Original Article

Comparative evaluation of 2% chlorhexidine gel and triple antibiotic paste with calcium hydroxide paste on incidence of interappointment flare-up in diabetic patients: A randomized double-blinded clinical study

ABSTRACT

Aim: Clinical evaluation and comparison of the effect of 2% chlorhexidine gel and triple antibiotic paste with calcium hydroxide on incidence of interappointment flare-up in diabetic patients.

Materials and Methods: Thirty-six diabetes mellitus patients seeking endodontic treatment were assigned to three groups: Group I - calcium hydroxide paste, Group II - triple antibiotic paste, and Group III - 2% chlorhexidine gel. Access opening and chemomechanical preparation was done followed by the placement of intracanal medicaments. Samples were then assessed for the incidence of intra-appointment flare-up at 1, 2, 3, 7, and 14 days using verbal rating scale. Obtained scores were statistically analyzed using one-way ANOVA test and Tukey's *post hoc* test.

Results: Total incidence of interappointment flare-up was found to be 13%. For all the groups, statistically significant difference ($P < 0.05$) was seen at days 1, 2, 3, and 7, with insignificant difference at day 14. Intragroup comparison showed statistically significant difference present between Group I and II and Group I and III with ($P < 0.05$) at days 1, 2, 3, and 7. No statistically significant difference was seen between Group II and III in all 14 days.

Conclusion: Both triple antibiotic paste and 2% chlorhexidine gel were significantly effective for minimizing the interappointment flare-up and postoperative symptoms in diabetic patients. 2% chlorhexidine gel found to be more effective clinically, as compared to other experimental groups.

Keywords: 2% chlorhexidine gel, calcium hydroxide paste, diabetes, interappointment flare-up, intracanal medicament, triple antibiotic paste

INTRODUCTION

The incidence of postoperative pain of mild intensity is not a rare event even after following all standard protocols. Mild pain after chemomechanical preparation can develop in 10%–30% of cases.[1-3] However, the development of interappointment flare-up accompanied or not by swelling of the facial soft tissues and oral mucosa has been demonstrated to be an unusual occurrence. It constitutes a true emergency and usually requires unscheduled visit for treatment. Its incidence ranges from 1.5% to 5.5%.[4]

Various risk factors that significantly influence the development of interappointment flare-up can be divided into patient presenting factors and treatment procedure by the dentist.[5] One of the patient presenting factors is

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diabetes mellitus.[6] It is associated with delayed healing and compromised immune responses[7] which predisposes to chronic inflammation, progressive tissue breakdown, diminished tissue repair capacity[8] and prone to severe endodontic infections, and increased flare-up.

The causative factors of interappointment flare-ups comprise mechanical, chemical, and/or microbial injury to the pulp or periapical tissues,[9,10] among which microbial injury being the most common.[11] Yoshida M *et al*. in 1987[11] frequently isolated *Prevotella* species and *Finegoldia magna* from cases showing acute clinical symptoms and *Peptostreptococcus* species, *Eubacterium* species, *Porphyromonas endodontalis, Porphyromonas Gingivalis,* and *Prevotella* species from flare-up cases having pain and tenderness.[12,13]

Calcium hydroxide most commonly used as medicament but failed to eliminate entire bacterial species including enterococci effectively.[14-16]

Chlorhexidine being more effective in eliminating calcium hydroxide-resistant microorganisms such as *Enterococcus Faecalis,* Ohara PK *et al*. in 1993[17] stated that chlorhexidine was most effective but does not act as a physical barrier against microbial recolonization and has no detoxifying ability against endotoxins.[17]

Local application of antibiotics in the root canal overcomes the potential risk of adverse systemic effects of antibiotics. It is an effective mode for drug delivery in teeth lacking blood supply due to necrotic pulps. This mainly consists combination of ciprofloxacin, metronidazole, and minocycline referred to as triple antibiotic paste.[18]

According to the entire accessible research database available till date, very less reported studies have been done comparing the efficacy of 2% chlorhexidine gel and triple antibiotic paste with calcium hydroxide paste in diabetic patients. Hence, the present study was conducted. The null hypothesis for the study is that there will be no differences on the incidence of interappointment flare-ups with any of the intracanal medicaments in diabetic patients.

MATERIALS AND METHODS

After taking an ethical approval from the Institutional Ethics Committee (SVEIC/ON/Dent/SRP 15143), a total of 36 diabetes mellitus patients' age 20 years and above having primary endodontic lesion, meeting following criteria, and ready to sign informed consent were included in the study.

- HbA1C ≤6.5%–7%
- Fasting plasma glucose (PG) ≤126 mg/dL (7.0 mmol/L)
- 2-h PG ≤200 mg/dL (11.1 mmol/L) during oral glucose tolerance test (75 g)
- Random PG ≤200 mg/dL (11.1 mmol/L).[19]

Teeth with root fractures/resorption, open apex, with intraoral and extraoral swelling, sinus opening, retreatment cases and patients requiring prophylactic antibiotic, with pregnancy or lactation, not willing to participate in the study, and any other systemic disease were excluded from the study.

Minimum sample size required 30 (10/group). A sample size of 30 achieves 80% power to detect an effect size (*W*) of 0.5000 using a 4° of freedom Chi-square test with a significance level (alpha) of 0.05000. But to compensate for dropout, 20% increase in sample size was considered (12 patients in each group). Patients were randomly divided within three groups using computerized randomization: Group I ($n = 12$) – calcium hydroxide paste, Group II ($n = 12$) – triple antibiotic paste, and Group III ($n = 12$) – 2% chlorhexidine gel.

After administration of local anesthesia, isolation of teeth was done using rubber dam. The teeth were then disoccluded followed by access opening and determination of working length. Subsequently, biomechanical preparation was done with crown-down technique, and canals were irrigated copiously with 2.5% sodium hypochlorite, 17% ethylenediaminetetraacetic acid, and normal saline. All teeth were treated by the principle investigator. Following chemomechanical preparation, canals were dried and intracanal medicaments were placed with bidirectional file as follows:

- Group I: Premanufactured calcium hydroxide paste (Prime Dental Product, India) was used
- Group II: Triple antibiotic paste was placed
  Preparation: Ciprofloxacin, metronidazole, and minocycline powders (active pharmaceutical ingredient) were weighed and mixed in 1:3:3 proportions, respectively. Total of 100 g of this mixture was mixed with 40 ml of vehicle (macrogol ointment and propylene glycol)
- Group III: Premanufactured 2% chlorhexidine gel (Cerkamed Medical Company) was used.

After the placement of medicament, teeth were restored with Samfil G (Dentokem, India) as a temporary restorative material.

- Patients were prescribed paracetamol tablets and given a questionnaire to record their pain on 1, 2, 3, 7, and 14 days
- Verbal rating scale (VRS) was recorded by a blinded investigator other than primary investigator
- Both patient and evaluator were kept blinded.

Interappointment flare-up was assessed using VRS:[18]

- VRS - 0 (no pain)
- VRS - 1 (slightly painful for a time, no analgesics)
- VRS - 2 (discomfort and/or pain, one tablet of paracetamol)
- VRS - 3 (discomfort and/or pain, two tablets of paracetamol/6-h)
- VRS - 4 (discomfort and/or pain, two tablets of paracetamol/6 h for 3 days)
- VRS - 5 (severe pain and/or swelling associated with treated tooth/disturbed normal activity/sleep and no effect of paracetamol).

Patients with VRS 4 and 5 were categorized as interappointment flare-up cases.

Fourteen days later, teeth were obturated using gutta-percha and AH Plus sealer followed by prosthesis in required cases. Collected data were analyzed using one-way ANOVA and Tukey's *post hoc* test.

RESULTS

Among 36 diabetic patients with six patients as dropout, thirty patients were evaluated. Thirteen percent (4/30) of patients developed interappointment flare-up. In Group I, 40% (4/10) of patients experienced interappointment flare-up, with no flare-up had seen in Group II and III.

Statistical significant difference was seen in the interappointment flare-up at 1, 2, 3, and 7 days for all the groups ($P < 0.05$), without statistically significant difference on the 14th day [Table 1].

Tukey's *post hoc* test for intragroup comparison showed statistically significant difference among Group I and II and Group I and III with ($P < 0.05$) at days 1, 2, 3, and 7. No statistical difference was seen between Group II and III in all 14 days [Table 2]. Least flare-up was seen in Group III, II, and I, respectively [Graph 1].

DISCUSSION

Among all medically compromised patients, diabetes is the third most prevalent condition looking for dental treatment.[20] Percentage of diabetic patients seeking endodontic treatment is close to 5.2%. Diabetics had twice the rate of flare-ups, i.e., 4.8% as compared to nondiabetics (2.3%).[21] Increased incidence of flare-up could be a result of alterations in immune functions or the presence of more virulent microorganisms in root canals.[20] According to Siqueira and Barnett,[4] a change

Table 1: Mean value and one-way ANOVA test

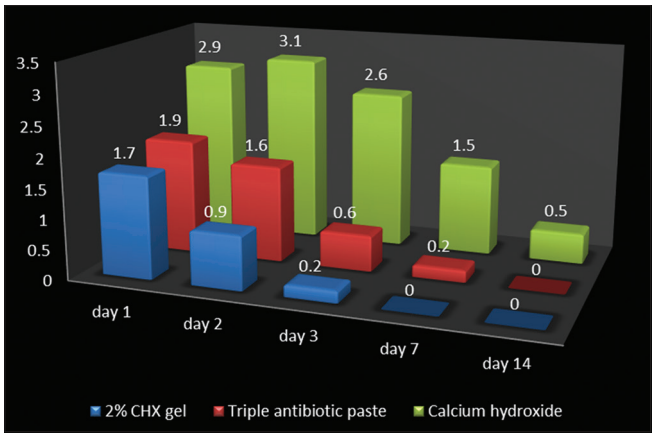
Days	Mean			One-way ANOVA				Significance
	Calcium hydroxide	Triple antibiotic paste	2% CHX	Between groups		Within groups		
				Sum of squares	Mean square	Sum of squares	Mean square	
Day 1	2.9000	1.9000	1.7000	8.267	4.133	11.900	0.441	0.001 (HS)
Day 2	3.1000	1.6000	0.9000	25.267	12.633	26.200	0.970	0.000 (HS)
Day 3	2.6000	0.6000	0.2000	33.067	16.533	36.400	1.348	0.000 (HS)
Day 7	1.5000	0.2000	0.0000	13.267	6.633	14.100	0.522	0.000 (HS)
Day 14	0.5000	0.0000	0.0000	1.667	0.833	6.500	0.241	0.046 (S)

HS: Highly significant; CHX: Chlorhexidine; S: Significant

Table 2: Tukey's *post hoc* test of all three group

Days	Mean	Triple antibiotic paste and 2% CHX		Calcium hydroxide and 2% CHX		Calcium hydroxide and triple antibiotic paste	
		Group II	Group III	Group I	Group III	Group I	Group II
Day 1	Mean difference	1.00000	1.20000	−1.00000	0.20000	−1.20000	−0.20000
	Significance	0.006 (HS)	0.001 (HS)	0.006 (HS)	0.781	0.001 (HS)	0.781
Day 2	Mean difference	1.50000	2.20000	−1.50000	0.70000	−2.20000	−0.70000
	Significance	0.006 (HS)	0.000 (HS)	0.006 (HS)	0.268	0.000 (HS)	0.268
Day 3	Mean difference	2.00000	2.40000	−2.00000	40000	−2.40000	−0.40000
	Significance	002 (HS)	0.000 (HS)	0.002 (HS)	0.724	0.000 (HS)	0.724
Day 7	Mean difference	1.30000	1.50000	−1.30000	0.20000	−1.50000	−0.20000
	Significance	0.001 (HS)	0.000 (HS)	0.001 (HS)	0.811	0.000 (HS)	0.811
Day 14	Mean difference	0.50000	0.50000	−0.50000	0.00000	−0.50000	0.00000
	Significance	0.076	0.076	0.076	1.000	0.076	1.000

HS: Highly significant; CHX: Chlorhexidine



Graph 1: Graphical representation of the mean values of all the groups at days 1, 2, 3, 7 and 14

in host resistance or microbial virulence may allow a previously asymptomatic situation to become more symptomatic. Ueta *et al*.[22] stated that diabetes was a predisposing condition for endodontic infections due to impaired glycemic control.

HbA1c reflects the mean blood glucose level during the preceding 6–8 weeks but fails to replace blood glucose measurements for recognizing acute metabolic abnormalities, and hence both tests were used.[23]

The multiple-visit protocol for root canal therapy with the placement of intracanal medicament was opted, owing to the long-term history of evidence-based clinical success associated with the same. Crown-down technique was used as literature reveals that its use leads to less extrusion of debris periapically and subsequently the lesser incidence of postoperative discomfort.[24,25]

However, recontamination of the canal may take place if the medicament is retained for 2 weeks. Considering a minimum 1-week retention period, medicaments were changed after 7 days. Flare-up occurs in 48 h after the initiation of the endodontic procedure. Furthermore, inflammation is said to take at least 10–14 days to subside.[18] Hence, incidence was evaluated on days 1, 2, 3, 7, and 14.

Pain is inherently subjective and its measurements primarily rely on the verbal report of the patients. Among various commonly used scales such as continuous visual analog scale, VRS, numerical rating scale, and a faces pain scales, VRS is considered to be a valid and reliable scale for the measurement of pain.[18] Scores of VRS were categorized into six groups to make the patient understand in better way and make it clinically more relevant.[18]

Calcium hydroxide is considered as the most favorable antimicrobial agent. In spite of various advantages, it is not equally effective against all bacteria, rather fails to eliminate enterococci effectively, and shows limited action against facultative anaerobes and *Candida* species.[26] Fouad[21] showed a positive association between the presence of diabetes and certain more virulent bacteria. There is increase in the number of *Fusobacterium nucleatum*, *Streptococcus* spp. *P. endodontalis, Bacteroides forsythus, Treponema denticola,* and *P. gingivalis* in diabetic patients. Hence, this might be the reason of all the flare-ups observed in this study.

In triple antibiotic paste, metronidazole exhibits broad spectrum of activity against protozoa and obligate anaerobes which are present deep in root canal dentin. It binds to the DNA, disrupts the helical structure, and leads to rapid cell death. Minocycline is primarily bacteriostatic, acts by inhibiting protein synthesis in susceptible organisms, but exhibits broad-spectrum activity against Gram-positive and Gram-negative organisms. Ciprofloxacin has rapid bactericidal action; it inhibits the enzyme bacterial DNA gyrase, leading to damage to DNA and more effective against Gram-negative bacteria but comparatively less effective against Gram-positive bacteria.[18] In the present study, none of the patient develop flare-up with triple antibiotic paste may be attributed to combination of antibiotics. The use of propylene glycol and macrogol as a vehicle leads to greater penetration of triple antibiotic paste[27] with significantly less reduction in microhardness of dentin.[28] Active pharmacological ingredients of drugs were selected for preparation so that the coating and other ingredients should not interfere with the formation of homogenous mixture.

Chlorhexidine is a broad-spectrum antimicrobial due to its cationic bisbiguanide molecular structure. It is bactericidal at higher concentrations. Best results with no interappointment flare-up are seen in this group might be because chlorhexidine has a reasonably wide range of activity against aerobic and anaerobic organisms as well as *Candida* species when compared to calcium hydroxide, especially in gel formulations at 2% concentration, and diabetic patients have increased rate *Candida*-based infections.[26]

Among four patients who developed flare-up, three of them were females with mandibular teeth. Several studies found higher numbers of posttreatment pain and flare-ups in females than males.[5] According to Torabinejad *et al*.,[10] mandibular teeth were more prone to flare-up than maxillary teeth.

Results of this study were in accordance of results shown by Pai *et al*.[18] that triple antibiotic paste is more effective than calcium hydroxide in preventing the occurrence of flare-up in diabetic patients. Krithikadatta *et al*.[29] showed that 2% chlorhexidine gel alone was most effective against *E. faecalis* when compared to 2% metronidazole, bioactive glass, and calcium hydroxide. Contradictory results are shown by Ordinola-Zapata *et al*.[30] that the triple antibiotic paste was most effective at killing the bacteria in the biofilms on the intraorally infected dentin model in comparison with 2% chlorhexidine gel and calcium hydroxide. The null hypothesis stated in the study was rejected.

The incidence of intra-appointment flare-up depends on many other factors such as type of tooth as well as age of the patient; according to Torabinejad *et al*.,[10] patients in the age group of 40–50 years had the most flare-ups, which were not taken into consideration in this study. Ultrasonic activation of the irrigating solutions may lead to greater penetration of the medicament, but this parameter was not taken into consideration of our research and less sample size which might be one of the shortcomings.

However, more controlled studies are required for further clinical validation of the findings pertaining to the present study and on microorganisms causing flare-ups, particularly in diabetic patients and action of intracanal medicament on them.

CONCLUSION

Within the limitations of this *in vivo* study, both triple antibiotic paste and 2% chlorhexidine gel when used as intracanal medicament were significantly effective for minimizing the interappointment flare-up and postoperative symptoms in diabetic patients. 2% chlorhexidine gel found to be more effective clinically, as compared to other experimental groups.

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Conflicts of interest

There are no conflicts of interest.

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