

Clinical outcomes of Bio-MA and ProRoot[®] MTA in orthograde apical barrier and root perforation repair: a preliminary phase of randomized controlled trial study

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Objective: To preliminarily evaluate treatment outcomes of Bio-MA, a new calcium-silicate based cement (CSC), compared with ProRoot[®] MTA, a commercial product, in orthograde apical barrier and root perforation repair.

Materials and Methods: Forty-seven patients were recruited at the Endodontic Clinic, Faculty of Dentistry, Mahidol University, Thailand. Non-surgical orthograde apical barrier (n = 23 teeth) and root perforation repair (n = 24 teeth) were performed under standard treatment protocols. Bio-MA or ProRoot[®] MTA was randomly used as orthograde apical barrier and root perforation repair material. The recall period was at least six months. Clinical outcomes based on clinical and radiographic criteria were assessed by calibrated examiners and interpreted as “healed”, “healing”, or “disease”. Outcomes of “healed” and “healing” were combined as “success”.

Results: Forty-one teeth, 19 teeth of orthograde apical barrier and 22 teeth of root perforation repair, were recalled with average periods of 11.3±2.8 and 12.8±3.7 months. Bio-MA and ProRoot[®] MTA orthograde were 77.8% and 80% “healed”, and 22.2% and 20% “healing”, respectively. Root perforation repair with Bio-MA and ProRoot[®] MTA were 92.3% and 100% “healed.” Only one tooth of root perforation repair with Bio-MA (7.7%) was “healing”. The overall results showed 100% success (“healed” and “healing”), and no “disease” case was observed. No significant difference in clinical outcomes was observed between Bio-MA and ProRoot[®] MTA, when used as orthograde apical barrier and root perforation repair materials ($p \geq .05$).

Conclusion(s): There were no significant difference in treatment outcomes of orthograde apical barrier and root perforation repair between Bio-MA and ProRoot[®] MTA. Clinical outcomes of Bio-MA and ProRoot[®] MTA were each a 100% success.

Keywords: Bio-MA, MTA, orthograde apical barrier, randomized controlled trial, root perforation repair, treatment outcome

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Introduction

Immature root development, mechanical instrumentation perforation and apical root resorption create the loss of apical constriction, which makes root canal treatment more complicated. Length control of the root canal in such cases is difficult, and the root canal is frequently overfilled [1]. Traditionally, long term calcium hydroxide intracanal medication is placed to induce a mineralized apical barrier before root canal obturation. However, this

calcium hydroxide apexification technique needs several appointments, achieves unreliable formation of mineralized barrier, and increases the risk of cervical root fracture [2].

Root perforation is an artificial communication between the root canal system and the periodontium/oral cavity that can be categorized into lateral perforation and furcation perforation [3, 4]. Lateral root perforation is a thick-edge perforation on the lateral site at any levels of the root, caused by improper techniques of root canal instrumentation or post space preparation [3, 5]. Root furcation perforation

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is a perforation on the furcal site and can be further classified into direct type and stripping type. The direct type of furcation perforation is located on the pulpal floor in a multi-rooted tooth, resulting from misdirection of the coronal access opening, or mislocating of root canal orifice. Stripping perforation is a perforation on the radicular part of the furcal site in a multi-rooted teeth. It frequently occurs on the thin or concaved root area of the coronal or middle portion of the root, and results from excessive coronal flaring or over-instrumentation [4]. The prognosis of root perforation repair was unpredictable until mineral trioxide aggregate (MTA) was introduced [6].

Mineral trioxide aggregate is a calcium silicate-based cement (CSC) that possesses several desired properties for orthograde or retrograde apical barrier, root perforation repair either in non-surgical or surgical treatment, and regenerative endodontics, due to its excellent biocompatibility and sealing ability [7]. To use as an orthograde apical barrier in the root canal with open apices or loss of apical stop, MTA is filled in 4-5 mm thick at the apical segment of the root canal, with or without the internal matrix, to create an immediate apical barrier for an apical seal and to control the length of the root canal filling [8]. In root perforation treatment, MTA is a root-repair material that provides good sealing and promotes tissue regeneration at the perforation site [9]. Clinical success of MTA in orthograde apical barrier and root perforation repair is as high as 80-92% [8, 10-12]. The success rate of MTA orthograde apical barrier is similar to or even higher than calcium hydroxide apexification. The MTA orthograde apical barrier has fewer treatment periods and a shorter duration of intracanal medication, and can thus reduce the chance of cervical root fracture [13,14]. The success rate of root perforation repair with MTA was 80-92% [9,10,12], compared to a 46-54% success rate of repairing using amalgam or glass ionomer cement [15,16].

MTA (ProRoot MTA, Dentsply, Tulsa, OK, USA) has been a gold-standard material for retrograde

root-end filling, vital pulp therapy, orthograde apical barrier, and root perforation repair [17]. However, the shortcoming of the original formulation of MTA is long setting time, 3-4 hours or longer [18]. Long setting time increases the risk of MTA dissolution when it contacts blood or tissue fluid, which might decrease the sealing ability of the material.

Bio-MA (M-Dent/SCG, Bangkok, Thailand) is a CSC that was developed to accelerate the setting time. The main ingredients are Thai White Portland Cement and bismuth oxide radiopacifier [19]. Settawacharawanich, et al. [19] reported the similarity in chemical compositions of Bio-MA and white ProRoot[®] MTA (WMTA), as well as similarities in solubility, water sorption, dimensional change, compressive strength, and pH value. Calcium chloride (CaCl₂) was added to Bio-MA in order to accelerate the setting time [20,21]. Warotamawichaya, et al. [22] reported that the setting time of Bio-MA containing CaCl₂ was 1 h 35 min, while that of WMTA was 2 h 45 min. Addition of CaCl₂ did not affect the viability of human dental pulp stem cells (DPSCs) [23]. Bio-MA and WMTA each had similarly high biocompatibility to mouse fibroblasts, and showed no or mild inflammation response when implanted in rat subcutaneous tissue for 12 weeks [24,25]. In a histological study of direct capping on exposed dental pulp in rat molars, both Bio-MA and WMTA initially induced mild pulpal inflammation that eventually subsided. Reparative dentin formation was observed at 7 days [26].

From the results of the previous *in vitro* and *in vivo* studies [19-26], the authors believe that Bio-MA is likely to provide similar excellent clinical results as ProRoot[®] MTA. However, a clinical study with well-controlled conditions must be performed to confirm these expectations. Therefore, the aims of this preliminary phase study are to evaluate, by a randomized controlled trial design, the clinical outcomes of Bio-MA and ProRoot[®] MTA when used as orthograde apical barrier and root perforation repair materials.

Materials and Methods

Case selection

This non-inferiority clinical trial [27] was performed following the CONSORT [28] and PRIRATE [29] guidelines for a randomized controlled trial. Ethics approval was given by the Faculty of Dentistry and Faculty of Pharmacy, Mahidol University, Institutional Review Board (MU-DT/PY-IRB 2016/DT043). The study's subjects were recruited at the Endodontic Clinic, Faculty of Dentistry, and the Mahachakri Sirindhorn Dental Hospital, Mahidol University, between July 2017 and December 2019. Informed consent was acquired from all participants. The sample size in this preliminary phase was set at 20 cases for each treatment. Patients with healthy condition or well-controlled systemic disease were recruited with the following criteria.

Inclusion criteria

Orthograde apical barrier

1. Immature permanent teeth with root formation in stages 4-6 according to Moorrees classification [30].
2. Mature permanent teeth whose apical stops were lost due to apical root resorption or over-mechanical instrumentation.

Root perforation repair

Mature permanent teeth with lateral perforation or furcation perforation (direct or strip type) from iatrogenic causes during root canal treatment or restorative procedure.

Exclusion criteria

Orthograde apical barrier and root perforation repair; teeth with unrestorable conditions; crack or root fracture; root resorption (except apical resorption); or chronic periodontitis with marginal bone loss more than 5 mm.

General information

Gender, age, tooth type, and tooth location were recorded. Dental history was taken, and clinical and radiographic examinations were performed. Types of treatment, i.e., primary treatment or retreatment, were defined. In orthograde apical barrier treatment, the stage of root development was estimated. For teeth with root perforation, the type and location of the perforations were identified.

The patients were randomly assigned into the Bio-MA group or ProRoot® MTA group, according to random numbers in sealed envelopes. To maintain patient privacy and bias control, patients' identifications were transformed into code numbers, and types of test material were masked by a person who was not involved in this trial. The standardized protocols of non-surgical root canal treatments with orthograde apical barrier or root perforation repair are briefly described below.

Treatment Protocols

All treatments were provided by postgraduates or endodontists in the Endodontic Clinic, employing an operating dental microscope (Carl Zeiss, Jena, Germany), rubber dam isolation, and aseptic techniques. Prior to initiating treatments, the postgraduates and endodontists received appropriate training to control the treatment protocols.

Orthograde apical barrier

After coronal access opening, root canals were cleaned and shaped by hand files or nickel-titanium rotary files. Root canals were irrigated with 2.5% NaOCl and 17% EDTA in combination with a passive ultrasonic irrigation (PUI) technique using Irrisafe tips (Acteon, Merignac, France). For immature teeth with thin root canal walls, root canal instrumentation was minimal. Calcium hydroxide powder mixed with sterile distilled water or injectable calcium hydroxide paste (UltraCal XS, Ultradent, South Jordan, UT, USA) was medicated in the root canals for at least 1-2 weeks and until any preoperative symptoms were absent and the root canals were dry. Bio-MA or ProRoot®

MTA was randomly selected and mixed according to the manufacturer's instructions. The mixed material was carried into the root canals by an MTA carrier (MAP System, Dentsply Tulsa Dental, OK, USA) and was plugged with endodontic pluggers and paper points until an MTA apical barrier thickness of at least 4-5 mm was obtained. A radiograph was taken (X-Mind DC, Acetone, Via Roma, Olgiate Olona, VA, Italy) to confirm adequacy of thickness and density of the barrier. A moist paper point was placed over the material as a source of moisture for hydration reaction. Coronal access was sealed with temporary restorative material (Cavition, GC Corporation, Tokyo, Japan; or IRM[®], Dentsply, Caulk, Milford, DE, USA). After 3-7 days, the temporary filling was removed, and material setting was checked with a small endodontic plugger. If required, gutta percha was filled in the remaining part of the root canal, up to 1-2 mm below the canal orifice. A glass-ionomer cement base (Vitrebond, 3M ESPE, St. Paul, MN, USA; or Fuji II LC or Fuji VII, GC Corporation, Tokyo, Japan) of 1-2 mm thickness was placed as a lining. A resin composite (Filtek Z350 or Filtek Z250, 3M ESPE) bonded with a bonding agent (Adper[™] Single Bond 2, 3M ESPE) was filled as a coronal restoration. If a prefabricated post was planned, a quartz fiber post (D.T. Light-Post, Bisco Inc., Schaumburg, IL, USA) was cemented in the prepared root canal with a resin-based core build-up material (LuxaCore, DMG, Hamburg, Germany) bonded with a self-etch dental adhesive (Contax, DMG).

Root perforation repair

After coronal access opening, root canal orifices were negotiated. All root canals were prepared by hand or rotary files. The perforation site was located using a dental operating microscope. Root canals and the perforation site were irrigated with 2.5% NaOCl and 17% EDTA, and dried with paper points. Calcium hydroxide medication was placed in root canals as well as the perforation site for at least 1-2 weeks and until the inflammatory reaction was diminished.

Whether the perforation was repaired before or after root canal obturation depended on the site of the perforation and the operator's decision. Bio-MA or ProRoot[®] MTA was randomly selected and mixed according to the manufacturer instructions.

For the direct-type furcation perforation at the pulpal floor, the repair material was carried into the perforated area using an MTA carrier and plugged with endodontic pluggers until at least 2-3 mm thickness was achieved. For the large perforation sites associated with alveolar bone destruction, a collagen sponge (CollaPlug, Zimmer Dental, Carlsbad, CA, USA) was placed as an internal matrix to prevent extrusion of repairing material. For the strip-type furcation perforation and the lateral perforation, the repair material was commonly placed to seal the perforated area and to fill the entire root canal, simultaneously. Occasionally, the perforated site was repaired, and the root canal was filled, separately.

A moist cotton pellet or paper point was placed over the repair material, and then Cavition and/or IRM was used to fill the coronal access temporarily. After 3-7 days, the material setting was checked. In the multi-root tooth, the remaining canal(s) with no root perforation were filled with gutta percha and a resin-based sealer (AH Plus[®], Dentsply, Tulsa, OK, USA) or a eugenol-based sealer (MU sealer, M Dent, Bangkok, Thailand). A direct resin composite or crown was then placed as a coronal restoration.

Recall Evaluation

The recall period was at least six months. Clinical signs and symptoms (pain, positive to percussion or palpation, sinus tract opening, gingival swelling, periodontal probing depth, and tooth mobility) were examined by one investigator (N.T.). Radiographic examinations were evaluated independently by two investigators (N.T. and D.B.), who were previously standardized and calibrated by interpreting ten periapical radiographs. The inter-examiner reliability was analyzed by the

Cohen kappa statistic [31]. The pre-operative and recall radiographs were adjusted to obtain similar contrast and brightness by Adobe Photoshop software (Adobe Systems Inc., San Jose, CA, USA). The radiographic angles were adjusted with ImageJ software with TurboReg plug-in (National Institutes of Health, Bethesda, MD, USA). The Interpretation of periapical lesions in the radiographs would be presence or absence. In cases with pre-operative lesions, the size of lesion was measured by the ImageJ software and compared between the pre-operative and recall radiographs. In a multi-rooted tooth, all roots were evaluated, and the outcome was finally determined from the root with persisting periapical lesion: newly emerging, unchanged, smaller, or (in the worst case) increased in size. If there was a conflict of interpretation, the two investigators would re-evaluate the radiograph together to reach a consensus.

Outcome Assessment

The outcome assessment criteria were based on the clinical and radiographic evaluation, according to Friedman, et al. (2002) [32]. The treatment outcomes were classified as “Healed”, “Healing” and “Disease”, as follows:

Healed. The following findings must be presented:

1. The tooth had no clinical signs and symptoms, such as pain to stimuli, gingival swelling, or sinus tract opening. In addition, percussion and palpation, tooth mobility and periodontal probing depth were within normal limits.

2. The periapical/periradicular area in the recall radiograph showed intact lamina dura and normal periodontal ligament space.

Healing. The following findings must be presented:

1. The tooth had no clinical signs and symptoms.
2. The periapical/periradicular radiolucency in the recall radiograph still existed, but its size was smaller than in the preoperative radiograph.

Disease. At least one of the following findings was presented;

1. The tooth showed clinical signs and/or symptoms of periapical disease.
2. The periapical/periradicular radiolucency in the recall radiograph was unchanged, or increased in size when compared to the preoperative radiograph. In cases without preoperative lesions, a new periapical radiolucency had developed.

Statistical Analysis

The outcomes of Bio-MA and ProRoot® MTA for orthograde apical barrier and root perforation repair were analyzed and compared by the chi-square test and Fisher's exact test with a .05 significance level. For the binary outcome analysis, the healed and healing cases were grouped as “success” while the cases with disease were categorized as “failure”. In addition, the healed and healing cases of Bio-MA and ProRoot® MTA groups were compared. Relative risk between Bio-MA and ProRoot® MTA was calculated with 95% confidence interval. Interpretation of the non-inferiority margin was set at 15%. The Statistical Package for the Social Sciences (SPSS) version 18.0 (IBM Corp, Somers, NY, USA) was used for statistical analysis.

Results

Flow diagrams of orthograde apical barrier and root perforation repair with Bio-MA and ProRoot® MTA according to CONSORT and PRIRATE guidelines are presented in Figure 1 and Figure 2. In this preliminary phase, 22 teeth were recruited for orthograde apical barrier and 24 teeth were for root perforation repair. Three orthograde apical barrier teeth were excluded because one tooth was incompletely treated and extracted for orthodontic reasons, while the other two teeth were lost to follow-up. Thus, the orthograde apical barrier had 19 teeth; 9 teeth in the Bio-MA group

and 10 teeth in the ProRoot® MTA group (Figure 3). Two teeth requiring root perforation repair were excluded due to detection of preoperative crack lines. Thus, 22 teeth were remained in the study, 13 teeth in the Bio-MA group and 9 teeth in the ProRoot® MTA group (Figure 4).

At the recall visits, the coronal restorations of all teeth were determined to be intact without leakage. The mean recall periods were 11.3±2.8 months for orthograde apical barrier and 12.8±3.7 months for root perforation repair. In the orthograde apical barrier group, the participants were 7 males and

12 females aged between 10-67 years (mean 32.3±18.9 years). The pre-operative data distribution is shown in Table 1. Fourteen out of 19 teeth were maxillary anterior teeth. Eighteen teeth showed pre-operative periapical radiolucency with similar distribution of the lesion size between the two groups. The majority of cases were immature teeth in Moorrees' stages 4-6, while a few cases involved mature teeth with the loss of apical stop. Fifteen teeth received primary endodontic treatment while four teeth were retreatment cases for inadequate root canal filling.

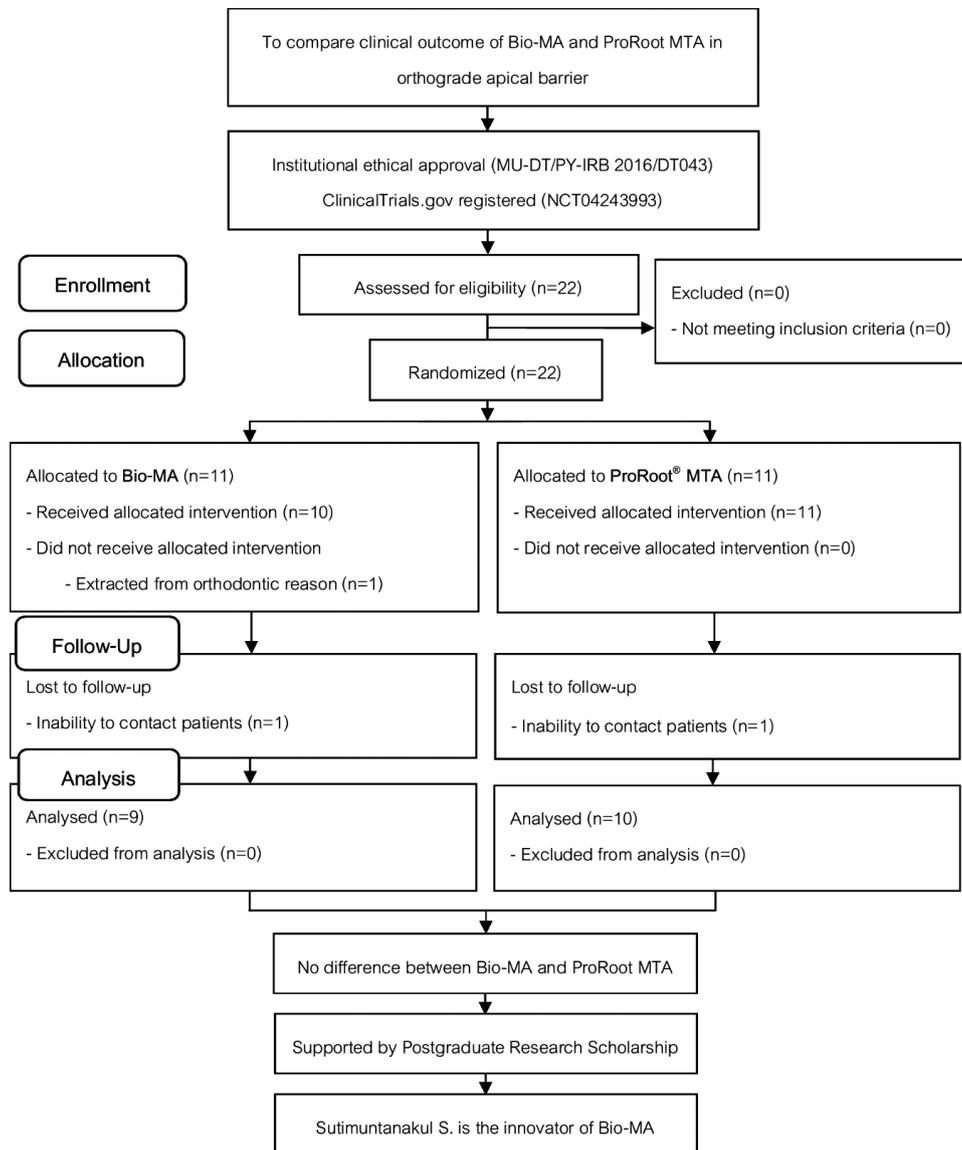


Figure 1 Flow diagram of orthograde apical barrier with Bio-MA and ProRoot® MTA according to the CONSORT (2010) and PRIRATE (2020) guidelines.

For the root perforation repair group, the data distribution is presented in Table 2. There were 7 males and 15 females aged between 24-70 years (mean 49.1±15.1 years). The majority of teeth were maxillary teeth, especially in molars. All perforation types and levels of root were observed. Eleven teeth had no pre-operative radiolucency at either the perforation site or the periapical area. Fifteen teeth received primary endodontic treatment, and seven teeth were retreatment cases for inadequate root canal filling and no previous perforation repair.

The Cohen's kappa value of radiographic calibration was 0.83, associated with the level of almost perfect agreement [31]. In all cases at recall visits, neither clinical signs and symptoms nor enlargement of periapical/periradicular lesions were found, and none of the analyzed teeth was interpreted as “disease”. The success rates, including “healed” and “healing”, were 100% for both the orthograde apical barrier treatment and the root perforation repair, with either Bio-MA or ProRoot® MTA.

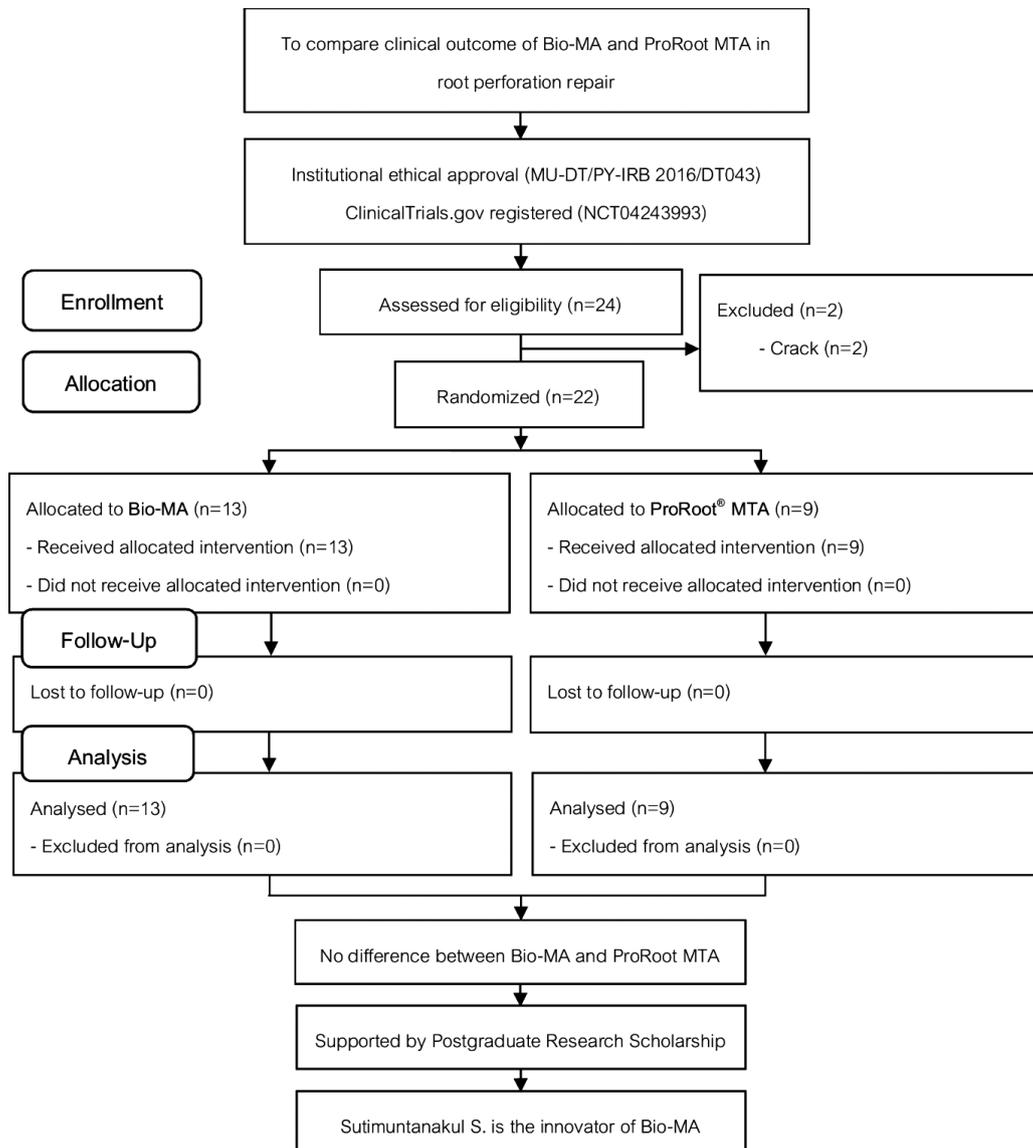


Figure 2 Flow diagram of root perforation repair with Bio-MA and ProRoot® MTA according to the CONSORT (2010) and PRIRATE (2020) guidelines.

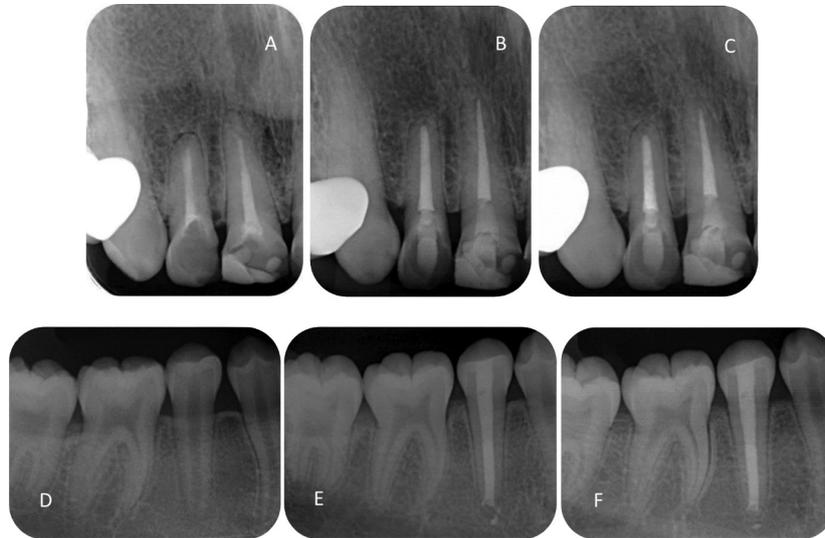


Figure 3 Radiographs of orthograde apical barrier. Pre-operative radiographs of tooth 12 (maxillary right lateral incisor) (A), and 45 (mandibular right second premolar) (D). Bio-MA orthograde apical barrier of 12 (B) and ProRoot® MTA apical barrier of 45 (E). Tooth 12, “healed” at 9-month recall (C), and tooth 45, “healed” at 12-month recall (F).



Figure 4 Radiographs of perforation repair. Pre-operative radiographs of tooth 12 (maxillary right lateral incisor) (A) and 36 (mandibular left first molar) (D). After root perforation repair with Bio-MA (black arrow) of 12 (B) and with ProRoot® MTA (black arrow) of 36 (E). Recall radiographs of tooth 12 at 12-month recall (C) and tooth 36 at 13-month recall (F) showed the “healed” periradicular areas.

Table 1 Pre-operative data distribution of teeth in orthograde apical barrier with Bio-MA and ProRoot® MTA

	Bio-MA (n = 9)		ProRoot® MTA (n = 10)		Total (n = 19)	
	n	%	n	%	n	%
Gender						
Male	4	44.4	3	30.0	7	36.8
Female	5	55.6	7	70.0	12	63.2
Age						
≤45	6	66.7	9	90.0	15	78.9
>45	3	33.3	1	10.0	4	21.1
Tooth type						
Anterior	8	88.9	6	60.0	14	73.7
Premolar	0	0.0	4	40.0	4	21.1
Molar	1	11.1	0	0.0	1	5.3
Tooth location						
Maxilla	9	100.0	7	70.0	16	84.2
Mandible	0	0.0	3	30.0	3	15.8
Pre-op periapical radiolucency						
Absent	1	11.11	0	00.0	1	5.3
Present	8	88.89	10	100.0	18	94.7
Pre-operative periapical lesion size						
≤5 mm	5	55.6	5	50.0	10	52.6
>5 mm	4	44.4	5	50.0	9	47.4
Stage of root development						
Stage 4-6	7	77.8	8	80.0	15	78.9
Stage 7 (loss of apical stop)	2	22.2	2	20.0	4	21.1
Type of endodontic treatment						
Primary treatment	7	77.8	8	80.0	15	78.9
Retreatment	2	22.2	2	20.0	4	21.1

Table 2 Pre-operative data distribution of teeth in root perforation repair with Bio-MA and ProRoot® MTA

	Bio-MA (n=13)		ProRoot® MTA (n=9)		Total (n=22)	
	n	%	n	%	n	%
Gender						
Male	3	23.1	4	44.4	7	31.8
Female	10	76.9	5	55.6	15	68.2
Age						
≤45	7	53.8	5	55.6	12	54.5
>45	6	46.2	4	44.4	10	45.5
Tooth type						
Anterior	2	15.4	1	11.1	3	13.6
Premolar	0	0.0	3	33.3	3	13.6
Molar	11	84.6	5	55.6	16	72.7
Tooth location						
Maxilla	9	69.2	7	77.8	16	72.7
Mandible	4	30.8	2	22.2	6	27.3
Perforation type						
Direct	3	23.1	4	44.5	7	31.8
Strip	6	46.2	2	22.2	8	36.4
Lateral	4	30.8	3	33.3	7	31.8
Perforation level						
Pulpal floor	3	23.1	4	44.5	7	31.8
Cervical	7	53.8	2	22.2	9	40.9
Middle	2	15.4	1	11.1	3	13.6
Apical	1	7.7	2	22.2	3	13.6
Pre-op periapical radiolucency						
Absent	6	46.2	5	55.6	11	50.0
At periapical area	4	30.8	3	33.3	7	31.8
At perforation site	1	7.7	1	11.1	2	9.1
At both site	2	15.4	0	0.0	2	9.1
Type of endodontic treatment						
Primary treatment	8	61.5	7	77.8	15	68.2
Retreatment	5	38.5	2	22.2	7	31.8

The average 'healed' rate of orthograde apical barrier was 78.9% (15/19 teeth), 77.8% in Bio-MA group (7/9 teeth) and 80% in ProRoot® MTA group (8/10 teeth). The 'healing' rate was 21.1% (4/19 teeth), 22.2% in Bio-MA group (2/9 teeth) and 20% in ProRoot® MTA group (2/10 teeth) (Table 3). The statistical analysis did not show any significant difference of the 'healed' and 'healing' rates between the two materials (p -value=1.00). The relative risk between Bio-MA and ProRoot® MTA was 0.97 with 95% confidence interval (0.61 to 1.55). For the non-inferiority trial analysis, Bio-MA tended to be non-inferior, but was inconclusive because the lower limit of the confidence interval in the relative risk ratio was overlapping with the 15% non-inferiority margin (Figure 5).

The average "healed" rate of root perforation repair was 95.5% (21/22 teeth), 92.3% in Bio-MA group (12/13 teeth) and 100% in ProRoot® MTA group (9/9 teeth). Only 7.7% (1/13 teeth) was "healing" in the Bio-MA group (Table 4). No statistically significant difference of the "healed" and "healing" rates was found between the two materials (p -value=1.00). The relative risk between Bio-MA and ProRoot® MTA was 0.92 with a 95% confidence interval (0.79 to 1.08). Bio-MA tended to be non-inferior, but was inconclusive because the 15% non-inferiority margin was overlapped by the range of the confidence interval in the relative risk ratio (Figure 5).

Table 3 Clinical outcomes of orthograde apical barrier with Bio-MA and ProRoot® MTA

Category	Bio-MA (n = 9)		ProRoot® MTA (n = 10)		Total (n = 19)	
	n	%	n	%	n	%
Healed	7	77.8	8	80.0	15	78.9
Healing	2	22.2	2	20.0	4	21.1
Disease	0	0.0	0	0.0	0	0.0

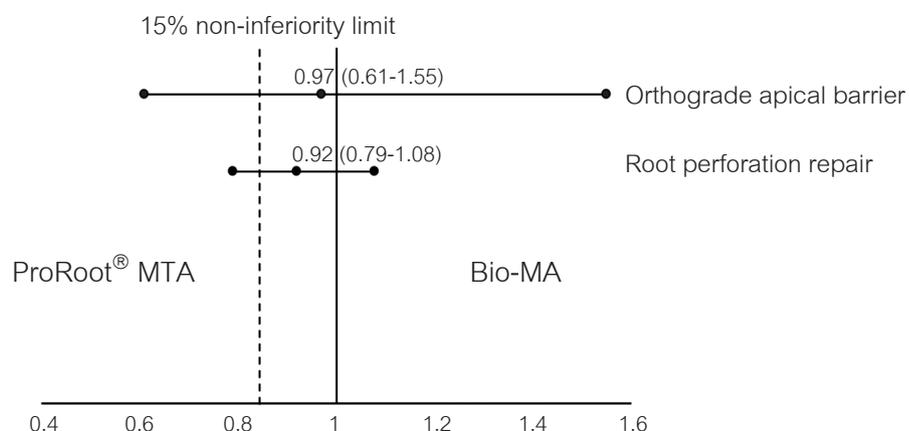


Figure 5 Non-inferiority analysis with 15% of non-inferiority limit comparing the relative risk between Bio-MA and ProRoot® MTA for orthograde apical barrier and root perforation repair. The ranges of 95% confidence interval lines overlapped with the non-inferiority margin of 15%. Bio-MA tended to be non-inferior, but results were inconclusive.

Table 4 Clinical outcomes of root perforation repair with Bio-MA and ProRoot® MTA

Category	Bio-MA (n=13)		ProRoot® MTA (n=9)		Total (n=22)	
	n	%	n	%	n	%
Healed	12	92.3	9	100.0	21	95.5
Healing	1	7.7	0	0.0	1	4.5
Disease	0	0.0	0	0.0	0	0.0

Discussion

At the average 12-month recall period, the clinical outcomes of orthograde apical barrier and root perforation repair using Bio-MA and ProRoot® MTA were both highly successful. Our study excluded those pre-operative factors that tend to negatively affect the clinical outcome, such as crack or root fracture [33]. The operators were endodontists or endodontic postgraduates who were observed to have generally done their best in the root canal disinfection and treatment procedures. Root canal disinfection is a key to reduce the number of microorganism in the root canal system and encourage the healing of periapical disease. The higher the level of intracanal disinfection, the more successful the root canal treatment was [34]. In this clinical trial, the adequate thickness of CSC was set at least 4 mm for apical barrier, and 2 mm for perforation repair, which allowed an adequate seal to prevent reinfection [32,35]. In addition, coronal leakage that would be a pathway of re-infection was not found in any cases. Therefore, the success rate in this clinical trial was higher than in the previous studies, in which these risk factors were included and uncontrolled [9,12].

The clinical outcomes using Bio-MA and ProRoot® MTA were not significantly different, which corresponds to the results from laboratory and animal studies that compared these two materials [19, 25, 26]. The composition of Bio-MA

that differed from ProRoot® MTA was calcium chloride accelerator [19, 22]. The setting time of Bio-MA was reduced, which was expected to improve sealing ability and clinical outcome. Nevertheless, this preliminary clinical trial phase demonstrated that the clinical outcomes of CSC materials with or without the accelerator were not significantly different. It seems that the setting-time reduction from 2 h 45 min of ProRoot® MTA to 1 h 35 min of Bio-MA was not clinically significant [22, 36]. In our cases, inflammatory exudate was well controlled before CSC placing, by calcium hydroxide intracanal medication until the signs of inflammation were subsided. Thus, the sealing ability of the materials was not affected by the reduction of setting time with no dissolution effect from tissue fluid.

Due to the divergent apex of immature teeth, obtaining a proper apical seal with the orthograde apical barrier with CSC is challenging [37]. However, the immature teeth in our study were in the moderate or late stage of root development with the parallel apex (stages 4-6), so an adequate apical seal could be well established with the CSC orthograde apical barrier. The placement of internal matrices such as CollaPlug into the area of periapical bone destruction provides a barrier so that the CSC material can be placed and packed in a proper length. In cases using an internal matrix, the apical barrier could be created with a good adaptation to the root canal walls and the minimal overextrusion that indicate the likelihood of a highly successful clinical outcome [17].

Regarding the orthograde apical barrier in this study, most of the teeth had pre-operative periapical lesions, and half of the lesion were larger than 5 mm. The large pre-operative periradicular lesions could delay the healing process, and one-fifth of cases in our study were still in the “healing” stage at the recall. A longer recall period is required to follow up on this initial healing outcome [16, 38].

Pre-operative radiolucency was the primary prognostic factor that might indicate a worse clinical outcome for non-surgical root canal treatment [10, 16]. In the root perforation repair of this clinical trial, approximately half of the cases had no pre-operative radiolucency at both periapical and perforation sites, which might favor a high success rate [10, 16]. Furthermore, the perforation size was not larger than 3 mm, and time before repairing was short in most of the cases. These factors tend to raise the success rate of perforation repair [3, 12]. Even though the prognostic factors of the cases in our study tended to improve the treatment prognosis, the management of root perforation must still be based strictly on the biological basis of the endodontic treatment [9].

Large perforation size, location of perforation close to the crestal bone level, and a delay in repair might induce periradicular bone destruction and create a communication to the oral cavity. These factors lead to difficulty in creating a proper seal of repairing material at the perforation site. In teeth with these prognostic factors, the treatment outcome would probably be lower than was shown in our study [39].

The perforation site adjacent to crestal bone level risked epithelium down-growth, bacterial contamination, and dissolution of slow-setting CSC material that impaired the success of perforation repair [3, 39]. Most of the perforation sites in our trial were at the coronal third of roots, but were at a distance from the crestal-bone level.

In addition, the pre-operative deep and narrow periodontal pocket (as a temporary drainage from endodontic infection), which could be a possible pathway to communicate between the perforation site and the oral cavity, was completely healed in all cases before repair [39]. Thus, whether fast- or slow-setting material was used, the successful outcome were similar between Bio-MA and ProRoot® MTA.

Recall rates in this trial were 91% in orthograde apical barrier and 100% in perforation repair at a one-year period. Patient compliance tended to be excellent in this short-term recall period, but the dropout rate in a long-term recall might increase [38]. This is a challenging point in the next phase of our long-term study. A one-year recall was the minimum period for assessing the healing of non-surgical root canal treatment [32, 38]. Ørstavik (1996) reported that the highest incidence of emerging new lesions as well as the healing of pre-operative periapical lesions could be observed within the first year [38]. In our study, most of the cases in both treatments were already “healed”, except for five teeth (four teeth of orthograde apical barrier and one tooth of perforation repair), with the large pre-operative periapical radiolucency still in the “healing” stage. However, a noticeable sign of healing (markedly reduced periapical lesion size) was observed in all of these cases that might require a longer period to “healed” [16,38]. In a long-term study, the defect or leakage of coronal restoration should be also monitored since coronal seal from a restoration is mandatory to keep the highest, long-term success [40].

This preliminary phase of a randomized clinical trial study was set up and conducted according to the CONSORT and PRIRATE guideline statements [28, 29]. The study design was at the highest level of clinical evidence. Nonetheless, while the non-inferiority analysis showed a non-inferiority trend, it was “inconclusive”

due to the small sample sizes. A longer follow-up period with a larger number of samples will be required to obtain a conclusive result.

Conclusion

Clinical outcomes of CSC containing or non-containing accelerator, Bio-MA or ProRoot® MTA, were highly successful and not significantly different, in either orthograde apical barrier or root perforation repair at average 11.3 ± 2.8 and 12.8 ± 3.7 months recall period.

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