

Comparative Evaluation of Mixture of Calcium Hydroxide and Chlorhexidine, with Triple Antibiotic Paste and Combination of Calcium Hydroxide, Chlorhexidine, and Lycopene on Incidence of Interappointment Flare-up: An *in vivo* Study

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ABSTRACT

Background: The present study was undertaken to evaluate the most suitable intracanal medicament with the least incidence on Interappointment flare-up.

Aim: To clinically evaluate and compare the effect of combination of calcium hydroxide (CH) and chlorhexidine (CHX) with triple antibiotic paste and combination of CH, CHX, and lycopene on interappointment flare-up.

Materials and methods: A total of 36 patients requiring root canal treatment were selected according to the selection criteria and divided into three groups: Group I – CH and CHX, group II – triple antibiotic paste, and group III – CH, CHX, and lycopene. Access opening and biomechanical preparation of all samples, and intracanal medicaments were placed respectively. Subsequently, interappointment flare-up was assessed at 1, 2, 3, 7, and 14 days using verbal rating scale.

Statistical analysis used: One way analysis of variance test and Tukey's *post hoc* test.

Results: There was no statistically significant difference seen in the clinical performance of CH + CHX, triple antibiotic paste, and mixture of CH + CHX + lycopene at the end of 14 days in terms of interappointment flare-up.

Conclusion: All the intracanal medicaments were effective in reducing interappointment flare-up at the end of 14 days.

Keywords: Calcium hydroxide, Chlorhexidine, Interappointment flare-up, Intracanal medicament, Lycopene.

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INTRODUCTION

Interappointment flare-up is the occurrence of severe pain, swelling, or both, following an endodontic treatment, which results in an unscheduled emergency visit of the patient. The frequency of flare-up ranges from 1.4 to 16%.^{1,2}

Various intracanal medicaments are advocated to eliminate bacteria and prevent multiplication of bacteria between the appointments. Calcium hydroxide (CH) has been the most commonly used medicament and is considered to be the gold standard.³ Calcium hydroxide is believed to have many properties of an ideal intracanal medicament, mainly due to its alkaline pH. However, CH cannot be considered as a universal intracanal medicament, as it is not equally effective against all bacteria found in the root canal.

Chlorhexidine (CHX) has been widely used in periodontics. It has antimicrobial activity against Gram-negative and Gram-positive microorganisms. The CHX has been shown to be more effective in eliminating CH-resistant microorganisms like *Enterococcus faecalis* inside dentinal tubules.⁴ So, a combination of the two medicaments has been used having synergistic effect.

There has been an increasing concern regarding evaluation of effect of natural antioxidants in dentistry. Of the various antioxidants, lycopene is the one that could be used as an effective intracanal medicament. Lycopene is the red pigment of tomato, which has got various properties like antibacterial, antifungal, oxygen scavenger. Also, it is used as an adjunct to treatment of gingivitis along with oral prophylaxis.⁵

However, no study has been performed *in vivo* to evaluate antibacterial efficacy in terms of Interappointment flare-ups with lycopene antioxidant as an intracanal medicament. Hence, one of the groups in the present study is the combination of CH, CHX, and lycopene.

Recently, Japanese researchers have reported that triple antibiotic mixture successfully disinfects the root dentin *in vitro*.⁶ This mixture consists of ciprofloxacin, metronidazole, and minocycline, which consistently sterilize bacteria of infected dentin and infected pulps.^{6,7}

Various studies have been done comparing the efficacy of CH, CHX, and triple antibiotic paste individually as intracanal medicament. But, no study has been done comparing the efficacy of mixture of CH and CHX with triple antibiotic paste and combination of CH, CHX, and lycopene.

Hence, the present study aims to compare and evaluate the efficacy of above-mentioned intracanal medicaments in interappointment flare-ups. 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.

MATERIALS AND METHODS

After taking prior permission from the ethical committee, a total of 36 patients requiring root canal treatment were selected and divided into three groups:

1. *Group I*: CH and CHX
2. *Group II*: Triple antibiotic paste
3. *Group III*: CH, CHX, and lycopene.

Patients with age 18 years and above requiring root canal treatment of any tooth with complete root formation without any medical history were included. Those teeth with root fractures, resorption, open apex, sinus opening, intra- or extraoral swelling or retreatment cases were excluded.

The distribution of materials and tooth locations was done by computerized randomization. All teeth were treated by the principal investigator. After administration of local anesthesia and rubber dam isolation, teeth were disoccluded followed by access opening, working length determined with apex locator, and biomechanical preparation with crowdown technique using various hand and rotary file systems was done. The canals were irrigated copiously with 2.5% sodium hypochlorite, 17% ethylenediaminetetraacetic acid, and normal saline. Canals were dried and intracanal medicaments were placed with bidirectional file as follows.

Group I

Mixture of CH and CHX was placed as an intracanal medicament using bidirectional file and temporary restoration was done.

A total of 1.5 gm of CH powder (Prime Dental Product, India) was dispensed and mixed with 1 mL of 2% CHX solution (Calypso, Septodont, India) as intracanal medicament.⁸

Group II

Triple antibiotic paste was placed as an intracanal medicament using bidirectional file and temporary restoration was done.

It was prepared by removing the coating and crushing of antibiotic ciprofloxacin (Ciplox 500 mg, Cipla, India), metronidazole (Metrogyl 400 mg, J. B. Chemicals and Pharmaceuticals Ltd., India), and minocycline (Minoz 100 mg, Cipla, India) tablets separately using a mortar and pestle. The crushed powder was passed through a fine sieve to remove heavy filler particles and obtain a fine powder. The ciprofloxacin, metronidazole, and minocycline powders thus obtained were weighed separately and mixed in a 1:3:3 proportions respectively, to obtain triple antibiotic mixture. A total of 100 mg of this triple antibiotic mixture was dispensed and mixed with one drop of propylene glycol to get a thick paste-like consistency, which was then used as an intracanal medicament.⁸

Group III

Combination of lycopene, CH, and CHX was placed as an intracanal medicament using bidirectional file and temporary restoration was done.

The paste was made by mixing 1.5 gm of CH powder, 1 mL of 2% CHX solution, and 1 mL of 5% lycopene solution. About 5% lycopene solution was prepared by mixing 5 gm of LP (Mynutramart, India), which is in the form of powder to 100 mL of distilled water.⁵

After placement of intracanal medicament, all teeth were restored with a temporary restorative material and patients were prescribed paracetamol tablets and given a questionnaire to record their pain on days 1, 2, 3, 7, and 14.

Interappointment flare-up was assessed using verbal rating scale (VRS) using the following criteria:

- Verbal rating scale 0 (the treated tooth felt normal)
- Verbal rating scale 1 (the treated tooth was slightly painful for a time, regardless of the duration, but there was no need to take analgesics)
- Verbal rating scale 2 (the treated tooth caused discomfort and/or pain, which was rendered comfortable by taking one tablet of paracetamol)
- Verbal rating scale 3 (the treated tooth caused discomfort and/or pain, which was rendered comfortable by taking two tablets of paracetamol at a 6-hour interval)
- Verbal rating scale 4 (the treated tooth caused discomfort and/or pain, which was rendered tolerable by taking two tablets of paracetamol at every 6 hours for 3 days)
- Verbal rating scale 5 (severe pain and/or swelling caused by the treated tooth that disturbed normal activity or sleep and paracetamol tablet had little or no effect).

Cases with VRS 4 and 5 were regarded as interappointment flare-up.⁸

Table 1: One-way ANOVA test

Group	n	Mean	Std. deviation	Std. error	95% confidence interval for mean		Minimum	Maximum	ANOVA p-value
					Lower bound	Upper bound			
CH + CHX	12	0	0	0	0	0	0	0	0.379
Triple antibiotic paste	12	0.08	0.289	0.083	-0.10	0.27	0	1	
Lycopene + CH + CHX	12	0	0	0	0	0	0	0	
Total	36	0.03	0.167	0.028	-0.03	0.08	0	1	

ANOVA: Analysis of variance

Table 2: Tukey's *post hoc* test

(I) group	(J) group	Mean difference (I-J)	Std. error	p-value	95% confidence interval	
					Lower bound	Upper bound
CH + CHX	Triple antibiotic paste	-0.083	0.068	0.447	-0.25	0.08
	Lycopene + CH + CHX	0	0.068	1.000	-0.17	0.17
Triple antibiotic paste	CH + CHX	0.083	0.068	0.447	-0.08	0.25
	Lycopene + CH + CHX	0.083	0.068	0.447	-0.08	0.25
Lycopene + CH + CHX	CH + CHX	0	0.068	1.000	-0.17	0.17
	Triple antibiotic paste	-0.083	0.068	0.447	-0.25	0.08

RESULTS

The results of the study showed that there is a statistically significant difference in the interappointment flare-up at days 1 and 2 for all the groups ($p < 0.05$). But at the end of 14 days, all the three groups performed equally without any statistically significant difference between the groups (Table 1). Also, when intragroup comparison was done using Tukey's *post hoc* test, the results showed statistically significant difference between all the groups ($p < 0.05$) at days 1 and 2. Least flare-up was seen in group III (CH + CHX + lycopene) followed by group I (CH + CHX) and group II (triple antibiotic paste) (Table 2).

DISCUSSION

The primary aim of endodontic treatment is biomechanical preparation of the root canal (cleaning, shaping, and disinfection) and to hermetically seal it with no discomfort to the patient, and provide conditions for the periradicular tissues to heal. A flare-up can be defined as pain and/or swelling of the facial soft tissues and the oral mucosa in the area of the endodontically treated tooth that occur within a few hours or a few days following root canal treatment.

Pain is inherently subjective and its measurements primarily rely on the verbal report of the patients. Several scales and methods have been used for the assessment of pain after endodontic therapy. Among them, the VRS is considered to be a valid and reliable scale for the measurement of pain.⁹ Therefore, VRS was used in this study to evaluate interappointment flare-up.

The recommended retention period for the intracanal medicament is no less than 14 days. However, recontamination of the canal may take place if the medicament is retained for 2 weeks.^{10,11} Considering a minimum 1-week retention period, medicaments were changed after 7 days in the current study. A flare-up is said to be those incidences of either severe pain or swelling in 48 hours (2 days) after the initiation of the endodontic procedure without any correlation with the number of visits of endodontic treatment.¹² Furthermore, inflammation is said to take at least 10 to 14 days to subside.¹⁰ Therefore, the incidence of interappointment flare-up in the present study was evaluated on days 1, 2, 3, 7, and 14.⁸

Interappointment flare-up can result due to apical extrusion of infected debris, changes in the root canal microbiota, and/or environmental conditions during the various techniques of biomechanical preparation that increase the oxidation–reduction potential in the root canal and, hence, favor the growth of facultative bacteria. One of the ways of preventing or rather reducing the flare-up incidence would be placement of an intracanal medicament. Sole use of the chemomechanical instrumentation does not help to eliminate the wide variety of bacteria within the root canal. Hence, placement of intracanal medicament has been advocated to eliminate remaining bacteria after chemomechanical preparation.^{1,2}

In the present study, least incidence of interappointment flare-up was seen in group III (CH + CHX + lycopene) at days 1 and 2.

This could be attributed to the antioxidant property of lycopene. Lycopene, by virtue of its high number of conjugated double bonds, has the maximum oxygen-quenching ability. Oxygen quenching by lycopene occurs via physical quenching, i.e., the carotenoid remains intact and can undergo further cycles of single oxygen quenching. Further, lycopene is an effective deactivator of electronically excited sensitizer molecules, which are involved in the generation of radicals and singlet oxygen.¹³ This could account for the drastic reduction of reactive oxygen species (ROS). The low molecular weight of lycopene ensures better penetration and, thereby, resultant decreased ROS formation. As ROS plays a major role in inactivation of bacterial proteins due to its bactericidal effect, significant decrease in ROS formation leads to increased antibacterial efficacy and, hence, decreased incidence of flare-up.^{5,14}

The subsequent group which shows decreased incidence of flare-up was group I (CH + CHX). The presence of Ca(OH)₂ in the paste formulation acts as a physical barrier, which will stay in the root canal for longer, preventing root canal reinfection, interrupting the nutrient supply to the remaining bacteria, and thus delaying recontamination. Moreover, the presence of CHX adds substantivity to the formulation, due to its adsorption capacity and slow liberation of active molecules by dental tissues. Therefore, CHX could maintain the canal free of microorganisms, even after being removed from the canal. The CHX's substantivity sustains the antimicrobial activity over a period of 48 hours, 72 hours, and up to 7 days after being removed from the root canal.¹⁵

But, on comparing group I (CH + CHX) with group III (CH + CHX + lycopene), flare-up rate was less with group III. This could be because of higher ROS formation. This is probably due to the formation of hydroxyl ion, which is the dissociation product of Ca(OH)₂ at an alkaline pH. This increased ROS formation ultimately leads to the flare-up.

Decreased flare-up rate with triple antibiotic paste may be attributed to the combination of antibiotics. Among the components, metronidazole has a wide bactericidal spectrum against obligate anaerobes, which are common in the deep dentin of infected root canals. Certain bacteria are resistant to metronidazole; hence, ciprofloxacin and minocycline were mixed with it to achieve higher antimicrobial action.¹⁶

Sato et al¹⁷ in their study have proved that a mixture of ciprofloxacin, metronidazole, and minocycline is useful for sterilization of infected root dentin, and that the drug mixture can be applied to root canals.

Although at the end of 2 days, least incidence of inter-appointment flare-up was seen by mixture of CH, CHX, and lycopene, at the end of 14 days, all the three groups showed decreased rate of interappointment flare-up.

CONCLUSION

Within the limitations of the study, at the end of 2 days, least incidence of interappointment flare up was seen by mixture of calcium hydroxide, chlorhexidine and lycopene, at the end of 14 days all the three groups showed decreased rate interappointment flareup.

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