could explain for these findings. When compared to higher concentrations, using the antibiotic pastes at a lower concentration was associated with more stem cell survival but less antibacterial efficacy.[25] Due to the liquid-like consistency of antibiotic pastes at lower concentrations, carrying the medicaments into the root canals might be challenging.[25] Therefore, in this research, the concentration was set to 1 mg/1 mL.

The antibiotic paste was left in the root canals for 3 weeks, in this study. The colors were recorded at the first, second, and third weeks following the placements. It was claimed that the antibiotic-induced discoloration increases over time.[5] The present study showed that the color changes at two and three weeks after antibiotic paste placement were more significant than those seen in the first week.

There is not a consensus on how whitening procedures should be practiced.[11] Previously, using 35% hydrogen peroxide, sodium perborate and 37% carbamide peroxide were found successful when used for bleaching of immature teeth after RET procedures in some in vitro studies.[6,7,26,27] The bleaching effect obtained with 35% hydrogen peroxide was shown to be greater than that of sodium perborate.[7] Hydrogen peroxide 35% had been advised to be used with caution in bleaching of immature teeth, since it has a caustic effect.[7,16] In such cases, it is recommended to use safer whitening agents such as sodium perborate, instead.[28] Sodium perborate has been shown to be effective in whitening the teeth discolored with TAP with minocycline.[13,26] The bleaching effect of sodium perborate was found similar on the teeth with open or closed apices, also.[13]

In this study, the impact of different antibiotic pastes on discoloration was assessed using bovine incisors. In a previous study, the tubules in bovine coronal dentin were reported to be similar with that of human dentin in terms of density or diameter.[29] Bovine teeth were previously used for spectrophotometric analysis in simulated immature teeth, as in this study.[5,27,30,31]

The absence of blood clot under the coronal barrier materials was a limitation for the current investigation. Red blood cell lysis generates blood metabolic byproducts, which penetrate into the denti-

nal tubules and cause discoloration.[32] Calcium silicate-based cements are generally used for coronal barrier materials, and these cements' components, such as bismuth, aluminum, magnesium, and iron, also cause discoloration.[33,34] Mineral trioxide aggregate was previously found to cause more discoloration than glass-ionomer cement as coronal barrier material in RET procedures.[27] The influence of antibiotic pastes on discoloration was the main subject of this study. It was thought that the use of blood clot or coronal barrier materials could produce controversial outcomes.

CONCLUSION

Within the limitations of this study, it was concluded that TAP-A had a significant contribution to tooth discoloration compared to TAP-C and TAP-D. The whitening effect of sodium perborate was similar for all the groups discolored with these three antibiotic pastes.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

This study is entirely author's own work and no other author contribution.

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