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Original Article

Comparative study of pulpal responses to ProRoot MTA, Vitapex, and Metapex in canine teeth

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KEYWORDS
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Abstract *Background/purpose:* ProRoot MTA, Vitapex, and Metapex are widely used for pulp treatment of primary tooth. The aim of this study was to compare the pulpal responses to ProRoot MTA, Vitapex, and Metapex in a canine model of pulpotomy.
Materials and methods: Pulpotomy procedure was performed to 34 teeth (21 incisors and 13 premolars) and ProRoot MTA, Vitapex or Metapex was applicated to artificially exposed pulp tissues. After 13 weeks, the teeth were extracted and processed with hematoxylin-eosin staining for histologic evaluation. All specimens were evaluated in several categorys related to calcific barrier, inflammatory responses and the area of calcific barrier formation was measured.
Results: Most of the specimens in the ProRoot MTA group developed a calcific barrier at the pulp amputation site and showed a low level of inflammatory response. However, in comparison to ProRoot MTA group, a small amount of calcific barrier formed in Vitapex and Metapex groups.
Conclusion: This *in vivo* study found that Vitapex and Metapex induced similar pulpal responses but showed poor outcomes compared with using ProRoot MTA. Vitapex and Metapex are therefore not good substitutes for ProRoot MTA in direct pulp capping and pulpotomy.

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Introduction

Pulpectomy is used instead of vital pulp therapy when an infection spreads to the root canal and the pulp is infected. The success of endodontic therapy applied to primary teeth is influenced by the reduction of the bacteria present in the root canal.[1] Such bacteria can be eliminated by mechanical debridement and chemical reactions using antibacterial agents and materials for filling the root canal.

Vitapex (Neo Dental, Tokyo, Japan) and Metapex (Meta Biomed, Cheongju, Korea) are premixed pastes of calcium hydroxide and iodoform that are universally used as canal-filling materials for primary molars because their resorption rates are similar to that of the primary root, and are also strongly antiseptic, easy to fill into root canals, and easy to remove if necessary.[2] The use of Vitapex or Metapex is reportedly associated with high clinical and radiological success rates in the pulpectomy of primary teeth.[3,4]

However, even when the pulp tissue is debrided, pulp tissue remaining in the root canal will come into contact with the filling material. Anatomical variations in roots include the presence of accessory root canals and root canals showing anomalous canal shapes.[5,6] In addition, when pulpectomy was performed, the apical pulp tissue may not be completely removed, and partial pulpectomy may be performed unintentionally. The presence of remaining pulp tissue means that filling the root canal with Metapex or Vitapex during a pulpectomy procedure will result in direct contact area between the material and the pulp tissue.

Unlike the pulpectomy, pulpotomy of primary teeth is a procedure that removes coronal pulp only. In the past, formocresol was mainly used in pulpotomy of primary teeth, but recently there has been a tendency to use mineral trioxide aggregate (MTA) or calcium silicate cement instead of formocresol. MTA has been recognized as a bioactive material that is hard-tissue conductive, hard-tissue inductive, and biocompatible.[7] The success rate of MTA pulpotomy has been reported to be over 90%.[8,9] Representative components of MTA include calcium oxide, silicon dioxide, and bismuth oxide, and MTA is used in various applications such as internal/external root resorption and perforation as well as vital pulp therapy.[10]

Previous studies of Vitapex and Metapex have been limited to investigating root apical responses in the pulpectomy model,[11] and there have been no *in vivo* experiments of the pulpal reactions that occur during direct contact with pulp tissue. Therefore, the aim of this study was to compare the pulpal responses to Vitapex, Metapex, and ProRoot MTA (Dentsply, Tulsa Dental Products, Tulsa, OK, USA) in a canine model of pulpotomy.

Materials and methods

Animal model

Thirty-four canine teeth (21 incisors and 13 premolars) from two beagles were used in the study. The beagles were 6 months old and the animals had intact dentition and a healthy periodontium. All procedures performed in this study were approved by the Institutional Animal Care and Use Committee of Yonsei University Health System (certification #2017-0085).

The teeth were allocated randomly to three pulpotomy treatment groups: ProRoot MTA (control group, $n = 12$), Vitapex ($n = 11$), and Metapex ($n = 11$).

Surgical procedure

The surgical procedures were performed in a sterile operating room. Zoletil (5 mg/kg; Virbac Korea, Seoul, Korea), xylazine (0.2 mg/kg; Rompun, Bayer Korea, Seoul, Korea), and inhaled isoflurane (Gerolan, Choongwae Pharmaceutical, Seoul, Korea) were used to induce general anesthesia. To prevent infection, enfloxacin (5 mg/kg) was injected subcutaneously just before and after treatment, and amoxicillin clavulanate (12.5 mg/kg) was administered intraorally for 5—7 days postoperatively.

Pulpotomy procedure

All procedures were carried out under sterilization. The pulpotomy procedure first involved inducing local anesthesia using lidocaine (2% lidocaine hydrochloride with epinephrine 1:100,000; Kwangmyung Pharmaceutical, Seoul, Korea). After performing occlusal reduction in each tooth, the pulp was mechanically exposed by making occlusal cavities using a high-speed carbide bur (No. 330, H7 314 008, Brasseler, Lemgo, Germany) with simultaneous lubrication provided by water spray. After exposing the coronal pulp tissue, the pulp chamber was removed at the level of the cementoenamel junction. The orifice was then rinsed with sterile saline, and hemostasis was achieved by placing a cotton pellet moistened with normal saline over the exposure site for 2 min. Vitapex, Metapex, or ProRoot MTA was then placed over the exposure site to a thickness of 1 mm, with cotton pellets moistened with saline used to facilitate the adaption of the materials onto the pulp wound area. The cavities were restored with conventional glass-ionomer cement (Ketac-Molar, 3M ESPE, Seefeld, Germany). The animals were euthanized 13 weeks after the procedure.

Histological analysis

The teeth were extracted using extraction forceps and the apical third of each root was sectioned using a high-speed diamond bur. Buffered formalin (10%; Sigma—Aldrich, St Louis, MO, USA) was used to fix the specimens for 48 h, and ethylenediaminetetraacetic acid (pH 7.4; Fisher Scientific, Houston, TX, USA) was applied for demineralization. The specimens were then embedded in paraffin, sectioned at a thickness of 3 μm in the buccolingual direction, and stained with hematoxylin-eosin. We made two slides for each tooth, each containing four histological sections. The specimens were observed with the aid of an optical microscope (BX40, Olympus Optical, Tokyo, Japan), and imaged using a CCD digital camera (Infinity 2.0, Lumenera, Ottawa, ON, Canada) and image-analysis software (InnerView 2.0, InnerView, Seongnam, Korea).

Blind assessments were performed to ensure that each section was evaluated fairly. Five investigators (W.K., I.-

H.K., C.-M.K., B.K., Y.S., and J.S.S.) selected a single representative histological section for each tooth for the evaluation. The histopathological analysis included assessing the calcific barrier formation (continuity, morphological aspects, and thickness), extent of the inflammatory reaction (chronic or acute, number of cells, and extent), hyperemia, and the formation of an odontoblast layer. All findings were scored from 1 to 4 using a previously reported scoring system (Table 1).[12–15] The final score was determined based on the majority consensus of the investigators.

Statistical analysis

Statistical analysis was performed with SPSS software (version 25, SPSS, Chicago, IL, USA). One-way analysis of variance ($P < 0.05$) and the post-hoc Scheffé test (Bonferroni correction, $P < 0.017$) were applied to analyze the area of the newly formed calcific barrier.

Results

After excluding specimens that failed during teeth extraction or histopathological processing (including pulpal tissue amputation), histopathological evaluations were performed for 8, 10, and 10 root specimens treated with Vitapex, Metapex, and ProRoot MTA, respectively. The score percentages for each material are presented in Tables 2–4. Overall, ProRoot MTA showed better biocompatibility than Vitapex and Metapex.

Calcific barrier formation

Fig. 1 shows a newly formed calcific barrier. The score percentages for calcific barrier formation for the three materials are listed in Table 2. A complete calcific barrier formed in 50% of the specimens in the ProRoot MTA group. A calcific barrier that was similar to dentin formed in 70% of the specimens in the ProRoot MTA group, while no barrier formed in only one specimen in that group. Quality and quantity of newly formed calcific barrier were lower in the Metapex and Vitapex groups than the ProRoot MTA group, with none of the specimens in the Vitapex group having a score of 1 for the morphology of the calcific barrier (Table 2).

Pulp reaction

No inflammation occurred in 60% and 20% of the specimens in the ProRoot MTA and Metapex groups, respectively, whereas all of the specimens in Vitapex group showed mild-to-moderate inflammation. Most specimens in the ProRoot MTA group showed no or only mild dental pulp congestion, whereas most specimens in the Vitapex and Metapex groups showed mild-to-moderate dental pulp congestion (Table 3).

Odontoblastic cell layer

There were no odontoblast cells or odontoblast-like cells in 70% of the specimens in the Metapex and ProRoot MTA groups, and 50% of those in the Vitapex group. Only 10% of

Table 1 Scores used during the histological analysis of calcific barriers and dental pulp.

Scores	Calcific barrier continuity
1	Complete dentin bridge formation
2	Partial/Incomplete dentin bridge formation extending to more than one half of the exposure site but not completely
3	Initial dentin bridge formation extending to not more than one half of the exposure site
4	No dentin bridge formation
Scores	**Calcific barrier morphology**
1	Dentin or dentin associated with irregular hard tissue
2	Only irregular hard tissue deposition
3	Only a thin layer of hard tissue deposition
4	No hard tissue deposition
Scores	**Tubules in calcific barrier**
1	No tubules present
2	Mild (tubules present in <30% of calcific barrier)
3	Moderate to severe (tubules present in >30% of calcific barrier)
4	No hard tissue deposition
Scores	**Inflammation intensity**
1	Absent or very few inflammatory cells
2	Mild (an average of <10 inflammatory cells)
3	Moderate (an average of 10–25 inflammatory cells)
4	Severe (an average > 25 inflammatory cells)
Scores	**Inflammation extensity**
1	Absent
2	Mild (inflammatory cells next to dentin bridge or area of pulp exposure only)
3	Moderate (inflammatory cells observed in one third or more of the coronal pulp or in the midpulp)
4	Severe (all of the coronal pulp is infiltrated or necrotic)
Scores	**Inflammation type**
1	No inflammation
2	Chronic inflammation
3	Acute and chronic inflammation
4	Acute inflammation
Scores	**Dental pulp congestion**
1	No congestion
2	Mild (enlarged blood vessels next to dentin bridge or area of pulp exposure only)
3	Moderate (enlarged blood vessels observed in one third or more of the coronal pulp or in the midpulp)
4	Severe (all of the coronal pulp is infiltrated with blood cells)

Table 1 (*continued*)

Scores	Odontoblastic cell layer
1	Palisade pattern of cells
2	Presence of odontoblast cells and odontoblastlike cells
3	presence of dontoblastlike cells only
4	Absent

the specimens in the Metapex and ProRoot MTA groups showed a palisade pattern of cells (Table 4).

Calcific barrier area

Since the coronal pulpal width differed between the tooth, the measured area of newly formed calcific barrier was divided by the coronal pulpal width of each specimen to ensure objective comparisons. There was a statistically significant difference between the ProRoot MTA and Vitapex ($P = 0.019$), and Metapex ($P = 0.035$) (Fig. 2).

Table 2 Score percentages for calcific barriers.

Scores	1	2	3	4
Calcific barrier continuity (%)				
ProRoot MTA	50 (5/10)[a]	40 (4/10)	—	10 (1/10)
Vitapex	12.5 (1/8)	50 (4/8)	—	37.5 (3/8)
Metapex	30 (3/10)	30 (3/10)	—	40 (4/10)
Calcific barrier morphology (%)				
ProRoot MTA	70 (7/10)	20 (2/10)	—	10 (1/10)
Vitapex	—	25 (2/8)	37.5 (3/8)	37.5 (3/8)
Metapex	50 (5/10)	10 (1/10)	—	40 (4/10)
Tubules in calcific barrier (%)				
ProRoot MTA	50 (5/10)	40 (4/10)	—	10 (1/10)
Vitapex	12.5 (1/8)	12.5 (1/8)	37.5 (3/8)	37.5 (3/8)
Metapex	30 (3/10)	20 (2/10)	10 (1/10)	40 (4/10)

[a] Number of teeth receiving the score/total number of teeth evaluated.

Table 3 Score percentages for inflammatory responses.

Scores	1	2	3	4
Inflammation intensity (%)				
ProRoot MTA	50 (5/10)[a]	20 (2/10)	—	30 (3/10)
Vitapex	—	25 (2/8)	25 (2/8)	50 (4/8)
Metapex	10 (1/10)	30 (3/10)	20 (2/10)	40 (4/10)
Inflammation extensity (%)				
ProRoot MTA	60 (6/10)	30 (3/10)	—	10 (1/10)
Vitapex	—	25 (2/8)	37.5 (3/8)	37.5 (3/8)
Metapex	20 (2/10)	30 (3/10)	20 (2/10)	30 (3/10)
Inflammation type (%)				
ProRoot MTA	60 (6/10)	30 (3/10)	10 (1/10)	—
Vitapex	—	50 (4/8)	50 (4/8)	—
Metapex	10 (1/10)	50 (5/10)	40 (4/10)	—
Dental pulp congestion (%)				
ProRoot MTA	40 (4/10)	50 (5/10)	10 (1/10)	—
Vitapex	12.5 (1/8)	37.5 (3/8)	50 (4/8)	—
Metapex	20 (2/10)	60 (6/10)	20 (2/10)	—

[a] Number of teeth receiving the score/total number of teeth evaluated.

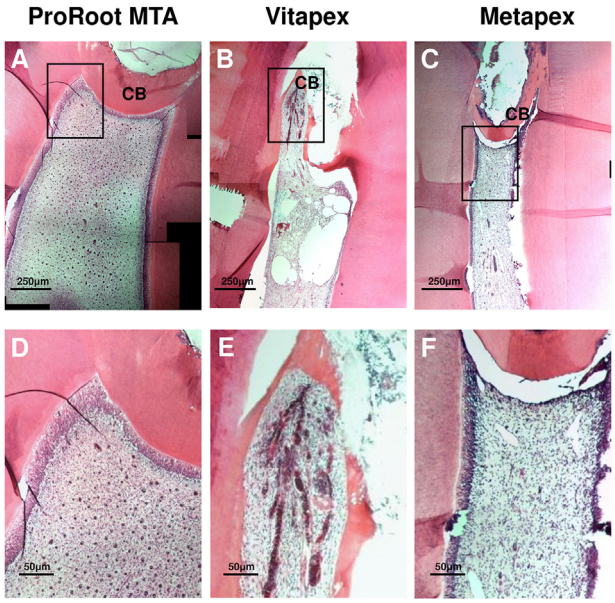

Figure 1 Hematoxylin-eosin staining for the evaluation of the histomorphologic characteristics of the newly formed calcific barrier (CB) after 13 weeks ((A–C): scale bars = 250 μm, (D–F): scale bars = 50 μm).

Discussion

This study evaluated and compared the pulpal responses to Vitapex, Metapex, and ProRoot MTA using a canine pulpotomy model. The use of ProRoot MTA resulted in the formation of a calcific barrier that was of higher quality and larger and exhibited a better inflammatory response compared with using Vitapex and Metapex, with no significant differences between the latter two groups.

MTA has good physical properties and biocompatibility, it stimulates tissue regeneration as well as a good pulp response,[16,17] and has an excellent long-term sealing ability. MTA is the optimum material for vital pulp therapy, and it is better than calcium hydroxide, which has traditionally been used.[18] In previous *in vivo* studies, ProRoot MTA showed better calcific barrier generation and pulpal response than TheraCal (Bisco, Schamburg, IL, USA) and Endocem zir (Maruchi, Wonju, Korea), as well as other types of MTA such as RetroMTA (BioMTA, Seoul, Korea), Ortho MTA (BioMTA), and Endocem MTA (Maruchi) in canine pulpotomy models.[12–14] The verified biocompatibility of ProRoot MTA meant that it was suitable to use in the present study as a positive control. The results showed that the pulpal response was better for ProRoot MTA than for Vitapex and Metapex, which implies that ProRoot MTA has better tissue affinity than Vitapex and Metapex in direct pulp capping and pulpotomy procedures where pulp tissue and the material are in direct contact.

Vitapex and Metapex are widely used as canal filling materials for primary teeth because of their radiopaque,

Table 4 Score percentages for the odontoblastic cell layer.

Scores	1	2	3	4
Odontoblastic cell layer (%)				
ProRoot MTA	10 (1/10)[a]	20 (2/10)	—	70 (7/10)
Vitapex	—	12.5 (1/8)	37.5 (3/8)	50 (4/8)
Metapex	10 (1/10)	10 (1/10)	10 (1/10)	70 (7/10)

[a] Number of teeth receiving the score/total number of teeth evaluated.

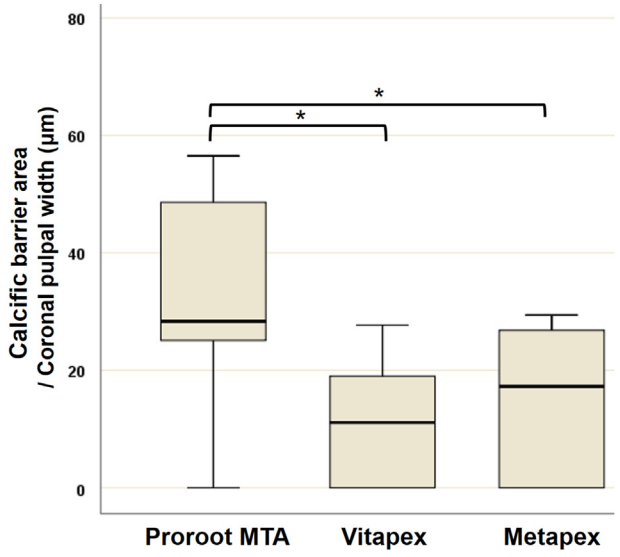

Figure 2 Calcific barrier area/coronal pulpal width for each material after 13 weeks. When the calcific barriers were standardized by coronal pulpal width, ProRoot MTA had a significantly higher value than Vitapex and Metapex. One-way ANOVA ($P < 0.05$) and the post-hoc Scheffé test (Bonferroni correction, $P < 0.017$) were performed for statistical analyses.

infection control, and absorbency properties. The clinical success rate when using Vitapex and Metapex is reportedly 90.5—100%.[19—23] The two main components of these products are calcium hydroxide and iodoform. It is thought that calcium hydroxide was first used clinically for root canal filling by Rhoner in 1940.[24] The most important reasons for using calcium hydroxide are that it maintains the health of periapical tissue, promotes healing, and exerts antimicrobial effects. The mechanism of action remains unclear, but it is known that free hydroxyl ions with a very high pH activate repair and calcification, neutralize lactic acid produced by osteoclasts, and prevent the dissolution of dental mineralized components.[25—27]

Products with several additives have been developed with the aims of improving the physiochemical properties and radiopacity of calcium hydroxide, maintaining the consistency and pH of the applied paste, and facilitating its clinical application.[28] Along with calcium hydroxide, iodoform is the other main constituent of Vitapex and Metapex, and has been used because of its antibacterial effect, healing properties and ability of resorption when in excess.[29,30] However, there are some reports in the literature that adding calcium hydroxide to another antibiotic preparation has deleterious effects on growth inhibition, and combining any two antimicrobial medicaments produces no additive or synergistic effects.[31] The compositions of Vitapex and Metapex are almost identical, with the main difference being the composition ratio of calcium hydroxide and iodoform. An *in vitro* study found that the antibacterial activity was lower for Metapex than for Vitapex as well as ZOE (a combination of zinc oxide and eugenol) and calcium hydroxide.[32,33] However, an *in vivo* study found that Vitapex and Metapex showed similarly good periapical reactions in the canine pulpectomy model.[11]

The pulpectomy procedure ideally involves removing all pulp tissues from the root canal, but unfortunately this is seldom achieved by debridement performed using physical and chemical methods. Pulp tissue may remain in the apical area, and also on the root canal wall if the curvature of the root canal is severe or there are accessory root canals that cannot be accessed. In particular, primary molars have many accessory canals in the furcation area compared with permanent teeth. This means that the Vitapex or Metapex used for pulpectomy will be in direct contact with pulp tissue at the apical end, on a severely curved root wall, or in the furcation area.[5,6] These situations prompted the present study to investigate the pulpal responses to Vitapex and Metapex, which revealed similar pulpal responses, with Metapex dominating calcific barrier formation but there was not a statistically significant difference. However, the above-mentioned study and the present study involved teeth without inflammation, and thus the obtained results may differ from actual clinical results.

The pulpal responses to ProRoot MTA obtained in this study were worse than those obtained in previous studies with similar designs.[12—14] This might have been due to the animals in the present study being euthanized after 13 weeks, in contrast to previous studies obtaining the analyzed specimens at 4—8 weeks after the procedure. Considering that both the previous and present studies using conventional glass-ionomer cement (Ketac-Molar) for coronal sealing, the sealing efficacy for crown restorations may have decreased due to the longer application period in the present study. It has been reported that failure of root canal treatment is related to poor restoration of the crown,[34] and the findings of several studies of the success or failure of root canal treatment suggest that apical leakage is not the most important factor influencing the failure of endodontic treatment, with coronal leakage instead being far more likely to be the main determinant.[35,36] Using resin-modified glass ionomer or composite resin is more advantageous in terms of microleakage or strength than using glass ionomer cement, and can improve the stability of crown restorations.[37]

This study is the first to investigate the pulpal responses to Vitapex and Metapex in animal experiments. A canine pulpotomy model was designed, and ProRoot MTA was used as a positive control. However, This study has a limitation in that reliability may be lowered because the sample size is small and the calcific barrier is analyzed in two dimensions. Also, this study was performed in a noninfectious model, which does not accurately reflect the clinical situation of inflammation being present in the pulp. Additional

validation in infection models and long-term studies are therefore needed in the future. In addition, considering the increased inflammatory responses to all three materials over a relatively short 13-week follow-up compared with the duration of drug application in actual clinical practice, clinicians must recognize that not only choosing the correct material but also the characteristics of the sterile environment and performing sufficient debridement are critical to successful pulp treatment.

In conclusion, this *in vivo* study found that Vitapex and Metapex induced similar pulpal responses but showed poor outcomes compared with using ProRoot MTA. Vitapex and Metapex are therefore not good substitutes for ProRoot MTA in direct pulp capping and pulpotomy.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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