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Histopathological Evaluation of Pulp Reaction to Potassium Nitrate in Polycarboxylate Cement Compared with Mineral Trioxide Aggregate in Immature Dogs' Teeth

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Abstract

Objective The vitality of the pulp and the formation of new dentin are important for the success of direct pulp capping (DPC). Accordingly, the present study aims to histologically evaluate the pulp reaction to potassium nitrate in polycarboxylate cement (KNO_3/PCA) compared with mineral trioxide aggregate (MTA) in immature dogs' teeth. DPC was done on 48 teeth in three dogs (16 for each dog, 8 for each material).

Materials and Methods After 2, 3, and 4 months, a dog was euthanized at each time interval. Capped teeth were extracted, demineralized, and processed for histopathological examination based on the presence of inflammation, granulation tissue, hard tissue, and dentin bridge.

Results Inflammatory changes were absent in both MTA- and KNO_3/PCA-capped teeth at the three time intervals. The incidence of granulation tissue formation was higher in MTA- (75, 87.5, and 87.5%) than in KNO_3/PCA-capped teeth (62.5, 75, and 75%) after 2, 3, and 4 months after DPC, respectively. Hard tissue was seen after 3 months of DPC with both MTA and KNO_3/PCA. It was more evident in MTA-capped teeth with an incidence of 75 and 75%, and 12.5 and 25% in teeth capped with KNO3/PCA after 3 and 4 months, respectively. Dentin bridge was only noticed in MTA-capped teeth after 3 and 4 months intervals.

Conclusion Taken all together, pulpal responses in the form of granulation and hard tissues, and dentin bridge formation are more evident in MTA-capped teeth than those capped with KNO_3/PCA in immature dogs.

Keywords
- dentistry
- dogs
- MTA
- KNO_3
- DPC

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Introduction

Dental caries is a prevalent chronic infectious disease that can lead to destruction of dental hard and soft tissues. It was reported as one of the oldest and most common diseases affecting humans.[1] It usually results from tooth-adherent cariogenic bacteria that metabolize sugars to produce acid. Such acid can demineralize tooth structure over time leading to inflammation and necrosis of the dental pulp.[2] When left untreated, pulpitis can result in pain, cellulitis, abscess formation, and systemic infection, as well as negatively affect child growth.[1]

Direct pulp capping (DPC) is a treatment protocol aiming to maintain the function and vitality of the pulp which can be injured by either the caries or the restorative procedures,[3] in which, a dental biomaterial is directly placed over the exposed pulp hoping to promote the formation of a mineralized tissue barrier that protects the pulp from microbial invasion.[4] As mineralized tissue barriers can only be formed when pulp inflammation and infection are significantly reduced, promoting the healing of pulp inflammation by capping materials may play an important role in maintaining the sustainability of DPC.[5] Besides reducing inflammation and inducing the formation of mineralized tissue barriers, capping materials should have the capability to bond to dentin and prevent microleakage.[6]

In practice, many dental materials are used for DPC with the goal of promoting good tissue response and optimizing patient outcomes.[7] However, new materials are continuously formulated and tested for preserving pulp vitality through restorative and conservative dental procedures.[8]

Mineral trioxide aggregate (MTA) is derived from Portland cement and its main components are calcium silicate, dicalcium silicate, and tricalcium aluminate, in addition to bismuth oxide for radiopacity.[9] It is largely accepted for DPC because of its potential to enhance wound healing of the dentin–pulp complex.[10] MTA showed excellent biocompatibility, low solubility, higher sealing ability, inhibition of bacterial invasion, and enhancement of dentin bridge formation.[11] Moreover, MTA was reported to reduce pulp inflammation, hyperemia, and necrosis.[12] On the other hand, MTA bears some disadvantages, most notably, long time setting, discoloration, difficult handling characteristics, and high cost.[5]

Potassium nitrate (KNO_3) is primarily used in toothpaste and mouthwash for hypersensitive teeth.[13] Its success as a tooth desensitizer (i.e., desensitizes nerves in tooth pulp) has encouraged dentists to explore its other uses in the field of dentistry. In this context, Hodosh et al[14] showed that the use of KNO_3 in polycarboxylate cement (PCA) preserved pulp vitality and diminished the incidence and severity of post-restorative pain when used as a base under deep restoration. Tsanova[15] found that indirect pulp capping with KNO_3/PCA for treatment of reversible pulpitis showed preserved vitality and functional condition. This may be due to KNO_3/PCA that (1) has thin film thickness and bonds firmly to the tooth structure, (2) possesses good adhesive properties that guarantee the closure of the cavity, (3) protects traumatically exposed dental pulp, and (4) releases KNO_3 that decreases the inflammatory intensity.[14]

To date, data about the effects of KNO_3/PCA cement in DPC are still limited. Therefore, our present study was designed to provide an evidence-based decision by comparing, in a randomized clinical trial, the histological evaluation outcomes of KNO_3/PCA cement and MTA as DPC biomaterials.

Materials and Methods

All experimental procedures in the current study were performed in accordance with the guidelines of the European Union Council (86/609/EU) and approved by the ethical committee (number: 83/532/2021, Minia University, Egypt). Three apparently healthy adult mongrel dogs aged 2 to 3 years and weighing 12 to 20 kg were selected for the present study. MTA was purchased from PD Company (India). KNO_3 was obtained from Sigma-Aldrich (Germany) and PCA cement was purchased from SpofaDental (Poland).

Experimental Procedures

Direct Pulp Capping

The study was performed on mandibular and maxillary left and right first, second, third, and fourth premolars. The teeth were divided into two groups (split mouth technique) according to the pulp capping materials, MTA (24 teeth) and KNO_3/PCA (24 teeth). After animals were anesthetized by intramuscular injection of a mixture of ketamine (10 mg/kg body weight [b.w.]) and xylazine (1 mg/kg b.w.), and maintained with 2.5% thiopental sodium (25 mg/kg b.w.), the working field was disinfected by 5% iodine tincture. A dry field was achieved using cotton rolls and gauze swabs on the facial surfaces of the teeth. Class V cavities (~2.5 mm wide, 3 mm long, 1.5–2 mm deep) were prepared on the buccal surface of teeth using a tungsten carbide pear-shaped bur, ISO #330 L, at ultra high speed with a copious water spray.

For each tooth, a new bur was used. The preparations were 0.5 to 1 mm above the free gingiva, parallel to the cementoenamel junction. Pulp exposure was performed in the middle of the cavity floor using a round carbide bur ISO # 1 (0.8 mm in diameter), at high speed and under water cooling. The produced pulp exposures were about the same size (0.8–1 mm). The cavities were washed with sterile saline and dried with cotton pellets. Light pressure was applied to control hemorrhage. Prepared materials were delivered according to groups, and were followed by glass ionomer restoration.[16]

Histopathological Examination

At the end of each time interval, one dog was euthanized by thiopental overdose. Both mandibular and maxillary jaws were surgically dissected and sectioned into two halves at the midline. Specimens were then fixed in 10% neutral buffered formalin for 72 hours and decalcified in 10% nitric acid for 10 to 20 days. Then, capped teeth were extracted and washed thoroughly under running tap water for 3 to 4 hours. Teeth were then embedded in paraffin and sectioned (4 µm) serially in a buccolingual plane parallel to the tooth's main

vertical axis through the prepared cavities and the pulp.[17] Tissue sections were stained with hematoxylin and eosin (HE) and Masson's trichrome, and examined under the light microscope (Olympus CX31, Japan) for the presence of inflammation, granulation tissues, hard tissues, and dentin bridge. After detailed examination, scores were given for each histological parameter per each tooth as: absent (0) and present (1). Representative photomicrographs were taken using a digital camera (Olympus, Camedia C-5060, Japan).

Statistics

Data were analyzed by SPSS version 22. Comparison between the two groups was done using McNemar's test. The $p \leq 0.05$ was considered as statistically significant.

Results

Histopathological examination of HE-stained coronal sections of both MTA- and KNO_3/PCA-capped teeth showed no evidence of inflammatory changes at the three time intervals (►**Table 1**).

Formation of granulation tissue was seen in 75, 87.5, and 87.5%, and 62.5, 75, and 75% in MTA- and KNO_3/PCA-capped teeth after 2, 3, and 4 months of DPC, respectively. No significant difference was seen between the two capping materials at the three time intervals (►**Table 1**). Granulation tissue consisted of paralleled fibroblasts with elongated large nuclei and small blood vessels (►**Fig. 1**). In MTA-capped teeth, granulation tissue was seen integrated with MTA materials (►**Fig. 1A, B**). In some KNO_3/PCA-capped teeth after 3 months of DPC, parts of granulation tissue were seen replaced by connective (►**Fig. 2E**) or cartilaginous tissues (►**Fig. 2F**). After 4 months of DPC, the amount of granulation tissue was decreased particularly in MTA-capped teeth (►**Fig. 3**).

Hard tissue was seen after 3 months of DPC with both MTA and KNO_3/PCA. It was more evident in MTA-capped teeth with an incidence of 75 and 75%, and 12.5 and 25% in teeth capped with KNO_3/PCA after 3 and 4 months, respectively (►**Table 1**). Hard tissues appeared structureless in context to the capped materials (►**Figs. 2C** and **3**).

Dentin bridge was only shown in MTA-capped teeth at the third- and fourth-month intervals (►**Table 1**). Its incidence was 62.5 and 75%, respectively. It was seen in between granulation tissues and capped material (►**Fig. 2D**). Odontoblasts were observed to play a role in the formation of dentin bridge (►**Fig. 2D**). In some MTA-capped teeth, dentin-bridge-like hard tissues were observed after 4 months of DPC (►**Fig. 3B**). Interestingly, MTA material was observed to be replaced by red-like matrix raising the possibility of its replacement by regenerative substances (►**Figs. 2A** and **3D**).

Table 1 The number of the teeth and the distribution of different pulpal responses following DPC with MTA and KNO_3/PCA cement

Criteria	Time intervals (mo)	Responses (number of teeth)		*p*-Value
		MTA	KNO_3/PCA	
Granulation tissue	2	6	5	1.0
	3	7	6	1.0
	4	7	6	1.0
Hard tissue	2	0	0	0
	3	6	1	0.13
	4	6	2	0.13
Dental bridge	2	0	0	0
	3	5	0	0.06
	4	7	0	0.02[a]

Abbreviations: DPC, direct pulp capping; MTA, mineral trioxide aggregate; KNO_3/PCA, potassium nitrate in polycarboxylate cement.

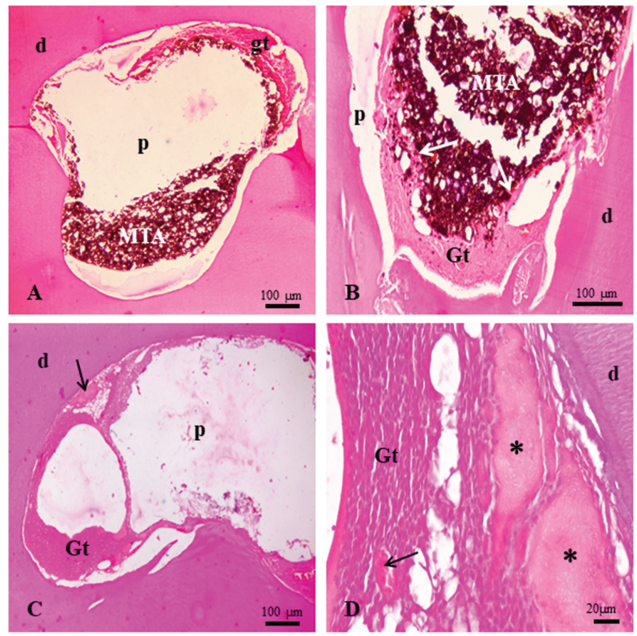

Fig. 1 Histopathological changes at the second month after pulp capping with mineral trioxide aggregate (MTA) and potassium nitrate in polycarboxylate cement (KNO_3/PCA) in immature dogs' teeth. (**A**) An MTA-capped tooth showing formation of granulation tissue (Gt). (**B**) An MTA-capped tooth showing formation of granulation tissue that appears integrated with the MTA material (white arrows). (**C**) A KNO_3/PCA-capped tooth showing formation of Gt. (**D**) A KNO_3/PCA-capped tooth showing formation of Gt) that consists of paralleled fibroblasts separated by pools of protein-rich materials (asterisks). Blood vessels (arrows), dentin (d) and pulp (p). HE, hematoxylin and eosin.

Discussion

The current study compared the pulpal response of the healthy immature dog teeth with two different DPC materials, KNO_3/PCA cement, and MTA, after three time intervals of 2, 3, and 4 months. The comparison was done based on histopathological evaluation of inflammatory changes, and formation of granulation tissues, hard tissues, and dentin bridge. There was no evidence of inflammatory responses for both the DPC materials after the three time intervals. Similarly, Nowicka et al[18] observed that DPC of human permanent molar teeth with MTA showed no inflammation after

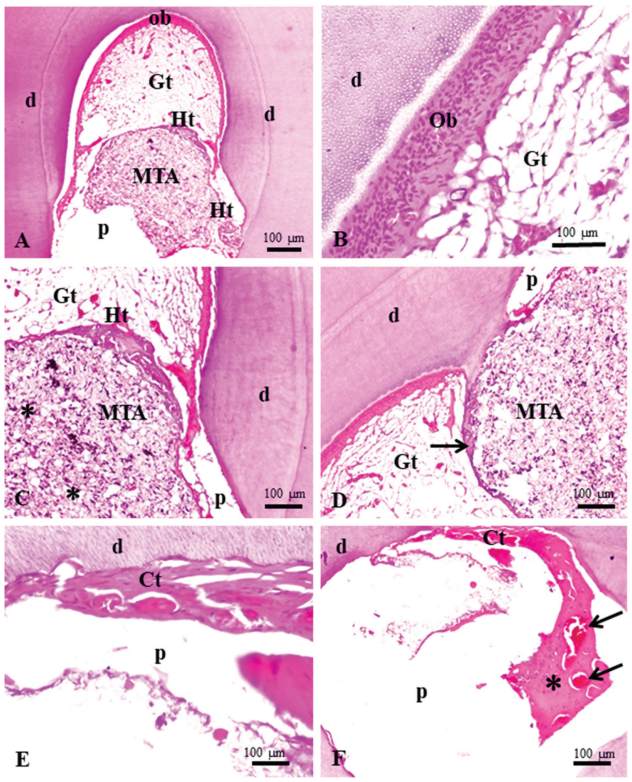

Fig. 2 Histopathological changes at the third month after pulp capping with mineral trioxide aggregate (MTA) and potassium nitrate in polycarboxylate cement (KNO_3/PCA) in immature dogs' teeth. (**A**) An MTA-capped tooth showing granulation tissue (Gt) with formation of small pieces of hard tissues (Ht) at the boundaries with MTA. (**B**) An MTA-capped tooth showing a layer of odontoblasts (Ob) and a loose area of Gt. (**C**) An MTA-capped tooth showing formation of Ht at the boundaries of MTA. MTA also appeared to be replaced by a faint-pink material (asterisks). (**D**) An MTA-capped tooth showing formation of a thin bridge of dentin (arrow) between the Gt) and MTA. (**E**) A KNO_3/PCA-capped tooth showing formation of connective tissue (Ct) that consists of paralleled fibrocytes. (**F**) A KNO_3/PCA-capped tooth showing formation cartilaginous material (asterisk). Dentin (d) and pulp (p). HE, hematoxylin and eosin.

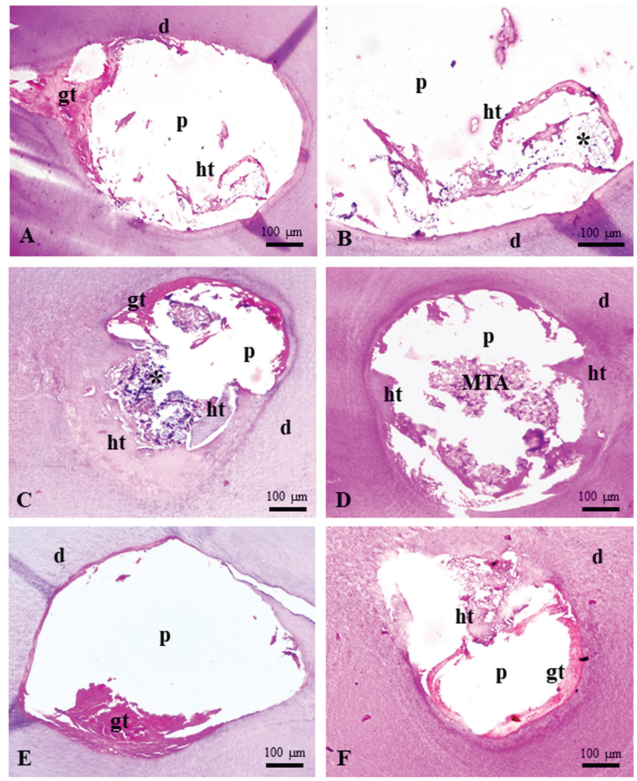

Fig. 3 Histopathological changes at the fourth month after pulp capping with mineral trioxide aggregate (MTA) and potassium nitrate in polycarboxylate cement (KNO_3/PCA) in immature dogs' teeth. (**A–D**) An MTA-capped teeth showing formation of granulation tissue (Gt) and hard tissues (Ht) in the vicinity of the MTA. (**E, F**) A KNO_3/PCA-capped teeth showing Gt and Ht formation. Dentin (d) and pulp (p). HE, hematoxylin and eosin.

6 weeks. Hoseinifar et al[19] reported no inflammatory changes in MTA-capped human premolar teeth after 6 weeks in a clinical trial study. Borissov et al[20] showed that pulp inflammation was over after 60 days following DPC of dog teeth with KNO_3/PCA cement. The absence of inflammation following DPC with both MTA and KNO_3/PCA cement in our study might return to the long time passed before examination (after 2, 3, and 4 months of DPC). In parallel, Abbas et al[21] reported that DPC of mongrel dog's premolar teeth with chitosan-based formulations revealed mild, mild to moderate, and complete absence of inflammation after 1 week, 1 month, and 3 months, respectively. However, Xu et al[22] reported that male ICR mouse teeth capped with MTA were free from inflammation after a short period of a week. Moreover, excellent sealing properties of both capping materials play a role in preventing inflammatory reactions after DPC.[23] Pulp inflammation after DPC is of great importance; on one hand, it can lead to stem cell proliferation and differentiation, laying down granulation and hard tissues, and completing repair,[24] and on the other hand, it can be also detrimental when persists.[25] This makes scientists state that subsiding of the pulp inflammation by capping materials indicates their better biocompatibility for DPC.[26]

DPC of immature dogs' teeth with MTA and KNO_3/PCA in our study showed the formation of granulation tissue at the three time intervals. Granulation tissue is formed from fibroblasts and small blood vessels. Consistent with these findings, Elwardany et al[27] reported that pulp therapies of premolar teeth from mongrel dogs with MTA resulted in the formation of granulation tissue consisting of fibroblasts and newly proliferated blood vessels after 7 days of DPC. Borissov et al[20] reported higher number of fibrocytes with collagen bundles following DPC of dogs' teeth with KNO_3/PCA. Regulated granulation tissue formation is an early stage prior to the formation of hard tissues. In another words, granulation tissue formation indicates progressing from the inflammatory phase to the proliferative phase of healing.

Hard tissue formation was seen after 3 months of DPC with MTA and KNO_3/PCA in our study. In MTA-capped teeth, the formation of hard tissues was more evident and with an incidence of 75 and 75% after 3 and 4 months, respectively. In this context, Akhavan et al[28] reported that DPC of dogs' teeth with MTA caused the highest amount of hard tissue compared with different dentin adhesive resin and calcium hydroxide. Xu et al[29] also found that MTA was capable of inducing hard tissue

formation in maxillary molars of Sprague-Dawley rats. Induction of hard tissue by MTA was reported to be attributed to stimulating hard-tissue-forming cells and preparing a suitable environment for mineralization.[28] More precisely, Guven et al[29] observed that MTA can stimulate cultured human gingival fibroblasts to produce bone morphogenetic protein (BMP-2) which is an osteoinductive cytokine belonging to transforming growth factor-β. BMP-2 was suggested to induce bone formation and to stimulate the differentiation of pulp cells into odontoblasts.[30] Compared with MTA, KNO_3/PCA induced hard tissue formation with a lower incidence of 12.5 and 25% in after 3 and 4 months, respectively. No studies have described hard tissue formation after DPC of teeth with KNO_3/PCA yet. Generally, the formation of mineralized tissues is considered a favorable reaction after DPC.[5]

Formation of dentin bridge after DPC is an important factor in determining the outcomes of vital pulp therapy[24] as it protects the dental pulp from bacterial toxins and irritants, and helps in maintaining pulp vitality.[5,31] In our study, DPC of dogs' immature teeth showed formation of dentin bridge in ~62.5 and 75% after the third and fourth months of capping with MTA, respectively. Parallel to our findings, Min et al[32] found that DPC of carries-free human third premolars with MTA caused formation of dentin bridge in all-capped teeth. Swarup et al[33] reported that MTA produced continuous dentin bridges in premolars of patients ranging from 11 to 15 years. Xu et al[22] reported the formation of a compact hard tissue barrier in infected and noninfected ICR mice teeth after 3 months of DPC with MTA. MTA was suggested to recruit and activate odontoblast cells which contribute to matrix formation and mineralization.[34] Compared with MTA, none of the capped teeth with KNO_3/PCA showed dentin bridge formation at the three time intervals in our study. Likewise, Borissov et al showed a lack of reparative dentin after capping of dogs' mandibular premolars with KNO3/PCA at 30- and 60-day intervals. However, it increased the appearance of fibroblasts which is an indicative for the beginning of reparative process.[20]

Limitations in our current study include (1) the small number of teeth/animals that are used in the study and (2) some drawbacks of the MTA. High cost of caring animals and used materials effectively limit the number of animals used in our study. Larger sample size is important to draw valid conclusions. However, MTA was seen to work better than KNO_3/PCA in DPC in terms of formation of hard tissue and dentin bridge; its high cost and disadvantages including discoloration and difficult handling characteristics limit their use to some extent.

Conclusion

In conclusion, DPC of immature dogs' teeth with MTA and KNO_3/PCA showed no inflammatory reaction at the three time intervals. Granulation tissue formation was nearly similar in MTA- and KNO_3/PCA-capped teeth. Capping of teeth with MTA resulted in marked formation of hard tissue compared with those that were capped with KNO_3/PCA. Formation of dentin bridge was only seen in MTA-capped teeth and reached significance at the fourth month interval.

Conflict of Interest
None declared.

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