Case Report

Tooth Discoloration of Immature Permanent Incisor Associated with Triple Antibiotic Therapy: A Case Report

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Abstract

Introduction: A triple antibiotic mixture of ciprofloxacin, metronidazole, and minocycline was used as an intracanal medicament in an attempt to disinfect the root canal system for revascularization of a tooth with a necrotic pulp. However, discoloration developed after applying the triple antibiotic mixture. Methods: Six weeks after a triple antibiotic paste had been applied to the root canal of tooth #8 of a 7-year-old girl, the tooth showed a dark discoloration. An in vitro experiment with human extracted teeth was performed to determine which of the 3 antibiotics caused the tooth discoloration. Another experiment was then carried out to examine whether a currently used dentin bonding agent would prevent or reduce such discoloration. The degree of discoloration was assessed by using a colorimeter. Results: Among the components of the triple antibiotic paste, only minocycline caused the tooth discoloration. Moreover, the dentin bonding agent reduced the intensity of the discoloration but did not prevent it. Conclusions: The possible esthetic problems with the tooth color should be considered when using minocycline as a canal medication. (J Endod 2010;36:1086–1091)

Key Words
Discoloration, immature teeth, minocycline, regenerative endodontics, revascularization, triple antibiotic paste

Although the precise mechanisms and outcomes are unknown, there have been an increasing number of reports showing that the regeneration/revascularization of nonvital immature permanent teeth might be another treatment option for restoring root development and apical closure (1–6). Disinfection of the root canal system is considered to be one of the very important procedures of this type of treatment. Several authors have used a triple antibiotic mixture (1, 2, 4), which has been extensively investigated by Japanese researchers for disinfection (7, 8). This triple antibiotic mixture consists of ciprofloxacin, metronidazole, and minocycline. This combination’s effectiveness was also proven in the animal study (9). However, the disadvantages of this mixture are not well-known. Among the components of the mixture, minocycline, a derivative of tetracycline, can induce tooth discoloration after long-term oral use (10–13). Kim et al (14) suggested that Ledermix (Haupt Pharma GmbH, Wolfratshausen, Germany) paste introduced in the canal might cause discoloration of teeth, and that such effects might be due to the demeclocycline in the Ledermix paste. However, there has been little concern about the effects of intracanal antibiotic therapy, including minocycline, causing tooth discoloration. The aim of this article was to present a coronal discoloration after triple antibiotic therapy in an immature tooth. Additional objectives were to (1) investigate the possible cause of the discoloration and (2) assess the performance of a dentin bonding agent in the prevention of tooth discoloration.

Case Report

A 7-year-old girl was referred to the Department of Conservative Dentistry of Gangnam Severance Hospital for an evaluation of the right maxillary central incisor. The patient had experienced a traumatic injury as a result of falling down the stairs 1 day prior. Clinical examination revealed that tooth #8 was fractured in the dentin without pulpal exposure. The tooth was sensitive to percussion but reacted normally to cold stimulation. On the day of the visit, the fractured tooth was restored with a light-curing resin-modified glass ionomer (Fig. 1). At the 3-month recall, the patient was asymptomatic and had no abnormal clinical manifestations. The glass ionomer filling was replaced with composite resin by using an etch-and-rinse dentin bonding system. The patient returned 8 months later, reporting a history of spontaneous pain in tooth #8. Tooth #8 had no response to a pulpal vitality test and was sensitive to percussion and palpation. Periapical radiographic examination revealed that tooth #8 had a periradicular radiolucency (Fig. 2). A diagnosis of pulp necrosis with symptomatic apical periodontitis was made for tooth #8. The tooth was isolated with a rubber dam. The access cavity was prepared without local anesthesia because we thought the tooth was nonvital. The patient did not report any painful sensation until the file reached the apex. Pus and necrotic tissue stump were obtained from the file. A revascularization technique was attempted to expect further root development and apical closure of tooth #8, as described elsewhere (4). Copious canal irrigation with 3% sodium hypochlorite was performed. Ciprofloxacin (Cyclin; Ilsung Pharmaceutical Co, Ansan, Korea), metronidazole (Flasimyl; CJ CheilJedang, Hwaseong, Korea), and minocycline (Minocin; SK Chemicals, Osan, Korea) were ground into a powder and mixed with distilled water to a creamy consistency. This antibiotic mixture was applied to the canal by using a lentulo spiral. The access cavity was sealed with Caviton (GC, Aichi, Japan). The patient did not show up at the next appointment and then returned in 6 weeks, complaining of a dark discoloration.
of tooth #8 (Fig. 3). The tooth was asymptomatic to percussion and palpation. Blue-grayish discoloration of coronal tooth structure was noted. Walking bleaching was planned to improve the esthetic problem after the root filling was completed. After removing the antibiotic mixture from the tooth, the root canal was flushed with sterile saline and 3% sodium hypochlorite. Paper points were used to evoke fresh bleeding within the canal, and bleeding was left for 10 minutes to allow clotting. Mineral trioxide aggregate (MTA) was mixed with distilled water and filled over the blood clot to a thickness of 4 mm (Fig. 4).

Figure 1. Radiographic image showing an incompletely developed apex of the central incisors. The fractured tooth (tooth #8) was restored with light-curing resin-modified glass ionomer.

Figure 2. Radiographic image showing periapical radiolucency associated with the apex of tooth #8 at the 11-month follow-up.

Figure 3. Photograph of the right maxillary central incisor showing discoloration.

Figure 4. Radiograph presenting the placement of MTA.
Most procedures were performed under a dental operating microscope. One week later, the patient returned as asymptomatic, and setting of the MTA was confirmed. After obtaining a cervical seal with a resin-modified glass ionomer base, a bleaching agent, sodium perborate mixed with distilled water, was set in place and changed twice with a 7-day interval. Because the cervical dark shade had not improved after the first trial of bleaching, a cervical seal was re-prepared for the placement of a bleaching agent more apically by using a microscope. After 3 walking bleaching procedures, the cervical shade had improved. However, the tooth did not return to its original shade; it appeared bluish-white.

Figure 5. Appearance after 3 consecutive walking bleach treatments illustrating the considerable whitening. The bluish-white tooth shade is still shown in tooth #8 compared with the adjacent teeth.

Continued root development was observed.

Figure 6. Radiographic image and clinical picture at the 8-month recall.

Figure 7. Photographs of the tooth sections at the time intervals after antibiotics application. Only triple antibiotic pastes and minocycline discolored the sections. (A) Mixture of triple antibiotic pastes (B) ciprofloxacin (Cycin), (C) metronidazole (Flasiny), and (D) minocycline (Minocin).
Experimental Study

Determination of Cause of the Discoloration

This experiment examined which antibiotics cause tooth discoloration. Freshly extracted human maxillary and mandibular anterior teeth were collected without any information of the donors. The teeth were sectioned 3 mm above and 5 mm below the cementoenamel junction by using water-cooled diamond points. Endodontic access cavities were prepared, and the root canals of the tooth sections were enlarged by using an Endo-Z bur and Gates-Glidden burs, followed by copious canal irrigation with 17% ethylenediaminetetraacetic acid and 6.0% NaOCl to remove the smear layer. The specimens were divided randomly into 4 groups. In group 1, triple antibiotic mixtures were applied to the root canals of 5 specimens by using a lentulo spiral, mimicking the clinical procedure. In groups 2, 3, and 4, ciprofloxacin, metronidazole, and minocycline pastes were filled in 5 canals, respectively. The specimens were then stored in the dark.

Effect of Dentin Sealing with Dentin Bonding Agent

This experiment examined whether a current dentin bonding agent would prevent or reduce the discoloration. Twenty-eight extracted human maxillary or mandibular incisors were used. The canal of each tooth was enlarged as in the first experiment and then divided randomly into 3 groups as follows: group 1 (10 teeth), minocyclin paste was applied into the root canal before the introduction of the antibiotic (adhesive); group 2 (10 teeth), a bonding layer was polymerized for 20 seconds by using a halogen curing light, and minocycline pastes were applied to the canals 10 minutes after. A 3-mm-diameter spot was made at the center of the crown surface in each sample. The specimens were then stored in the dark for 2 weeks.

The color changes were measured with a colorimeter, Chromameter CR-321 (Konica Minolta Sensing Inc, Tokyo, Japan), and the samples were mounted on a specific sample positioning system for consistent assessments. The colorimeter was calibrated at each time interval, and the tooth colors were measured before the endodontic treatment (baseline) and then once a day for 14 days. The records by the colorimeter were reported in terms of the CIE L*a*b* system.

These 3 parameters for measuring the color changes (ΔL, Δa, Δb) were calculated by subtracting the baseline values from the values taken at each time. In addition, the ΔE* values, which are used to assess the color differences between 2 samples, were obtained by using the following equation:

$$\Delta E^* = \sqrt{(L_2 - L_1)^2 + (a_2 - a_1)^2 + (b_2 - b_1)^2}.$$ 

One-way analysis of variance was used to analyze the change in the CIE Lab parameters by using SPSS 12.0 analytic software (SPSS Inc, Chicago, IL), which confirmed a normal data distribution. Scheffe’s tests were used for a post hoc comparison. A P value <.05 was considered significant.

Results

Determination of Cause of the Discoloration

One day after applying the triple antibiotic mixture, a dark green-brown shade began to appear in the samples. The discoloration became darker with time (Fig. 7). The discoloration was similar to the dark shade in our clinical case. Among groups 2, 3, and 4, only the group 4 (minocycline) specimens showed discoloration in the same manner as the triple antibiotic specimens (Fig. 7).

| Table 1. Mean Change in the CIE Lab Parameters between Baseline Examination and 14 Days after Introduction of Minocycline (mean ± standard deviation) |
|-----------|-----|-----|-----|-----|
| Group     | N   | ΔL* | Δa* | Δb* | ΔE*  |
| 1 (no adhesive) | 10  | −19.9 ± 6.3a | −2.8 ± 1.2c | 1.9 ± 2.9d | 20.4 ± 6.3h |
| 2 (adhesive) | 10  | −13.3 ± 3.2b | −0.3 ± 0.5e | 2.6 ± 2.4f | 13.7 ± 3.4i |
| 3 (control) | 8   | −0.4 ± 2.4c | −0.3 ± 0.6e | −1.3 ± 2.6g | 2.9 ± 2.4i |

Different superscripts denote statistical significance (P < .05).

Figure 8. Mean change in L* values at each time interval (ΔL*).
Effect of Dentin Sealing with Dentin Bonding Agent

Table 1 lists the changes in the CIE Lab parameters before applying the medication and 14 days after medication. The mean changes for each parameter in the different experimental periods are depicted in Figs. 8–11. The changes in brightness $\Delta L^*$ were significantly different in the 3 groups ($P < .05$). Group 1 showed the greatest change, followed by group 2. Significant color changes along the red-green axis $\Delta a^*$ were observed in group 1 ($P < .05$). The dentin bonding agent prevented the color change along this axis significantly ($P < .05$). The color changes $\Delta b^*$, which determine the degree of yellowness and blueness, in the medicated groups were also significantly different from those of the control group ($P < .05$). All medicated teeth showed significant color differences ($\Delta E^*$) compared with the control teeth ($P < .05$). However, the dentin bonding agent reduced the discoloration significantly ($P < .05$).

Discussion

These results showed that among the 3 antibiotics, minocycline was the only cause of tooth discoloration. Minocycline is a semisynthetic derivative of tetracycline and is effective against gram-positive and gram-negative bacteria (9). It binds to calcium ions via chelation to form an insoluble complex. Hence, the minocycline incorporated into the tooth matrix causes the discoloration (15). Therefore, minocycline cannot stain the tooth matrix unless it comes in contact with the coronal dentin. On the basis of this hypothesis, Reynolds et al (16) recommended the use of a special device during the introduction of triple antibiotic pastes to prevent coronal discoloration. However, this procedure requires special appliance such as a Root Canal Projector. Dentin bonding systems are more familiar to dentists and are easy to apply and remove. Accordingly, this study examined the performance of a dentin bonding agent in the prevention of tooth discoloration. An assessment of the color change by the naked eye in a pilot study showed that the bonding agent was effective in preventing discoloration (Fig. 12). Therefore, the color changes were evaluated more precisely and objectively by using a colorimeter. However, the results were somewhat disappointing. The $L^*$ value stands for brightness (17). Groups 1 and 2 had a negative $\Delta L^*$ value (Table 1), which means that the teeth became darker. The results showed that the dentin bonding agent can reduce the change in darkness of the teeth but cannot prevent it. The $a^*$ value indicates red on the positive axis and green on the negative (17–19). Therefore, the negative $\Delta a^*$ values in group 1 (Table 1) indicate that the samples showed a greenish hue, and the dentin bonding agent was effective in preventing this kind of color change. The $b^*$ value represents yellow on the positive axis and blue on the negative (17–19). The positive $\Delta b^*$ values in groups 1 and 2 (Table 1) indicate that the samples had become yellowish. These changes might be due to the color of minocycline itself (yellow). If this were true, it is unlikely that a transparent bonding agent will block the yellowish color emitted from the antibiotics completely. The overall changes in these 3 color coordinates can be expressed in terms of $\Delta E^*$. $\Delta E^*$ is used to determine whether the changes in the overall shade are perceptible by a human observer (18). The results showed that the dentin bonding agent reduced the overall color change but did not prevent it. Because only 1 product among the many dentin bonding agents available was used, we could conclude that AdheSE,
which is a light-curing, self-etching, 2-component adhesive dentin bonding system, cannot prevent minocycline-induced discoloration.

Reducing the application time of the pastes might also prevent discoloration associated with use of minocycline. Experimental studies of triple antibiotic therapy reported that 24- to 48-hour application is sufficient for effective disinfection of infected root dentin (7, 8). However, it is not likely that this short application period is enough to prevent the discoloration on the basis of the results of the present study, wherein discoloration began to appear 24 hours after application (Fig. 7).

It is well-known that the discoloration by the tetracycline family is thought to be a photoinitiated reaction (20). Kim et al (14) also suggested that the effect of sunlight was important in the discoloration of the teeth by the Ledermix paste. However, the tooth samples in our experiment became dark after minocycline treatment despite a lack of sunlight. Therefore, further investigations are needed to clarify the effect of sunlight on minocycline-induced discoloration.

Sato et al (7) suggested that minocycline should be used only for limited periods and attempted to find substitutes for minocycline in the triple antibiotic paste as a result of the risk of tooth discoloration. They reported that cefaclor and fosfomycin are possible alternatives for minocycline in terms of their antibiotic effectiveness. Further clinical studies should be carried out to demonstrate the efficacy of these medications in the root canal.

Another issue is whether discoloration caused by minocycline has the same prognosis after bleaching as trauma- or necrosis-induced discoloration. There are few rigorous scientifically based studies on the prognosis of tooth whitening, despite the many clinical reports. Brown (21) suggested that the discoloration caused by root canal medication has a dubious prognosis. In our case, the cervical shade was unsatisfactory, despite 3 consecutive walking bleach treatments. However, this does not mean that the discoloration caused by minocycline has a poor prognosis because the cervical barrier might prevent the bleaching paste from entering the cervical dentinal tubules in our case.

In conclusion, minocycline should be limited to the root canal because of the potential risk of tooth discoloration, despite the biologic success. Suitable techniques for preventing contact with the coronal dentin can be investigated and suggested for the safe use of minocycline.

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References

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