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BMJ Open Comparison of antimicrobial efficacy of Calcipex and Metapex in endodontic treatment of chronic apical periodontitis: a randomised controlled trial study protocol

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ABSTRACT

Introduction Various intracanal medicaments have been used in cases of chronic apical periodontitis for appropriate disinfection of the root canal system to eliminate microbes especially from the inaccessible areas. Calcium hydroxide is the most common intracanal medicament available in various forms, but its effectiveness with or without iodoform using microbial culture is unknown. Therefore, our aim is to compare the antimicrobial efficacy of Calcipex and Metapex in endodontic treatment of teeth presenting with chronic apical periodontitis by assessing the bacterial load reduction. **Method and analysis** 60 single rooted teeth of patients with diagnosis of chronic apical periodontitis will be selected and the canals debrided chemomechanically. The patients will be randomised into two groups: Calcipex and Metapex. The first sample (S1) for bacterial culture will be taken before placement of intracanal medicament and the second sample (S2) will be taken after 7 days, before final obturation from the canal and sent to lab for culture. Colony-forming unit will be evaluated. Paired t-test will be used to assess difference between antimicrobial efficacies within the group of medicaments. Independent sample t-test will be used to assess antimicrobial efficacies between groups. Level of significance will be kept at 0.05.

Ethics and dissemination Approval from Aga Khan University Hospital Ethical review committee is taken. Findings will be reported according to the Standard Protocol Items for Randomised Trials guidelines. Research findings will be disseminated through annual reports, peer-reviewed journals and conferences.

Trial registration number NCT04336709.

BACKGROUND

Pulpal necrosis may lead to spread of the infection from the pulp to involve the apex of the tooth and surrounding bone, which when asymptomatic with periapical radiolucency on radiograph, is called chronic apical periodontitis.^{1,2} In order to eliminate the virulent bacteria and to overcome the inflammation in the root apex, endodontic treatment is the treatment of choice. For the long-term success of endodontic treatment, complete

Strengths and limitations of this study

- Our study is first of its kind to determine efficacy between Calcipex and Metapex using bacterial count.
- Bacterial culture (colony-forming unit/mL) is one of the accurate methods in determining presence of viable bacteria and medicament efficacy.
- Adequate randomisation, blinding and standardised protocols will be followed to obtain optimum result outcome.
- There may be lost to follow-up, flare-ups or unexpected results.
- It is a single-centred study, which may be a limitation and multiple medicaments may be compared in future. More specific methods like RT-PCR could be used.

debridement and reduction of the bacterial count using mechanical cleaning and chemical irrigation seems to be necessary.³ Yet there is no definitive evidence in the literature regarding any of the chemomechanical debridement methods resulting in complete elimination of bacteria from the root canal system.^{4,5} The complex anatomy of the root canal system and presence of many inaccessible areas like lateral canals and dentinal tubules, makes elimination of bacteria from the infected root canal system challenging.⁶

The bacteria that survived in the root canal system might multiply between the appointments or following obturation often reach the previous pathogenic level, thus ending up in endodontic failure.⁷ In order to eliminate the remaining bacteria, various intracanal medicaments have been used widely. However, there is lack of consensus over their use and efficacy.⁸ According to Trope *et al*,⁹ use of calcium hydroxide (CH) dressing in periapical infection reduced the percentage of bacteria upto 90% to 100%; and thus, significantly improved periapical healing.

CH is the most commonly used intracanal medicament that is employed between root canal treatment sessions and available in different combinations. Calcipex (CalcipexII, Nishika, Yamaguchi, Japan) is a water-based CH paste but it is also available with additional substances like iodoform in oil vehicle (Metapex, Meta Biomed, Korea) which is claimed to enhance its antimicrobial activity against *Enterococcus faecalis*.^{10–12}

Multiple studies have been conducted to evaluate the effect of various types of CH-based medicaments.^{13–16} Cwikla *et al* compared CH mixed with water, CH mixed with iodine-potassium iodide, and CH mixed with iodoform and silicone oil (Metapex). He concluded that Metapex is the most effective dentinal tubule disinfectant.¹⁷ On the contrary, Estrela *et al*¹⁰ examined the antimicrobial efficacy of CH with certain vehicles and concluded that the vehicles did not influence the antimicrobial activity of CH.¹⁸ Estrela *et al*¹⁰ in another study concluded that addition of iodoform does not improve the antimicrobial efficacy of CH-saline solution. Whether CH with iodoform is more effective than CH alone against endodontic pathogens is yet to be established.

There are several methods to evaluate the antimicrobial effectiveness of intracanal medicaments. PCR is the most sensitive method for microbial species identification with less interference but it is costly and not readily available in dental clinics.¹⁹ In order to evaluate the true reduction in microbial load from the infected canals, microbial culture is a predictable and convenient tool. There is a paucity of literature related to the effectiveness of CH with or without iodoform using microbial culture.

Thus, this study aims to evaluate the antimicrobial effectiveness of interappointment intracanal medicament with either CH alone (Calcipex) or CH with iodoform (Metapex) for the treatment of infected root canals of teeth diagnosed with chronic apical periodontitis by assessing the bacterial load reduction.

Alternate hypothesis

There is difference in the antimicrobial efficacy of Calcipex and Metapex in root canals of teeth presenting with chronic apical periodontitis.

Study objectives

To compare the antimicrobial efficacy of Calcipex and Metapex in endodontic treatment of teeth presenting with chronic apical periodontitis

Trial design

Two-arm parallel design, randomised controlled trial.

METHODS AND ANALYSIS

Study setting and duration

Dental Clinics, Aga Khan University Hospital (AKUH), Karachi. One year after approval by Ethical research committee of AKUH.

Sampling technique

Block randomisation.

Sampling size determination

Sample size was calculated using WHO sample size calculator (Software V.2.0).²⁰ Dutta *et al*¹³ showed that the population mean and SD of teeth treated with CH-based intracanal medicaments were 50.3±13 colony-forming unit (CFU)/mL. Keeping the absolute precision at 0.05 and level of confidence at 95%, the required sample size turned out to be 26 teeth. The sample is inflated to 30. As we have two groups, therefore, a total of 60 teeth will be taken.

Patient and public involvement

Patients will not be involved in the recruitment and conduct of study. They only will participate as research participants. They will be informed about the details and research being conducted and then consent signed. The consent has all the information mentioned regarding the study. The results of the study will be emailed to the study participants at the end of the study.

Sample selection

Inclusion criteria

- ▶ Single rooted human permanent teeth with single root canal.
- ▶ Clinically diagnosed with chronic apical periodontitis.
- ▶ No history of antibiotics use in last 3 months.

Exclusion criteria

- ▶ Periodontally compromised teeth with grade III mobility.
- ▶ Endodontically non-salvageable teeth.
- ▶ Immunocompromised patients/systemic illness.
- ▶ Excessive root resorption.
- ▶ History of allergy to CH or iodoform.
- ▶ Endodontic retreatment cases.

Interventions

Drugs: Intracanal medicaments

1. Calcipex (CalcipexII, Nishika, Yamaguchi, Japan).
Water-based intracanal medicament.
Colour—white.
Formulation—water based.
Duration—7 days.
Form—aste.
Frequency—used once on first day only till canal fills.
Composition—water-based CH paste without radio contrast agent (barium sulfate).
Packaging—(1 syringe of Calcipex Plain II (1.8g), two needles of Nishika Spin with two needle caps).
Storage requirement—room temperature (1°C–30°C).
2. Metapex (Meta Biomed, Korea)
Oil-based intracanal medicament.
Colour—yellow.
Formulation—oil based
Duration—7 days.
Form: paste.

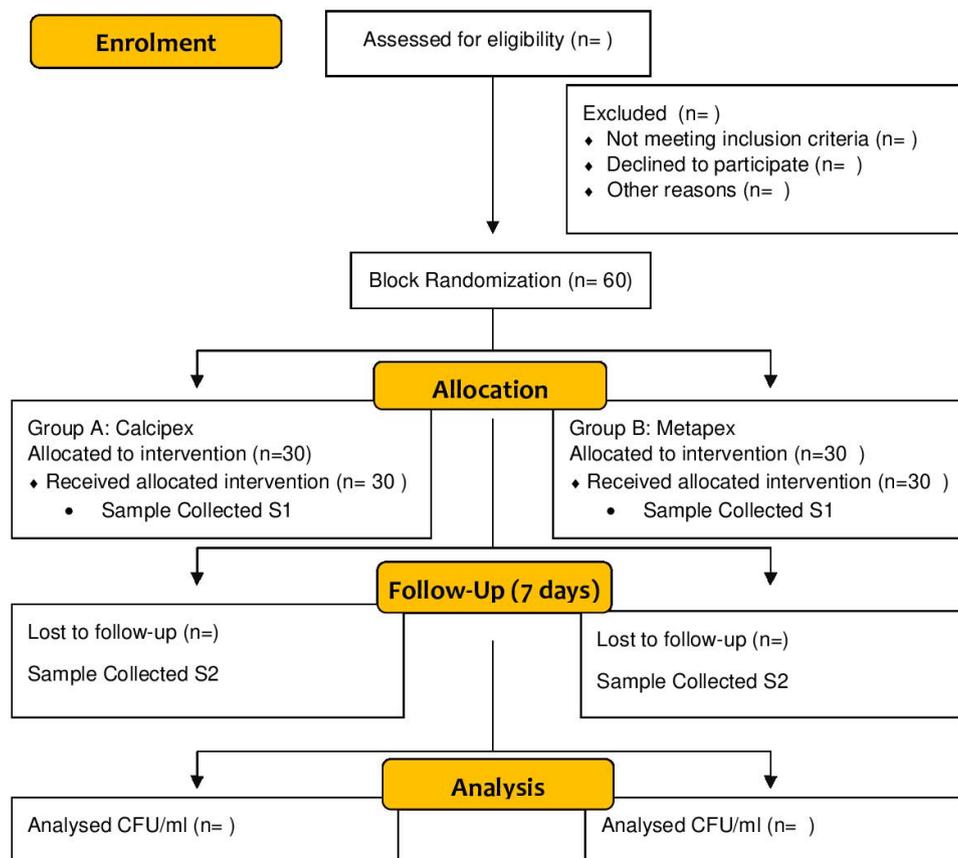


Figure 1 Flow diagram. CFU, colony-forming unit.

Frequency: used once on first day only till canal fills.

Composition—premixed oil-based paste composed of CH with Iodoform and silicon oil.

Packaging—2.2g paste in one syringe. Twenty disposable tips. One ring rotator for direction control of the tip.

Storage requirement—room temperature (1°C–30°C).

These intracanal medicaments will be placed inside the root canals at one point in time.

Outcomes

Antimicrobial efficacy (time frame: 7 days).

Antimicrobial efficacy of intracanal medicament as measuring using CFU/mL via bacterial culture. The higher CFU/mL suggests more bacterial colonies. We expect the counts to reduce after using the intracanal medicament

Participant recruitment

All the patients visiting the dental clinics of Aga Khan University Hospital will be included who fulfil our inclusion criteria and give consent.

Randomisation, blinding and treatment allocation

The selected subjects will be assigned to one of the two study groups only known to the researcher who is not involved in the outcome assessment using block randomisation (figure 1). This would be facilitated by clinical trial unit (CTU). The block size would be 6.

Group A (control group)—Calcipex group (n=30).

Group B (intervention group)—Metapex group (n=30).

The sample in Eppendorf Tubes will be sent in a zip lock bag to the microbiology laboratory labelled with either group A or B. Patient, analyser and the statistician will be blinded about the intervention groups. The recruitment of patients, collection of samples and placement of intracanal medicament will be performed by a single investigator. The investigator placing the intracanal medicament cannot be blinded as the colour of the two medicaments is different. In case of adverse event, unblinding will be done

Data collection procedure

Approval from AKUH Ethical review committee was taken. All patients falling in inclusion criteria will receive detailed information regarding the study, its advantages, benefits and risks. Informed consent will be obtained by a third investigator not involved in data/sample collection. Ethical review committee approval is obtained. (Ethics Review Committee (ERC), Ref No: 2020-0304-9040).

Training of the examiner

The participating investigator with at least 4 years of prior experience will be trained on the development of the trial, case selection, measurement techniques, sample

collection, data compilation sheets and precise role in the study.

Procedure

First visit

The tooth diagnosed with chronic apical periodontitis will be anaesthetised using 2% lidocaine (with 1:100 000 epinephrine) and isolated with the rubber dam. Access opening will be performed using high and low speed round bur. Coronal and radicular necrotic pulp will be extirpated using barbed broaches. The root canal will be initially prepared by using hand K-files (Endoflex; K-File, Size 8–20, NiTi) with quarter turn and pull motion. A 23-gauge side vented needle will be used to deliver 1 mL of sodium hypochlorite for irrigation after each instrument size. The working length will be established with an apex locator and confirmed by the periapical radiographs. Chemomechanical preparation will be completed using Protaper Next (Dentsply; Sirona, USA) depending on both root anatomy and initial diameter of the root canal. The preparation will be completed in the same appointment in all cases. After completion of the preparation, the canals will be irrigated with saline and dried with paper points. A sterile paper point (size 20; EZ Endo, USA) will be inserted to the confirmed working length of the canal, and retained in position for 60 s for sampling¹⁸ (S1) to soak all the canal contents. Afterwards, the paper point will be gently removed and placed in an Eppendorf tube (5 mL) containing Brain Heart Infusion Broth and sent directly to the microbiology laboratory for microbial cultivation.

In group A, the canal will be medicated with Calcipex (CalcipexII, Nishika, Yamaguchi, Japan) which will be placed by means of lentulo spiral fillers at low speed of about 5000 rpm²¹ and packed with a cotton pellet at the level of canal entrance. Access cavity will be filled with a temporary resin based filling material, Dia-Temp (DiaDent Europe BV, Almere, Netherlands) which has the least microleakage and best sealing ability.²² In group B, the canal will be medicated with Metapex (Meta Biomed, Korea) using the same protocol as mentioned above.

Second visit

Patient will be followed up on 7 ± 3 days as the effect of medicament is at its maximum at seventh day and longer placement of the medicament may make the tooth brittle and prone to fracture.²³ The tooth will be isolated and the protocol will be followed the same way as described before. The temporary filling will be removed and the paste carried out of the canal by using sterile file and irrigated with normal saline to wash out the medicament. A postmedication sample will be taken with the help of sterile paper point in both groups as described previously (S2). The canals will be then obturated with gutta-percha and CH sealer (Sealapex, Kerr Dental, USA) by lateral compaction technique. A definitive restoration will be placed subsequently.

Outcome assessment

It will be done in the microbiology laboratory on the basis of CFU/mL.

Microbiology lab protocol

The paper point will be taken out from the container and inserted into the other container filled with enhancement medium of Brain-Heart Infusion Broth (BHIB), vortexed for 60 s to remove all bacteria and spread on BHIB. One mL of BHIB will be added with 1 mL NaCl 0.9%, diluted and repeated in five series until it reached 10^5 CFU bacteria. Each spiral dilute inoculate each dilution in a sterile petri dish containing blood agar and incubated anaerobically for 24 hours at 37°C in CO₂ incubator. After 24 hours incubation period, the bacterial growth will be counted and CFU/mL will be calculated.

Data analysis procedure

Data will be analysed using SPSS V.23.0. Mean and SD of continuous variable will be computed. Frequency distribution and proportion of categorical variables will be determined. Paired t-test will be used to assess difference between antimicrobial efficacies within the group of medicaments. Independent sample t-test will be used to assess antimicrobial efficacies between groups. Level of significance will be kept at 0.05.

Data monitoring

Data collection and maintenance would be reviewed timely by the principal investigator and CTU.

Adverse events

The chances of adverse events in healthy patients are almost negligible. The product-related adverse events would be managed, reported and recorded to ERC within a specified period of time.

Ethical considerations

Ethical approval is obtained from institutional ERC. Patients who fulfilled the inclusion criteria will receive detailed information regarding the study and only those participants will be recruited who will sign the written consent form. The study will be conducted according to the World Medical Association's Declaration of Helsinki and the principles of Good Clinical Practice (GCP). Any subsequent protocol amendments will be submitted to ERC and regulatory authorities for approval. The trial will be conducted in compliance with regulations, particularly specifying pharmacovigilance reporting and a copy of final study report will be submitted to ERC.

Dissemination plan

No publication related to this study has been published or submitted to any journal. Findings will be reported according to the Standard Protocol Items for Randomised Trials guidelines. Research findings will be disseminated through annual reports. Main study protocol amendments will be reported when findings are disseminated.

DISCUSSION

There is no risk involved in this study as the study is based on routine procedure of endodontic treatment. It will be a benefit for future patients which will help us to decide which intracanal medicament is more effective to use in infected canals.

The data will be collected on case report form (CRF) on first and second visit. The CRF has been developed by investigator and reviewed by experts of the field. Data will be stored in a password-protected database. To assure quality, data will be double checked to avoid discrepancies and errors. The information provided by the participant will remain confidential. Nobody except investigators will have access to it. Participants' name and identity will not be disclosed at any time. However, the data may be seen by ethical review committee, DSMB or any local regulatory body. As per GCP and other guidelines, data will be retained for 3 years.

Recruitment of patients is started and will be completed by the end of December 2020.

Contributors All the authors contributed fairly in the study. MAM: Conceptualisation, methodology, data collection, analysis and interpretation, writing-original draft. SH: data collection, visualisation, writing-original draft. RG: supervision, validation, writing-reviewing and editing, project administration. SI: laboratory analysis and interpretation.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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