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The Efficacy of Different Antibiotic Compounds in Regenerative Treatment of Immature Necrotic Teeth

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A B S T R A C T

Objectives: Endodontic treatment of immature teeth poses a significant challenge, especially in achieving a proper seal using traditional obturation methods. Revascularization presents itself as an alternative approach to this problem, and the application of triple antibiotic paste (TAP) has been suggested as a means to achieve disinfection during the procedure. This study aims to compare the antibacterial properties of three different antibiotic combinations to assess their effectiveness on root canal disinfection.

Materials and Methods: Eighty samples were employed to assess the impact of three antibiotic combinations on *Enterococcus faecalis*, *Escherichia coli*, *Streptococcus mutans*, and a combination thereof. The antibiotics included metronidazole, ciprofloxacin, and cefaclor (CCM), the commonly used TAP, and a double antibiotic paste (DAP) composed of metronidazole and ciprofloxacin. Dentin shavings collected using Gates-Glidden drills were placed in microtubes containing a 2ml standard bacterial suspension. Microtube contents were diluted and cultured on BHI agar plates, with colony counts calculated based on dentine shavings' weight in CFU/mg. Kruskal-Wallis and Dunn's post-hoc tests were used for statistical analysis and $P<0.05$ was considered significant.

Results: A significant difference in mean CFU was observed among all bacterial groups ($P<0.05$). Dunn's post-hoc analysis showed a significant difference only between the control group (methylcellulose) and the other antibiotic groups. There was no significant difference between the other antibiotic groups in two-by-two comparisons.

Conclusion: There was no significant difference in the antimicrobial properties of DAP, TAP and CCM. Therefore, DAP and CCM may be used during regenerative treatment.

Keywords: Cefaclor; Tooth, Nonvital; Minocycline, Regeneration; Tooth Discoloration

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INTRODUCTION

Endodontic treatment for immature teeth presents significant challenges attributed to two primary factors: the thin dentin encasing the root canal and the open apex. These factors collectively render the achievement of a proper seal nearly impossible through conventional obturation methods. The conventional method of action in these cases is apexification by calcium hydroxide or MTA apical plug, both of which inhibit the development of the root [1]. Such hindered

developments of the dentin increase the tendency of the teeth to fracture. The European Society of Endodontology endorses revascularization as an alternative treatment strategy for immature necrotic teeth in appropriately selected cases, offering a viable alternative to apexification. This approach facilitates continued tooth development. [2].

Various methods have been suggested for disinfecting root canals in the revascularization procedure. The American Association of Endodontists recommends the use of triple antibiotic paste (TAP), a composition of minocycline, ciprofloxacin and metronidazole antibiotics for this purpose [3]. The primary drawback associated with TAP lies in its potential to induce severe tooth discoloration due to the presence of minocycline, a tetracycline antibiotic [4]. Therefore, an alternative known as double antibiotic paste (DAP), comprising metronidazole and ciprofloxacin [5], has been introduced. However, there is currently insufficient conclusive evidence to firmly recommend the use of DAP over TAP [6]. Several studies and case reports have proposed alternative substances, such as cefaclor instead of minocycline found in TAP [7-9], while others have suggested calcium hydroxide [10] or formocresol [11] as potential alternatives to TAP.

The use of TAP in revascularization procedure is important for disinfecting and preparing proper environment for tissue regeneration and infiltration [12]; However, its aesthetic complications due to the minocycline, necessitates an analysis of possible alternatives. This study assesses the potential of cefaclor as a substitute for minocycline in TAP while also conducting a comparative analysis of the antibacterial properties among three formulations: TAP, CCM (cefaclor, ciprofloxacin, metronidazole), and DAP. The objective is to explore these formulations as potential alternatives to TAP for revascularization. The null hypothesis of this study was that the use of DAP and TAP with cefaclor are not as effective as TAP antimicrobial paste with minocycline.

MATERIALS AND METHODS

The research protocol for this study received approval from the ethical committee of Mashhad University of Medical Sciences under approval number IR.MUMS.REC.1393.79.

Sample preparation.

The effects of CCM, TAP and DAP were analyzed on 80 samples consisting of five consecutive examinations for every 16 cases of single-rooted central incisor human teeth with closed apices. Methylcellulose, owing to its neutral nature and lack of inherent antibacterial properties, served as the positive control group in this study [13]. Subsequently, the impact of antibiotics was assessed across four bacterial groups: *Enterococcus faecalis*, *Escherichia coli*, *Streptococcus mutans* and a combination of these bacteria (Mix). Any form of calculus or periodontal tissue was removed using an ultrasonic hand-piece. The samples were preserved in a 3% chloramine-T solution. Using a slow-speed hand-piece diamond disc (Dorsa, HLF 86, Tehran, Iran) under water cooling, the crown was cut below the cementoenamel junction (CEJ) on the coronal third of the root and a root length of 12mm was achieved. The length of each canal was then determined using a digital periapical radiograph with a #15 K-file (Mani; Utsunomiya, Tochigi, Japan) and the crown-down preparation of root canals was carried out using Gates-Glidden drills #4, #3, #2 and #1 (Mani Inc, Takanezawa, Japan). Ultimately the canals were prepared up to a #60 file. During the preparation, physiological serum was used for irrigation. Following the previous steps, the smear layer was removed using consecutive three-minute irrigation with a 5.25% sodium hypochlorite solution and 17% Ethylene diamine tetra acetic acid. Final irrigation was performed using normal saline. The complete removal of the smear layer was then confirmed by a scanning electron microscope (SEM) on two specimens as the control.

The samples were processed inside an autoclave at 121°C at 15psi for 20 minutes. They were then incubated in a brain, heart infusion (BHI) broth for 24 hours at 37°C to ensure a successful sterilization.

Each sample was carefully deposited within a

microtube, each containing 2ml of standard bacterial suspension. To establish the standard bacterial suspension, the culture media underwent incubation at 37°C for 24 hours, with bacterial growth occurring in a BHI broth at a density of 10^8 cells/ml. The density of the suspension was quantified using a spectrophotometer set at an optical density of 600 nm, in accordance with a 0.5 McFarland standard. To maintain continuous growth, the culture media were refreshed every 3 days, with the samples consistently kept at a temperature of 37°C throughout these procedures.

Medicaments preparation

To prepare antibiotic pastes, the antibiotic coatings were removed by scraping tablet coatings and opening capsules. Subsequently, materials were mixed with equal weight ratios. For the CCM group, cefaclore (250mg) (Losefar; Zentiva Co, Istanbul, Turkey) was mixed with ciprofloxacin (250mg) (Aria, Tehran, Iran) and metronidazole (250mg) (Daroopakhsh, Tehran, Iran) in a one-to-one ratio. The TAP group consisted of minocycline (50mg) (Ratiopharm, Ulm, Germany) combined with ciprofloxacin and metronidazole in the same ratio. The DAP group included a combination of ciprofloxacin and metronidazole in a one-to-one ratio.

Infectious specimen preparation

After the incubation period, the specimens were washed using 1ml normal saline for 10 minutes to clean off the residual broth. The external surface of the samples was covered using nail polish. Each bacterial group was tested against 4 subgroups: CCM, TAP, DAP and the control group, which had their canals only filled with methylcellulose and did not receive any medication. The antibiotic pastes were applied using a #40 lentulo and both sides of the canal were sealed using wax, simulating the clinical procedure. The specimens were then incubated for 3 weeks at 37°C and 100% humidity.

After 3 weeks, the wax was removed and the canals were washed with 10ml normal saline. Gates-Glidden drill #5 and #6 were used to collect dentin shavings for sampling at 200µm and 400µm depths from all areas of the canal and were placed in weighed microtubes using digital scale with 10^{-4} accuracy. The weight of the dentin shavings was determined by measuring the difference in weight between the microtubes with and without the shavings. Each microtube then received an addition of 1ml physiological serum and 1ml tryptic soy broth (TSB). These microtubes were then incubated for 24 hours at a temperature of 37°C.

After 24 hours, 1ml of the microtubes' contents was diluted in 9ml normal saline. Finally, 50µl of the mixture was spread onto BHI agar plates (BHI, Merck, Darmstadt, Germany) and incubated for 24 more hours at 37°C. The count of the formed colonies was calculated based on the weight of the dentine shavings in colony-forming units (CFU)/mg [14]. The experiment was repeated 5 times for every group. The purity assessment of the cultures was carried out using gram staining and Bile Esculin Azide Agar culturing.

Statistical analysis

Statistical analyses were conducted to compare the mean CFU values between the bacterial groups for each studied compound, as well as to compare different antibiotic compounds within each bacterial group. The Kruskal-Wallis test was initially performed, followed by pairwise multiple comparison using the Dunn test. Additionally, the mean CFU values of the bacterial groups in the control compound, methyl cellulose, were compared using ANOVA and Tukey test. All statistical analyses were conducted at a significance level of 5%.

RESULTS

In this study, CFU of four bacterial groups, *E. faecalis*, *E. coli*, *S. mutans* and Mix, were measured in response to three disinfectant groups including CCM, TAP, DAP and a methylcellulose as the control group.

The results revealed no significant difference in the effects of the three antibiotics (TAP, DAP, and CCM) within each of the four bacterial groups ($P > 0.05$). However, Dunn's post hoc analysis demonstrated that the number of remaining colonies (CFU) in each of the bacterial groups was significantly higher in response to methylcellulose compared to the other three antibiotics ($P=0.004$, 0.001, 0.001, and 0.008 for the E. faecalis, E. coli, S. mutans, and mix groups, respectively). Additionally, there was no

significant difference in the mean CFU value between the same antibiotic compounds in the four bacterial groups and the only significance was observed in control groups (P=0.238, 0.238, 0.773 and 0.001 for CCM, TAP, DAP, and control, respectively).

Pairwise comparisons between control groups of different bacteria showed that the mean CFU was significantly greater in the mixed bacterial group (P<0.001); Furthermore, E. faecalis was found to have a significantly higher CFU than S. mutans and E. coli (P<0.001), but the difference between S. mutans and E. coli in itself was statistically insignificant (P=1).

DISCUSSION

Revascularization therapy in immature necrotic teeth has been found to significantly increase the thickness of the root wall and improve the length of the root [15]. There are three key factors involved in revascularization of necrotic teeth: 1) effectively disinfecting the canal, 2) creating a suitable scaffold for cell growth, and 3) ensuring a complete seal of the access cavity. When a proper scaffold for cell growth, such as blood clots containing platelet growth factors, is available, the angiogenetic factors present in the dentin can stimulate tissue regeneration in sterile canals [16,17].

Disinfecting the canals in immature teeth is challenging due to the thinness of dentinal walls and the large diameter of the root canals, making mechanical instrumentation risky and nearly impossible [18]. Therefore, chemical disinfection using various canal irrigators and medicaments is recommended. An effective combination that is often recommended as a medicament is triple antibiotic paste [19].

Due to the discoloration caused by minocycline in TAP [4] and the need to remove or replace this compound, some case reports have used cefaclor instead of minocycline and shown favorable antimicrobial results. Also, studies that compared the effect of TAP with DAP did not completely agree that their effect was the same [6]. For this reason, cefaclor was used instead of minocycline in this study, in the hope of achieving a combination with equal or even better effect than TAP.

The rationale for combining different antibiotics was the inability of single empirical antibiotics to eradicate poly-microbial dental infections. On the other hand, using a broad spectrum non-specific antibiotic may destruct normal bacterial flora and residual microorganisms replicated in the canal [20].

Bacterial groups included in this study were *E. faecalis*, *E. coli*, *S. mutans* and a combination of them because these bacteria are predominant in teeth with persistent lesions. *E. faecalis* is the persistent bacterium that exist in infected root canals [21]; *E. coli* is a standard organism in antimicrobial testing [22] and *S. mutans* is an important microorganism in initial pulp lesions and also subsequent pulpal pathologies [23]. Due to the poly-microbial nature of canal infections, a combination of these bacteria used as a separate group.

There are various methods to evaluate the antimicrobial effect of antibiotics, such as agar diffusion, use of natural teeth, use of dentin powder and use of dentin blocks, etc. In this study, we used a modified model of the Haapasalo and Orstavik method [24]. The advantages of using extracted teeth to evaluate the antimicrobial effect of various compounds is a better simulation of the clinical situation and that the results reflect their true activity clinically [25].

The findings of this research indicated that unsurprisingly the antibiotic compounds significantly reduced the colony counts of bacteria in relation to control groups; However, there was no significant difference between the use of cefaclor, ciprofloxacin and metronidazole, or minocycline, ciprofloxacin and metronidazole, or even only ciprofloxacin and metronidazole in terms of bacterial colony counts. Our findings contradict those of Devaraj et al. [6], who demonstrated that TAP, when compared to DAP, effectively disrupted the biofilm, while DAP did not. In line with our research, Sabrah et al. [5] concluded that both TAP and DAP have an equivalent impact on the reduction of *E. faecalis*. Discrepancies in results may be attributed to variations in methodology.

In accordance with our findings, in a similar study Sato et al. [26] found a combination of metronidazole, ciprofloxacin and minocycline effective in disinfecting the canals. Metronida-

zole was found to have significant bactericidal effects against anaerobic microorganisms, protozoa, gram-positive and gram-negative bacteria; it was however not effective against aerobic microorganisms [27]. Ciprofloxacin exhibited antibacterial effects against aerobic microorganisms, gram-positive and gram-negative bacteria, but not against anaerobic microorganisms. Consequentially, studies have shown a greater efficiency in disinfecting the teeth when the two antibiotics are combined [28]. Moreover, minocycline, a tetracycline antibiotic, has been found effective against gram-positive, gram-negative, facultative anaerobic bacteria and spirochaeta [29]. This drug chelates the Ca^{2+} ions found in teeth, even in the first 24-48 hours, causing discoloration; Furthermore, the acidity of minocycline has cytotoxic effects on stem cells [29,30].

Cefaclor is a second-generation cephalosporin antibiotic used to treat gram-negative and gram-positive aerobic infections, which has been proposed as an alternative to the minocycline in TAP by some studies [8,9]. A study by Akcay et al. [31] demonstrated that the use of TAP with cefaclor instead of minocycline, causes a lower degree of discoloration that unlike the minocycline case becomes less evident over time. In accordance with other studies we found that cefaclor has a positive impact on regenerative treatments of immature permanent teeth with the same bactericidal effects and less discoloration [7]. Interestingly, some have reported a lower bactericidal effect for cefaclor in comparison with minocycline. This may be due to their different method of action or sample size [32]. The antibiotic pastes used in our study were mixed with the non-toxic methylcellulose for a longer-lasting effect and a greater convenience in their application inside the canals [33]. In control groups, only methylcellulose was applied.

E. faecalis is a gram-positive facultative anaerobic bacterium that exhibits a high resistance to antibacterial compounds and can result in the failure of root canal treatments [21]. In the present study, *E. faecalis* displayed the most resistance to the antibacterial compounds, such that it had the greatest count of remainder colonies across all other bacterial groups (the other two bacterial groups did not present a significant difference). Due to such high resistance to the absence of nutrients and oxygen in dentin tubules, various studies have used *E. faecalis* to measure the effectiveness of antibacterial products [34].

Considering the limitations of this study, the null hypothesis of the study was not confirmed and the results revealed that the antibiotic combination CCM (cefaclor, ciprofloxacin, and metronidazole) exhibited comparable effectiveness to the TAP mixture (minocycline, ciprofloxacin, and metronidazole) in reducing the microbial counts of all three micro-organisms. Additionally, the DAP mixture (ciprofloxacin and metronidazole) was found to be marginally less effective than the aforementioned formulations. The novel mixture (cefaclor, ciprofloxacin, and metro-nidazole) could potentially address the complications associated with minocycline in TAP. However, further randomized clinical trials with larger sample sizes and extended follow-up periods are essential to confirm the suitability of this mixture as a viable alternative to TAP.

CONCLUSION

DAP (ciprofloxacin and metronidazole) was marginally less effective compared to the TAP and CCM formulations. Substituting minocycline, as found in the triple antibiotic paste, with cefaclor in the regenerative treatment of immature permanent teeth may potentially mitigate the discoloration complications associated with minocycline, while maintaining comparable bactericidal efficacy. Consequently, in clinical cases, the utilization of CCM and DAP as alternatives to TAP appears viable, given the relatively similar results observed among the three antibiotic compositions in this study. However, it is essential to exercise caution when extrapolating results from in vitro studies to clinical practice.

CONFLICT OF INTEREST STATEMENT

None declared.

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