

## Comparative Evaluation of Triple Antibiotic Paste, Propolis with Moxifloxacin, and Calcium Hydroxide as Intracanal Medicaments against *Streptococcus* spp. and *Enterococcus faecalis* in Type II Diabetes Mellitus Patients: A Randomized Clinical Trial

### Abstract

**Aims:** The antimicrobial efficacy of intracanal medicaments such as calcium hydroxide, propolis with moxifloxacin, and triple antibiotic paste (TAP) was assessed against *Streptococcus* spp. and *Enterococcus faecalis* in chronic apical periodontitis (AP) patients with Type II diabetes mellitus (DM). **Settings and Design:** This study design was a randomized clinical trial. **Subjects and Methods:** Forty-five Type II DM patients with single-rooted teeth diagnosed as AP were instrumented, randomly divided into three groups, and medicated with either TAP, propolis with moxifloxacin, or calcium hydroxide. Bacteriological samples obtained from the root canals after instrumentation (S1) in the first treatment session, and after medication (S2) in the second session 1 week later, were assessed for bacterial growth of *E. faecalis* and *Streptococcus* spp., by viable colony-forming unit counts. **Statistical Analysis Used:** Intragroup, intergroup, and pair-wise comparisons were done by Wilcoxon's signed ranked test, Kruskal–Wallis test, and Mann–Whitney test, respectively ( $P > 0.05$ ). **Results:** The microbiological analysis showed a significant reduction in microbial count from (S1) to (S2) in all the study groups. However, intergroup comparisons revealed no significant difference in decrease of microbial load between all three groups at the end of 1 week. **Conclusions:** Within the limitations of the study, it was concluded that antimicrobial efficacy of TAP, propolis with moxifloxacin, and calcium hydroxide were comparable.

**Keywords:** Antimicrobial, calcium hydroxide, intracanal medicament, propolis with moxifloxacin, triple antibiotic paste

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### Introduction

Endodontic medicine has evolved with an increasing number of reports describing the association between periapical inflammation and systemic diseases.<sup>[1]</sup> Studies suggest an association between apical periodontitis (AP), root canal treatment (RCT), and systemic conditions such as diabetes mellitus (DM), tobacco smoking, hypertension, coronary heart disease (CHD), osteoporosis, bleeding disorders, chronic liver disorders, etc., Several studies have reported a higher prevalence of periapical lesions, delayed periapical repair, greater size of osteolytic lesions, greater likelihood of asymptomatic infections, and poorer prognosis for root-filled teeth in diabetic patients. DM was found to be associated with significantly reduced endodontic treatment outcome of teeth with preoperative infections,

suggesting that diabetes may serve as a disease modifier. It predisposes to chronic inflammation, diminishes tissue repair capacity, and causes a greater susceptibility to infections. The relationship between oral health and diabetes has been extensively reported in the literature.<sup>[2]</sup> The success rate of RCT is 95% which is reduced to 68% in immunocompromised patients. DM compromises the immune response aggravating periapical chronic inflammation and impairing bone turnover and wound healing, increasing the prevalence of persistent AP 1, greater size of the osteolytic lesions, greater likelihood of asymptomatic infections, and worse prognosis for root filled teeth.<sup>[3]</sup> Diabetics have reduced likelihood of success (10%–20%) of endodontic treatment in cases with preoperative periradicular lesions. There is a significant association between the presence of *Streptococcus* spp.

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and infected root canals of patients with a history of DM. *In vitro* studies have also shown coaggregation between *E. faecalis* and *Streptococcus* species.<sup>[4]</sup>

On the other hand, recent studies have found that a poorer periapical status correlates with higher HbA1c levels and poor glycemic control in type 2 diabetic patients.<sup>[1]</sup> *Streptococcus* species are commonly identified microorganism (16%–50%) recovered from the root canals of teeth.<sup>[5]</sup> These microorganisms have an ability to cause initial infection and invade into the dentinal tubules, where they accumulate and form communities organized in a biofilm. This biofilm helps them to resist destruction in harsh ecologic milieu and also share phenotypic characteristic with each other.<sup>[6]</sup> *E. faecalis* is found in high prevalence, levels and proportions in infected root canals,<sup>[7]</sup> and from nonhealing cases in DM.<sup>[8]</sup> This is the most common species recovered in over one-third of the canals of root-filled teeth with persisting periapical lesion.<sup>[7]</sup> Regardless of the thorough chemomechanical preparation and three dimensional obturation, bacteria can persist in the complex anatomy of root canal space. Thus, the

ability of intracanal medicament to restrain or eliminate residual bacteria and prevent reinfection may play an increasingly important role in achieving and maintaining a higher success rate of RCT. Calcium hydroxide is the most commonly used and studied intracanal medication which was introduced in dentistry by Herman in 1920. Its antimicrobial effect is chiefly related to the release and diffusion of hydroxyl ions (OH<sup>-</sup>) which injures cytoplasmic membrane and interferes cell metabolism.<sup>[9]</sup> Propolis, a resinous product rich in flavonoid, is ten times less cytotoxic than calcium hydroxide and has a distinguished antibacterial, antifungal, antiviral, immunomodulatory, and antioxidant effect. Recent studies have reported that propolis is more effective against resistant microorganisms and is biocompatible.<sup>[10]</sup> Moxifloxacin is a new fluoroquinolone with expended spectrum of activity, including anaerobes and Gram-positive organisms, especially the multiresistant ones. Moxifloxacin has been found to be one of the most active antibiotics against *E. faecalis* with the lowest MIC50 and MIC90. Triple antibiotic paste (TAP) containing metronidazole, ciprofloxacin, and minocycline has been reported to be a successful regimen in controlling the root canal pathogens.<sup>[11]</sup> Till date, no *in vivo* study has been done to check the combined efficacy of propolis with moxifloxacin as intracanal medicament and to compare the results with that of TAP and calcium hydroxide against



Figure 1: Digital colony counting device



Figure 2: Transfer of paper point into transport medium



Figure 3: Incubator

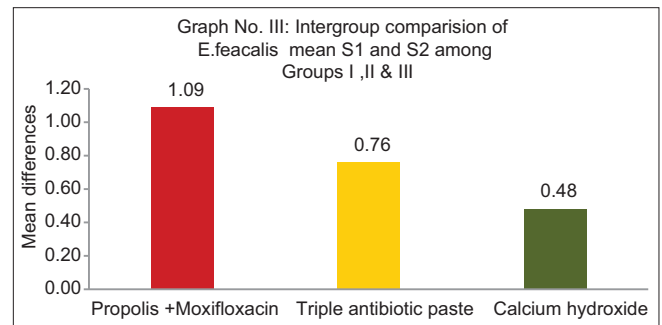


Figure 4: Graph comparison

**Table 1: Total microbial count by culture test in Group I (propolis with moxifloxacin)**

Samples	<i>Enterococcus faecalis</i> (CFU/ml)		<i>Streptococcus</i> spp. (CFU/ml)	
	S1	S2	S1	S2
1	2.9	1.4	6.1	1.9
2	0.0	0.0	6.3	1.5
3	0.0	0.0	0.0	0.0
4	3.1	1.3	5.9	1.7
5	2.7	0.9	6.7	2.4
6	0.0	0.0	0.0	0.0
7	1.9	0.0	5.6	1.8
8	0.0	1.2	0.0	0.0
9	3.1	0.0	6.0	2.1
10	0.0	0.0	7.4	2.3
11	0.0	0.0	0.0	0.0
12	0.0	0.0	6.9	1.9
13	0.0	0.0	0.0	0.0
14	2.5	0.0	6.3	2.1
15	0.0	0.0	0.0	0.0

CFU: Colony-forming unit

**Table 2: Total microbial count by culture test in Group II (triple antibiotic paste)**

Samples	<i>Enterococcus faecalis</i> (CFU/ml)		<i>Streptococcus</i> spp. (CFU/ml)	
	S1	S2	S1	S2
1	2.6	0.9	7.4	1.6
2	0.0	0.0	6.8	1.9
3	3.4	1.6	6.2	1.3
4	3.2	1.4	7.1	2.7
5	0.0	0.0	0.0	0.0
6	0.0	0.0	0.0	0.0
7	3.7	1.8	6.5	1.8
8	0.0	0.0	5.9	2.1
9	2.1	0.0	0.0	0.0
10	2.3	0.0	6.3	1.5
11	0.0	0.0	0.0	0.0
12	2.9	1.2	6.7	2.3
13	0.0	0.0	0.0	0.0
14	3.1	0.0	7.4	1.7
15	0.0	0.0	6.6	2.7

CFU: Colony-forming unit

*Streptococcus* spp. and *E. faecalis* in type II DM patients with chronic AP. Therefore, the current study proposes to compare and evaluate the antimicrobial efficacy of TAP, propolis with moxifloxacin, and calcium hydroxide as intracanal medicaments against *E. faecalis* and *Streptococcus* spp. in chronic AP patients with Type II DM.

## Subjects and Methods

### Sample size calculation

The data required for determining the sample size were based on a previously published scientific article.<sup>[12]</sup> Sample

size calculation estimated that a minimum sample size of 15 individuals per group would be required for an effect size of 0.80 to achieve 95% confidence of a true difference between groups.

### Patient selection

Type II DM patients with chronic irreversible pulpitis with AP indicated for endodontic treatment, between the age groups 35 and 50 years visiting to the Department of Conservative Dentistry and Endodontics in Bapuji Dental College and Hospital, Davangere, Karnataka. The inclusion criteria include chronic AP patients with Type II DM whose HbA1c levels 6%–8%.<sup>[13]</sup> The patients with Minimal (dull aching pain) or no subjective symptoms (not tender to percussion) and who had no necessity of antibiotics in the past 3 months. The tooth which showed no response to thermal and electric pulp tests were included in the study.

### The exclusion criteria

Exclusion criteria include fractured tooth, root resorption, retreatment cases calcified canals, perforated tooth and tooth with endo perio lesions, and extraoral sinus tracts. Patients with systemic diseases such as type I DM, CHD, chronic liver disease, osteoporosis, and inherited coagulation disorders (hemophilia A or B or Von Willebrand disease).

### Procedural steps

Ethical clearance was obtained from the Institutional Review Board. Patient’s demographic details and a thorough clinical history of presenting illness were recorded. Clinical evaluation was performed with visual and tactile examination, thermal tests, electrical pulp testing, percussion, periodontal probing, and mobility assessment. Radiographic evaluation was performed with periapical radiograph, and the periapical index score was recorded. Provisional pulpal and periradicular diagnosis was determined based on history, clinical, and radiographic examination.

### Methodology

Forty-five diabetic patients whose HbA1c levels were between 6% and 8% and of the age groups of 35–50 years with single-rooted tooth/teeth, diagnosed with irreversible pulpitis and chronic AP and requiring endodontic treatment were selected. After obtaining informed consent and initial screening, 45 diabetic patients were allocated into three groups of 15 each by the simple randomization technique (table of numbers). The randomization process was conducted before the clinical steps. Triple antibiotic paste intracanal medicament was obtained by crushing the minocycline (MINOZ 100 mg, RANBAXY) ciprofloxacin (CIFRAN 500 mg RANBAXY) and metronidazole (METROGYL 400 mg, J B CHEMICALS) tablets in the ratio of 1:1:1 by weight and was mixed with glycerin.<sup>[14]</sup> For obtaining the intracanal medicament propolis with moxifloxacin, the moxifloxacin (MOXICIP

**Table 3: Total microbial count by culture test in Group III (Ca (OH)<sub>2</sub>)**

Samples	<i>Enterococcus faecalis</i> (CFU/ml)		<i>Streptococcus spp.</i> (CFU/ml)	
	S1	S2	S1	S2
1	0.0	0.0	5.9	3.2
2	3.2	2.4	6.2	3.5
3	0.0	0.0	0.0	0.0
4	2.8	2.1	5.7	2.8
5	2.4	1.6	6.5	3.7
6	0.0	0.0	0.0	0.0
7	2.1	0.0	5.4	0.0
8	0.0	0.0	5.8	2.3
9	0.0	0.0	6.1	0.0
10	1.9	0.0	0.0	0.0
11	0.0	0.0	7.2	3.9
12	2.6	2.9	6.8	3.3
13	3.4	2.3	5.3	0
14	0.0	0.0	0.0	0.0
15	0.0	0.0	4.9	2.1

CFU: Colony-forming unit

400 mg, CIPLA) and propolis powder were mixed in the ratio of 1:1 by weight with glycerin.<sup>[10]</sup> Preparation of intracanal medicaments was done in BAPUJI Institute of Pharmaceutical Sciences, Davangere. Depending on the type of intracanal medicament used:

- Group I: Propolis with moxifloxacin used as intracanal medicament in 15 patients with type II DM with chronic AP.
- Group II: TAP used as intracanal medicament in 15 patients with type II DM with chronic AP.
- Group III: Calcium hydroxide used as intracanal medicament in 15 patients with Type II DM with chronic AP.

#### First visit – day 1

Teeth were first isolated with rubber dam. Access cavity preparation was done using arotor and access preparation kit. A k-file of suitable size was introduced into the root canal and working length was verified with apex locator [Figure 1].

Root canals were instrumented using k-files along with intermittent irrigation using 1% sodium hypochlorite. Canals were enlarged to size 30 at the working length. All canals were prepared 1 mm short of the radiographic apex using a step-back flared technique. At the completion of chemomechanical preparation, canals were rinsed with 2 ml of 1% sodium hypochlorite followed by 2 ml of 10% sodium thiosulfate for inactivation of the sodium hypochlorite and then a final flush with 2 ml of sterile saline. Following final flush and drying of canals using paper points, the first set of samples was collected as described under sample collection and microbiological analysis [Figure 2].

After sample collection, canals were dried with sterile paper points and intracanal medicaments assigned to each group were placed in the root canals up to their working lengths with lentulo spirals.

Lentulo spirals were coated with the intracanal medicament and then introduced into the root canal, slowly rotating the paste into the canal. The procedure was repeated until the medicament paste will be seen at the canal orifice. The pulp chamber was then closed with a cotton pellet and cavitated. Patient was recalled after a period of 7 days for further treatment.<sup>[15]</sup>

#### Second visit- day 7

The tooth crown was isolated with rubber dam and was then scrubbed with 30% hydrogen peroxide and 1% sodium hypochlorite for 1 min each to disinfect the operative field. Temporary restoration was removed, and reaccess was obtained. A sterile cotton pellet was placed on the floor of the chamber and the access cavity was disinfected with 30% hydrogen peroxide and 1% sodium hypochlorite. Intracanal medicament was removed and canal walls were cleaned with a Hedstrom file of the same size as the master apical file and irrigated with sterile saline solution. Canals were dried using sterile paper points. The second set of samples was collected as described under sample collection and microbiological analysis. Following collection of sample, teeth were obturated.<sup>[15]</sup>

#### Sample collection and microbiological analysis

A volume of 0.5 ml of 0.5% sterile saline solution was flooded into the canal using a sterile syringe. Hedstrom file was placed to within 1 mm of estimated working length and pumped with slight reaming motion. Sterile paper points were placed in the canals for 60 s to absorb the canal contents. Paper points and the cut-fluted part of Hedstrom file were then transferred to test tubes containing 1 ml of thioglycolate transport media. Tubes were vortexed for a period of 60 s to suspend attached bacteria into the media. Samples were then inoculated on blood agar plates with Vitamin K and hemin. Plates were incubated in an anaerobic chamber at 37°C for 7 days [Figure 3]. Colony-forming units (CFU) were counted after 7 days with the help of a digital colony counter. The colony counts before and after placement of each intracanal medicament were noted. The percentage reduction in colony counts was calculated and the results were statistically analyzed.

#### Results

Due to the low bacterial concentrations found in samples – postinstrumentation samples (S1) and postmedication samples (S2), all numeric values were transformed to log<sub>10</sub> values. After chemomechanical preparation, 46% canals showed positive culture results for *E. faecalis* and 66% canals showed positive culture

for *Streptococcus* species. After placement of intracanal medicaments for a 7-day period, 31% canals showed positive culture results for *E. faecalis* and 60% canals showed positive culture for *Streptococcus* species.

At the end of 7 days, Wilcoxon's signed ranked test showed that intragroup differences in *E. faecalis* and *Streptococcus* species mean CFU counts in postinstrumentation samples (S1) and postmedication samples (S2) were statistically significant ( $P > 0.05$ ) for each of the Groups 1, II, and III.

At the end of 7 days, Kruskal–Wallis test showed that intergroup differences of *E. faecalis* and *Streptococcus* species mean CFU counts from S1 to S2 were statistically nonsignificant ( $P > 0.05$ ) among all the study groups [Figure 4 and Tables 1-3].

At the end of 7 days, Mann–Whitney U-test showed that pair-wise comparison of *E. faecalis* and *Streptococcus* species (CFU/ml) between Groups I, II, and III was statistically nonsignificant ( $P > 0.05$ ).

## Discussion

Patients with diabetes have documented alterations in immune functions and may also have pathogenic endodontic microbial flora which makes them susceptible to more severe periradicular disease.<sup>[16]</sup> Hence, in the present study, type 2 diabetic patients with necrotic root canals and AP were chosen as the test samples.

In the present study, Type 2 diabetic patients were evaluated for glycemic control by HbA1C. HbA1c reflects average plasma glucose over the previous 8–12 weeks.<sup>[17]</sup> In the present study, randomly selected patients with a history of Type 2 DM having a WHO-recommended cutoff point of HbA1C  $\geq 6.5\%$  were considered.

Streptococci adapt to extreme environmental changes by expressing numerous extracellular proteins.<sup>[18]</sup> Studies of primary infected teeth with AP have shown a prevalence of around 23% (Sundqvist *et al.* 1992) by culture method and 22%–41% (Fouad *et al.* 2002; Siqueira *et al.* 2002) by checkerboard DNA–DNA hybridization and polymerase chain reaction. According to Distel JW *et al.*<sup>[19]</sup> (2003), virulence factors of *E. faecalis* play an important role in the bacterium's pathogenesis which ranges from life-threatening disease in compromised individuals such as bacteremia, septicemia, endocarditis, and urinary tract infections to less severe conditions such as infections of the obturated root canal with chronic peri AP.<sup>[20,21]</sup>

Hence, the present study considered the evaluation of *E. faecalis* and *Streptococcus* species in cases with AP.

The present study sought to investigate the efficacy of three intracanal medicaments in teeth indicated for endodontic treatment diagnosed as pulpal necrosis with chronic AP. Since calcium hydroxide is the most

commonly used intracanal medicament, it was used as the positive control (Group III – calcium hydroxide) and standard against which the other two (Group I – propolis with moxifloxacin and Group II – TAP) relatively new medicaments were compared.

In the present study, the findings were relatively higher in comparison to the results obtained in various studies where the number of positive samples ranged from 11% to 60%.<sup>[22]</sup> It was lesser in comparison to other studies which reported 100% positive cultures in postinstrumentation samples.<sup>[23]</sup>

This difference may be attributed to variations in study designs, disinfection protocols, irrigating solutions, application time of medicament, sampling methods, and transport media used.

At the end of 7 days, Wilcoxon's signed ranked test showed that intragroup differences in *E. faecalis* and *Streptococcus* species mean CFU counts in postinstrumentation samples (S1) and postmedication samples (S2) were statistically significant ( $P > 0.05$ ) for each of the Groups 1, II, and III. These results were in accordance with Mattigatti *et al.*,<sup>[24]</sup> Marickar *et al.*,<sup>[25]</sup> Malathum *et al.*,<sup>[26]</sup> Mehta *et al.*,<sup>[18]</sup> and Shrivastava *et al.*<sup>[10]</sup> suggesting that calcium hydroxide, propolis with moxifloxacin, and TAP it could be used as an alternative intracanal medicament.

At the end of 7 days, Kruskal–Wallis test showed that intergroup differences of *E. fecalis* and *Streptococcus* species mean CFU counts from S1 to S2 was statistically nonsignificant ( $P > 0.05$ ) among all the study groups. At the end of 7 days, Mann–Whitney U test showed that pair-wise comparison of *E. faecalis* and *Streptococcus* species (CFU/ml) between Groups I, II, and III was statistically nonsignificant ( $P > 0.05$ ).

These results were in accordance with Lakhani *et al.*<sup>[27]</sup> Bhandari and Patil<sup>[28]</sup> and Madhubala *et al.*,<sup>[29]</sup> suggesting that propolis with moxifloxacin was comparable with TAP and calcium hydroxide in terms of antimicrobial efficacy.

Results of this *in vivo* study should be considered within the experimental design that was used, facing limitations of sensitivity and specificity of the culture techniques and CFU counts. Results of the current study showed that, in teeth diagnosed as pulpal necrosis with chronic AP, application of intracanal medicament with propolis with moxifloxacin, TAP, and calcium hydroxide for a time period of 7 days, significantly reduced the mean total microbial load, but there was no significant difference in reduction of microbial load among the three groups.

Studies have shown that, when no intracanal medicament was used in between appointments in multivisit endodontics, bacteria that survived during instrumentation and irrigation rapidly increases to near original numbers.<sup>[23,30]</sup> Thus, the clinical importance of intracanal medicament cannot

be underestimated in multivisit endodontics. Therefore, the results of the present study show that intracanal medicament placement had a clinically significant role in multivisit endodontics, by not allowing bacterial regrowth in the root canal system.

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### Conflicts of interest

There are no conflicts of interest.

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