Original Article

# Outcomes of endodontic microsurgery with retrofilling of calcium silicate cements with or without calcium chloride accelerator: A randomized controlled clinical trial

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## Abstract

**Introduction:** Calcium silicate-based cement (CSC) with calcium chloride ($CaCl_2$) accelerator sets faster than the cement without accelerator. For endodontic microsurgery, CSC with the accelerator tends to be less soluble in tissue fluid that may improve clinical outcome. This study aimed to evaluate the outcome of endodontic microsurgery by retrofilling with CSC containing accelerator (Bio-MA) compared to the original CSC (ProRoot® mineral trioxide aggregate [MTA]).

**Materials and Methods:** Forty-eight teeth required surgical root canal retreatment was included according to the eligible criteria. Endodontic microsurgery with standardized protocol was performed under the dental operating microscope. Bio-MA or ProRoot® MTA was randomly selected for retrofilling. At recall visit, treatment outcomes were evaluated as "healed," "healing" or "diseased," based on clinical and radiographic assessments. The Chi-square test and Fisher's exact test were used in the statistical analysis of the outcome.

**Results:** Seven teeth were excluded because of vertical root fracture detected in surgery ($n = 5$) and inadequate retrofilling depth ($n = 2$). Two cases were lost to follow-up. For thirty-nine teeth with 14.9 ± 5.2 months recall, "healed" rates were 85% in Bio-MA and 84.2% in ProRoot® MTA, and "healing" rates was 15% in Bio-MA and 15.8% in ProRoot® MTA. None of "disease" was observed. No significant difference in the clinical outcome was observed between groups of Bio-MA and ProRoot® MTA ($P = 1.00$).

**Conclusions:** The endodontic microsurgery outcome of Bio-MA containing $CaCl_2$ accelerator was similar to that of ProRoot® MTA without accelerator.

**Keywords:** Calcium silicate cement, endodontic surgery, randomized controlled trial, retrofilling, treatment outcome

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**Submission:** 13-07-21 **Revision:** 08-08-21 **Acceptance:** 09-08-21 **Web Publication:** 08-01-22

## INTRODUCTION

Endodontic microsurgery is a surgical procedure to treat persistent apical periodontitis when nonsurgical root canal retreatment is unsuccessful or not possible.[1,2] The current endodontic microsurgical technique is based on using microsurgical instruments, ultrasonic retrograde

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| Quick Response Code: | Website: www.saudiendodj.com |
| | DOI: 10.4103/sej.sej_152_21 |



**How to cite this article:** Tungsuksomboon N, Sutimuntanakul S, Banomyong D. Outcomes of endodontic microsurgery with retrofilling of calcium silicate cements with or without calcium chloride accelerator: A randomized controlled clinical trial. Saudi Endod J 2022;12:31-7.

preparation, and biocompatible retrofilling material. The operation is performed under a dental operating microscope with high magnification and illumination to improve visualization and detection of canal, isthmus, or crack.[3] The microsurgical technique allows small osteotomy size and retrograde preparation following the root canal. The success rate of endodontic microsurgery is approximately 90%, which is superior to that of the traditional technique.[4]

Mineral trioxide aggregate (MTA) is a calcium silicate-based cement (CSC) that has been a material of choice for retrograde filling in endodontic microsurgery. The main ingredients in the original MTA powder are tricalcium silicate, dicalcium silicate, tricalcium aluminate, and bismuth oxide radiopacifier, which is mixed with distilled water.[5] The material possesses excellent biocompatibility, sealing ability, antimicrobial effect, and ability to induce hard tissue formation.[6] The clinical outcome of endodontic microsurgery with MTA retrofilling is significantly higher than the traditional endodontic surgery with other retrograde fillings.[1,7] However, the important shortcoming of MTA is a long-setting time for approximately 4 h.[8] The slow setting time increases a risk of MTA dissolution when the unset material contacts with blood or tissue fluid, which might decrease the sealing ability.

To accelerate the setting time, adding calcium chloride ($CaCl_2$) into CSC has been suggested. Recently, CSC with this accelerator have been launched, such as RetroMTA (BioMTA, Seoul, Korea), or Bio-MA (M-Dent/SCG, Bangkok, Thailand).[9,10] The physical, chemical, and biological properties of these accelerator-containing CSC are similar to the original MTA without accelerator, but the setting time is faster that reduced the risk of solubility of the cement.[11,12] The clinical outcome of CSC with accelerator might be comparable to or, at least, not worse (noninferiority) than the original MTA. However, a clinical evidence comparison between the CSC with or without the accelerator is still lacking.

Therefore, the purpose of this randomized clinical trial was to compare the treatment outcomes of endodontic microsurgery retrofilling with CSC containing $CaCl_2$ accelerator (Bio-MA) or not (ProRoot® MTA) with a recall period at least 12 months.

## MATERIALS AND METHODS

### Case selection

The study protocols were approved by the Institutional Ethics Committee (MU-DT/PY-IRB 2016/DT043). The study has been registered with the ClinicalTrials.gov (NCT04243993). This randomized clinical trial were conducted according to the CONSORT and PRIRATE guidelines, in a double-blind, noninferiority design.[13,14] The participants with healthy or well-controlled systemic disease (American Society of Anesthesiologists class 1–2) were recruited from the Endodontic Clinic between July 2017 and December 2019, which informed consents were acquired from all participants. The patient identifications were transformed into code numbers to keep the privacy of patients. The treatments were provided by the postgraduate students and the endodontists.

### Inclusion criteria

Endodontically treated teeth with periradicular pathology (PAI score 3–5) required surgical root canal retreatment or endodontic re-surgery, including all tooth types (i.e., anterior tooth, premolar and molar) with the depth for retrofilling at least 3 mm.

### Exclusion criteria

The teeth with root crack/fracture, root resorption, or chronic periodontitis were excluded.

### Sample size calculation

The sample size of patients was calculated using a statistical software (Sealed Envelope, London, UK), available at www.sealedenvelope. com/power/binary-noninferior, for the noninferiority trial.[15] The success rate of endodontic microsurgery with ProRoot® MTA root-end filling was previously reported at 95%.[16] The outcome of Bio-MA was assumed to be comparable to or not worse than ProRoot® MTA. For the noninferiority level at 15%, a statistical power at 0.8 and a significant level at 0.05, the sample size of clinical trial phase was calculated at 18 teeth/group. The sample size increased to 20 teeth/group to compensate for a possibility of 10% dropout rate.

### Randomization method

The random-order table of the assignment was created in Microsoft Excel (Microsoft Corp., Redmond, WA, USA) by the person who was not involved in the treatment procedure. The random order was sealed in an envelope and disclosed to the provider only on the day of the appointment. The orders of random in material sequences was generated using a block randomization (block size = 30) with an allocation ratio of 1:1. According to the random order in the sealed envelopes, the patients received endodontic microsurgery with the standardized protocol/procedure and randomly assigned into a group of the retrofilling materials, Bio-MA or ProRoot® MTA.

The types of material were blinded to all of patients and the investigators who assessed the outcome.

## Surgical protocols

In brief, the surgical procedures were done under dental operating microscope (Carl Zeiss OPMI PROergo, Carl Zeiss, Oberkochen, Germany). It was modified from Kim and Kratchman 2006, with a preclinical training for calibration and standardization of the treatment procedures.[1] The patients were premedicated with 400 mg Ibuprofen or 500 mg Acetaminophen 30 min before the surgery. An adequate amount of local anesthesia (2% Mepivacaine with epinephrine 1:100,000 [Scandonest, Septodont, Saint-Maur-des-Fossés, France]) was administered using an appropriate technique. Triangular flap design was typically used. In some cases, submarginal or papillary-base flap design was used to prevent or minimize loss of interdental papillary height. The incision was performed using a surgical blade. A full-thickness flap was reflected and followed by osteotomy with a Lindemann surgical bur (Hu-Friedy, Chicago, IL, USA), or an ultrasonic tip (ENDO Success, Satelec Acteon, Mérignac, France). Granulomatous tissue was removed with a surgical or periodontal curette. The root surface was stained with 2% methylene blue for the identification of any crack or fracture. According to the exclusion criteria, the tooth with crack or fracture was excluded from this study.

The root end was sectioned perpendicular to the long axis of the root for approximately 3 mm length by the bur or the ultrasonic tip under copious irrigation with normal saline solution. After the root resection, the staining with 2% methylene blue was repeated for re-evaluating any crack line(s) as well as identification of root canal and/or isthmus. The root-end cavity was prepared following the root canal by the ultrasonic tip with a depth at least 3 mm. Epinephrine cotton pellet (Racellet, Pascal Co., Bellevue, WA, USA) or ferric sulfate (Viscostat, Ultradent Products Inc., South Jordan, UT, USA) was used as a hemostatic agent for bleeding control.[17]

A randomly selected root-end filling material, Bio-MA or ProRoot® MTA, was mixed according to the manufacturer's instruction, carried into the root-end cavity with an MTA carrier (MAP system, Dentsply Maillefer, Ballaigues, Switzerland), and condensed with a root-end plugger. Adequate thickness (at least 3 mm), density and adaptation of the retrofilling were checked from a digital periapical radiograph. No bone grafting or guided tissue regeneration was used. The surgical flap was repositioned and sutured by simple interrupted technique with 4-0 or 5-0 Vicryl (Ethicon, Somerville, NJ, USA). Postoperative instructions were given to the patients. The analgesic, i.e., 400 mg Ibuprofen or 500 mg Acetaminophen, was prescribed, but no antibiotic was given. The sutures were removed within 5–7 days after surgery.

## Clinical and radiographic evaluation

The patients were periodically recalled after the surgery at 6 months, 1 year, and annually thereafter. At recall, clinical and radiographic examinations were performed by one investigator. The groups of retrofilling were blinded by a person who was not involved in the trial to control any bias.

The radiographs were evaluated by the two investigators, independently. The two investigators were previously calibrated and standardized in the presence or absence of periradicular lesions, using the ten periapical radiographs; the Cohen's kappa was used to calculate the inter-examiner reliability. In a case with disagreement, the two investigators re-evaluated the radiograph together to reach a consensus.

Postoperative and recall radiographs were adjusted to minimize the difference in the radiographic angles, using the ImageJ software (National Institutes of Health, Bethesda, MD, USA) with the TurboReg plug-in. The periapical lesion sizes in these radiographs were measured using the ImageJ software and compared.

## Outcome assessment

The evaluation unit was considered as a "tooth" unit, which the retrofilled roots were assessed in a multi-rooted tooth. The evaluation criteria were based on the clinical and radiographic assessments from the Friedman's criteria.[18] The treatment outcome was defined as "*healed*," "*healing*" and "*disease*."

"*Healed*"-no clinical signs and symptoms; and "complete healing" or "incomplete healing" (scar tissue) in radiographs, according to criteria of Rud *et al*. and Molven *et al*.[19,20]

*"Healing"*-no clinical signs and symptoms; and 'uncertain healing' in radiographs (the periapical radiolucency smaller than the original).

*"Disease"* with any clinical signs and symptoms and/or "unsatisfactory healing" in radiographs (the size of periapical lesion unchanged or enlarged).

## Statistical analysis

The clinical outcomes of endodontic microsurgery retrofilling with Bio-MA and ProRoot® MTA were analyzed using the Chi-square test and the Fisher's exact test, with a significance level of. 05. The binary outcome analysis, the cases with *"healed"* and *"healing*" were grouped as "success"

while the cases with *"disease"* were categorized as "failure." The relative risk between Bio-MA and ProRoot® MTA was calculated with the 95% confidence interval. The Statistical Package for the Social Sciences (SPSS) software version 18.0 (IBM Corp, Somers, City, NY, USA) was used for the statistical analysis.

## RESULTS

The flow diagram of this randomized controlled trial, according to the CONSORT and PRIRATE guidelines, is presented in Figure 1.[13,14] Forty-eight teeth were initially recruited; seven teeth were excluded because of vertical root fractures detected in the surgery ($n = 5$) and <3 mm of retrofilling depth ($n = 2$). A total of 41 teeth were randomly allocated to Bio-MA group (22 teeth) and ProRoot® MTA group (19 teeth). Two cases in the Bio-MA group were lost to follow-up and could not be contacted.

For the remaining 39 teeth with the mean recall period of 14.9 ± 5.2 months, 20 teeth were in the Bio-MA group and 19 teeth were in the ProRoot® MTA group. The participants were 17 males and 22 females aged 25–70 years (mean 50 ± 11.1 years). The distribution factors of the analyzed cases are present in Table 1, according to the type of retrofilling material. No significant difference in the distribution of factors was found between the two retrofilling groups ($P = 1.00$).

Cohen kappa calculation for the agreement in the radiographic evaluation was 0.83, which indicated the almost perfect agreement between the two examiners. The

**Table 1: The distribution of analyzed cases in Bio-MA and ProRoot® mineral trioxide aggregate retrofilling groups**

| | Bio-MA (*n*=20), *n* (%) | ProRoot MTA (*n*=19), *n* (%) | Total (*n*=39), *n* (%) |
|---|---|---|---|
| Gender | | | |
| Male | 9 (45.0) | 8 (42.1) | 17 (43.6) |
| Female | 11 (55.0) | 11 (57.9) | 22 (56.4) |
| Age | | | |
| ≤45 | 5 (25.0) | 7 (36.8) | 12 (30.8) |
| >45 | 15 (75.0) | 12 (63.2) | 27 (69.2) |
| Tooth type | | | |
| Anterior | 13 (65.0) | 14 (73.7) | 28 (70.0) |
| Premolar | 6 (30.0) | 4 (21.0) | 10 (25.0) |
| Molar | 1 (5.0) | 1 (5.3) | 2 (5.0) |
| Tooth location | | | |
| Maxilla | 16 (80.0) | 18 (94.7) | 34 (87.2) |
| Mandible | 4 (20.0) | 1 (5.3) | 5 (12.8) |
| Size of periapical lesion (mm) | | | |
| ≤5 | 10 (50.0) | 10 (52.6) | 20 (51.3) |
| >5 | 10 (50.0) | 9 (47.4) | 19 (48.7) |
| Surgery type | | | |
| Primary surgery | 18 (90.0) | 17 (89.5) | 36 (89.7) |
| Re-surgery | 2 (10.0) | 2 (10.5) | 4 (10.3) |

MTA: Mineral trioxide aggregate

cases in the Bio-MA group showed *"complete,"* *"incomplete,"* and *"uncertain"* periapical healing at 80%, 5%, and 15%, respectively. These periapical healings were 73.7%, 10.5%, and 15.8%, respectively, in the ProRoot® MTA group.

For the outcomes based on clinical and radiographic assessments, the *"healed"* rates were 85% in the Bio-MA group (17/20 cases) and 84.2% in the ProRoot® MTA group (16/19 cases). The *"healing"* rates were 15% and 15.8% in the Bio-MA (3/20 cases) and ProRoot® MTA (3/19 cases), respectively. None of cases were evaluated as *"disease."* The *success rate* of combining the *"healed"* and *"healing"* was 100% in both Bio-MA and MTA groups.

The statistical analysis did not show a significant difference between the *"heale"'* outcomes of the two retrofilling groups ($P = 1.00$). The relative risk between the Bio-MA and ProRoot® MTA groups was 0.01 (−0.22–0.23) and 1.01 (0.77–1.32) with the 95% confidence interval. Bio-MA was noninferior to ProRoot® MTA, with the lower limit of confidence interval in the relative risk ratio overlapping on the noninferiority level at 15% [Figure 2].

The representative cases of endodontic microsurgery retrofilling with Bio-MA and ProRoot® MTA are presented in Figures 3 and 4.

## DISCUSSION

This randomized controlled trial study showed that the endodontic microsurgical technique was a predictable procedure and corresponded to other clinical studies.[21,22] The bioactive retrofilling material, i.e., CSC, was one of the important factors responsible for the improvement of a successful outcome. Calcium silicate cement created a good apical seal to prevent the migration of remaining intraradicular bacteria into the periapical area.[5]

The outcomes of CSC with or without $CaCl_2$ accelerator in this study were 84%–85% healed rate within the strict criteria evaluation or 100% healed/healing within the loose criteria. Nevertheless, most of the teeth in this clinical trial were anterior teeth and premolars. The molars had more complex root canal anatomy and were more difficult to approach during the surgery. If there were more molars, the treatment outcome would probably be lower.[23]

ProRoot® MTA, a nonaccelerator containing material, was widely used as a retrofilling material with clinical evidence of a high success rate.[21,22] The success rate of ProRoot® MTA in this clinical study was also similar to

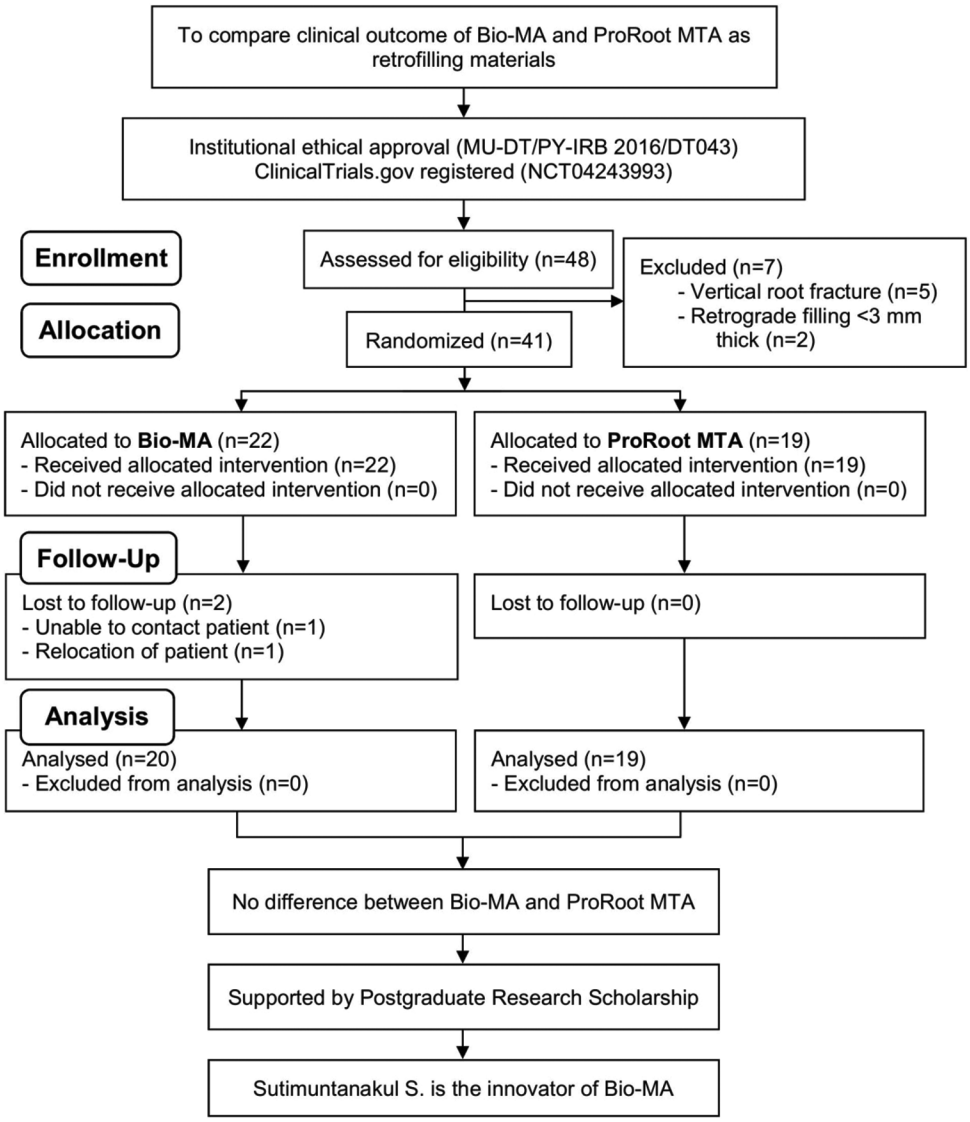


**Figure 1:** Flow diagram of the study according to the CONSORT (2010) and PRIRATE (2020) guidelines for this clinical trial in endodontic microsurgery with Bio-MA and ProRoot® mineral trioxide aggregate retrofilling

the one reported in previous studies.[21,22] Bio-MA, a $CaCl_2$ accelerator containing CSC with a faster setting time, was expected to reduce the risk of solubility to provide better sealing ability and clinical outcome. However, the result showed no difference between these two materials. The setting time of the Bio-MA and ProRoot® MTA was 1 h 35 min and 2 h 45 min, respectively.[24,25] The difference in the setting time between these two materials might not be clinically significant.

At the 1-year recall, almost all teeth in the Bio-MA and ProRoot® MTA groups were healed, and 6 teeth were healing. The healing teeth had preoperative periapical lesions larger than 5 mm with recall periods between 12 and 15 months. The healing of periapical lesion was commonly observed at least 1 year after surgery,[26,27] but teeth with large periapical lesions might require more time to completely heal.[23] However, the 1-year follow-up period was able to predict the long-term outcome.[28,29] Only a few success cases at 1 year could turn to disease at a longer observation period.[16,30] Nonetheless, the periapical lesion after endodontic surgery was rapidly healing by the 1st year since the surgical procedure immediately enhanced the environment for periapical healing and created the apical seal. However, intracanal infection, which could not be completely eliminated, remained inside the canal and might later cause a relapse of disease.[31] Long-term follow-up should be performed to confirm the short-term success of surgical endodontic treatment.

"Incomplete healing" was a bony defect detected in radiographs frequently observed after the surgical treatment

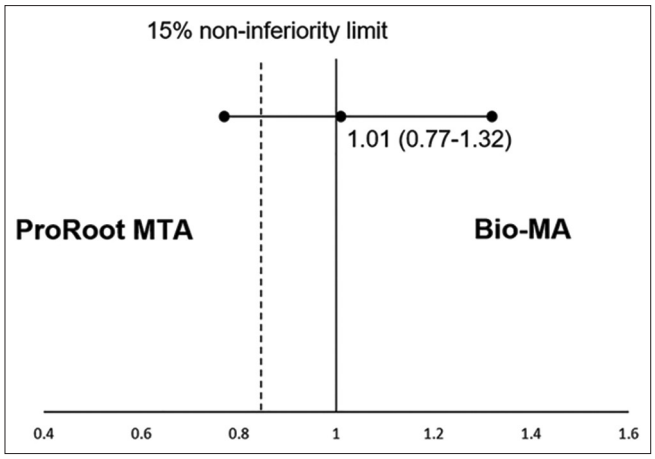


**Figure 2:** Noninferiority analysis with 15% noninferiority limit comparing the relative risk between Bio-MA and ProRoot® mineral trioxide aggregate retrofilling. The range of 95% confidence interval overlapped with the noninferiority limit, which Bio-MA tended to be noninferior to ProRoot® mineral trioxide aggregate

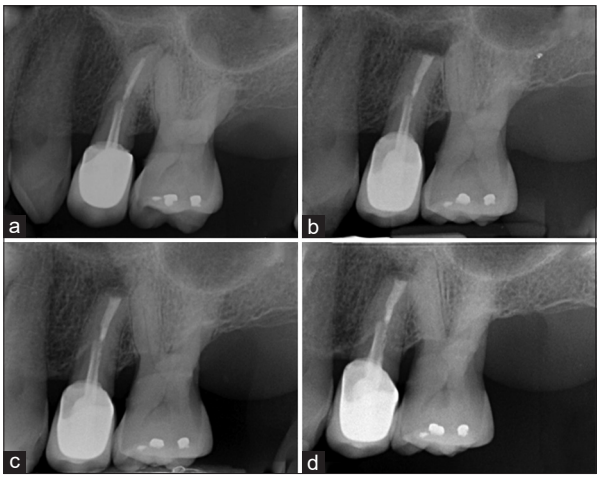


**Figure 3:** (a) Preoperative radiograph of the Bio-MA retrofilling of maxillary left first premolar with symptomatic apical periodontitis and persistent periapical pathosis, (b) Immediate postoperative radiograph, (c) 6-month recall radiograph, and (d) completely "healed" in 13-month recall radiograph

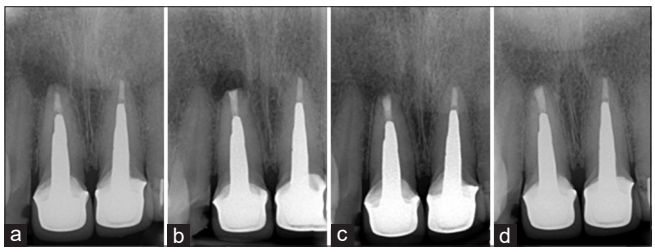


**Figure 4:** (a) Preoperative radiograph of the ProRoot® mineral trioxide aggregate retrofilling case of maxillary right central incisor with metal post and crown that had persistent periapical pathosis (b) immediate post-operative radiograph, (c) 6-month recall radiograph, and (d) completely "healed" in 12-month recall radiograph

of large cystic lesions and through-and-through defects.[32] The "incomplete healing" teeth at 1-year recall would change to "complete healing" at the longer follow-up time, while a few teeth still exhibited "incomplete healing" with a size reduction.[32] This might correlate to the scar fibrous tissue formation in the histological characteristics.[20] "Incomplete healing" is kind of "healed" and considered as success.[32]

In the randomized controlled trial, any confounding factors that tended to affect the clinical outcome would be controlled. This clinical trial excluded teeth with crack/fracture or insufficient thickness of CSC retrofilling. Crack or fracture was the important prognostic factor that significantly worsened the clinical outcome.[33] The thickness of retrofilling material was also directly correlated with an apical seal, and at least 3 mm retrocavity depth was recommended for this.[6] In a comparative clinical study between MTA and EndoSequence root repair material, teeth with root crack/fracture and/or inadequate thickness of retrofilling materials were included. The outcome of "disease" was reported at a higher rate than in the current study.[33] Nevertheless, the failure cases in that study were not directly associated with the tested retrograde filling materials.

In this study, digital periapical radiographs were generally used for assessing the endodontic microsurgical outcome, according to Rud *et al*., and Molven *et al*., criteria.[19,20] Nonetheless, the sensitivity of two-dimensional radiograph in detecting the minor changes of periapical lesion was relatively limited due to the superimposing of anatomical structures. Three-dimensional images from cone-beam computed tomography showed the superior sensitivity in periapical change detection, which should be used (if applicable) in a future study.[33]

This randomized controlled clinical trial was set up and conducted according to the CONSORT guideline statement and the PRIRATE guideline.[13,14] Due to the randomized allocation, the risk of bias would be minimized, and the level of evidence was considerably high for the clinical implication. Endodontic microsurgery can be successful when retrofilling by either CSC with or without the accelerator.

## CONCLUSIONS

At average 14.9 ± 5.2 months recall period, the clinical outcomes in endodontic microsurgery were not significantly different between the retrofillings with Bio-MA (with accelerator) and ProRoot® MTA (without accelerator).

### Financial support and sponsorship

This study was financially supported by Postgraduate Research Scholarship (Faculty of Dentistry, Mahidol University, Bangkok, Thailand).

## Conflicts of interest

Dr. Nuttida Tungsuksomboon declares no conflict of interest. Prof. Supachai Sutimuntanakul declares that he is the innovator of Bio-MA, which the material is used in the Faculty for non-profit purpose. Dr. Danuchit Banomyong declares no conflict of interest.



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