



# **Comparison of Single Antibiotic Paste Nitrofurantoin and Calcium Hydroxide Paste as Intracanal Medicaments in Alleviating Post-Operative Pain in Patients with Symptomatic Irreversible Pulpitis -A Randomized Controlled Trial**

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## **Authors' contributions**

*This work was carried out in collaboration among all authors. Author HA designed the study, performed the formal analysis, wrote the protocol, and wrote the first draft of the manuscript.*

*Author HA managed the literature searches, final review and edited the manuscript.*

*Author AL wrote the original draft, performed the formal analysis and did the conceptualization.*

*Author ASJ wrote the original draft, Initial review of the manuscript. All authors read and approved the final manuscript.*

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## **ABSTRACT**

**Aims:** This study aims to compare the efficacy in alleviating pain between intracanal medicaments, namely Nitrofurantoin and Calcium Hydroxide Paste.

**Study Design:** Randomized Controlled Trial.

**Place and Duration of Study:** Sample: Department of Operative Dentistry, Sir Syed College of Medical Sciences, Pakistan, between January 2021 and May 2021.

**Methodology:** 60 patients were randomly divided into 3 groups, each group having 20 patients as following: Group 1: Nitrofurantoin, Group 2: Calcium Hydroxide and Group 3: Control. Preoperative

pain was recorded using a numerical pain scale. After access preparation, chemomechanical preparation was performed with subsequent placement of intracanal medicaments. Pre-operative pain score was initially recorded, followed by post-operative pain at 12, 24, 48, and 72 hours, respectively. Root canal treatment was performed in single rooted teeth with patients suffering from symptomatic irreversible pulpitis

**Results:** Majority of the patients in all 3 groups were initially presented with moderate to severe pre-operative pain. After 72 hours post-operatively, 50% patients in Group 1 reported no pain, while 5% patients in both Group 2 and 3 had no pain. Pain significantly subsided in Group 1 as compared to Group 2 and 3. Regarding age and gender, both had no significant relationship with the pain scores in all of the 3 groups

**Conclusion:** Nitrofurantoin has been proven to be an effective intracanal medicament in alleviating immediate post-operative pain in patients with symptomatic irreversible pulpitis as compared to calcium hydroxide. While the control group with no intracanal medicament showed little reduction in pain scores. So, nitrofurantoin can be used as a substitute to currently available standard intracanal medicaments.

*Keywords: Nitrofurantoin; calcium hydroxide; intracanal medicaments; irreversible pulpitis.*

## 1. INTRODUCTION

Root canal treatment is a dental procedure that is most of the time performed by endodontists for the elimination of bacteria and necrotic pulp from the infected root canals. A variety of factors are associated with a tooth requiring endodontic treatment such as caries, periodontitis, trauma, infection (periradicular, intraradicular, extraradicular), and cysts. In all of these factors, bacteria are one of the main culprits that lead to all of this, especially *Enterococcus faecalis*. *Enterococcus Faecalis* is known to be resistant to many drugs such as Vancomycin and Fosfomycin, respectively, however, Nitrofurantoin has been reported to be effective against these pathogens [1]. Since these bacteria are one of the primary causes of root canal treatment failures, drugs that are effective against these bacteria should be used when mandated.

Nitrofurantoin, is a product of nitration of heterocyclic compounds, leading to the formation of nitrofurans, among which nitrofurantoin is the best known. Various in-vitro studies have evaluated the effects of Nitrofurantoin on *Enterococcus faecalis* [2]. For patients suffering from urinary tract infections, these bacteria report being amongst the prime candidates that need eradication to cure the patient [3]. Studies have concluded Nitrofurantoin to be successful to eradicate *Enterococcus faecalis* as many have developed resistance to penicillin, ampicillin, imipenem, and vancomycin, respectively [4]. Nitrofurantoin has been used for a long time to treat urinary tract infections because of the bactericidal effects on *Enterococcus Faecalis*. Trans-dentinal and antimicrobial effects of

nitrofurantoin have been evaluated with positive outcomes in eradicating *Enterococcus faecalis* but limited trans-dentinal diffusion of the medicament [5]. Nitrofurantoin has been used experimentally as an intracanal medicament with positive results in the elimination of *Enterococcus faecalis* [6].

Intracanal medicaments have been used in treating endodontic infections for many years, which acts as local application of antibiotics in the area where required, avoiding its systemic application which is unnecessary that might lead to allergic reactions and toxicities [7]. With the advantage of local application, a fine locus of the area where the bacteria are present, they are targeted that cannot be accomplished by using conventional root canal treatment and irrigation methods. Intracanal medication has several benefits to hand such as near or complete elimination of microorganisms including the *Enterococcus faecalis* and high concentration of drug being present locally [8]. One major drawback of using this technique of bacteria removal is the possibility of developing bacterial resistance which then mandates a change in the drug. It is a well-known fact that improper use of antibiotics where they are not required is the main cause of developing resistance [9].

According to the American Association of Endodontics, Calcium hydroxide is the currently recommended intracanal medicament to be used for multi-visit root canal treatment procedures when required [10]. Several studies have been carried out which report the clinical efficacy and antimicrobial action of Calcium hydroxide in alleviating post-operative pain in patients [11]

Calcium hydroxide has been proven to be effective *Enterococcus faecalis* with a decrease in viable and colony-forming units of these bacteria.[12]

At the present moment, no studies are reporting the efficacy and use of nitrofurantoin in root canal treatment although one study does report its use in eliminating *enterococcus faecalis*. Furthermore, no comparison has been made in the literature in regards to nitrofurantoin with the standard intracanal medicaments used today such as Triple Antibiotic Paste (TAP), Double Antibiotic Paste (DAP), and Calcium Hydroxide. Since Nitrofurantoin offers greater coverage against anaerobic bacteria which could prove to be more beneficial in relieving pain, therefore, this study aims to explore the effect of nitrofurantoin in alleviating the pain of patients with symptomatic irreversible pulpitis and compare the possible effects of Single Antibiotic Paste Nitrofurantoin with Calcium Hydroxide Paste.

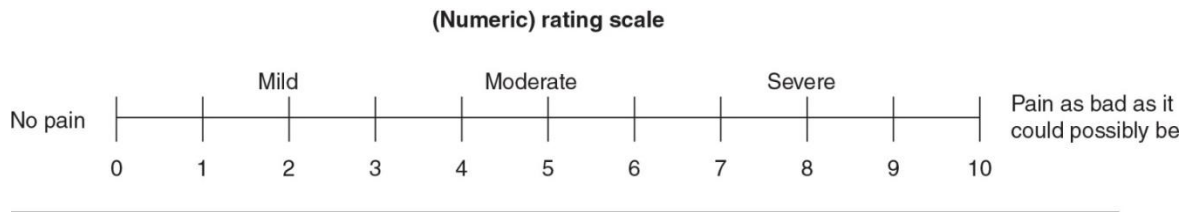
## 2. MATERIALS AND METHODS

This randomized controlled trial study was carried out in the Department of Operative Dentistry, Sir Syed College of Medical Sciences, Karachi, Pakistan (Pakistan) from January 2021 till May 2021. This trial has been registered with ClinicalTrials.gov (United States National Library of Medicine) identifier number (NCT04900571). To calculate the sample size, OpenEpi software was used, keeping the confidence interval at 95% and 50 as the desired percentile. The sample size came out to be 28 (14 in each of the two groups) [13]. The patients who were about to undergo root canal treatment were briefed about the procedure they are about to undergo and the medication that will be used in their treatment. After a careful explanation, patients were asked to give verbal and written consent to participate in the study. For participation in this study, inclusion criteria were kept as patients above 18 years of age with no medical history, no history of allergy to medications used in root canal treatment in this study, and patients suffering from Symptomatic Irreversible Pulpitis, patient belonging to American Society of Anesthesiologists (ASA) Class 1, with BMI ranging from 18.5 to 24.9, weight between 50-70 Kgs, Height between 5-6 feet, and only single-rooted teeth. Patients requiring treatment for multi-rooted teeth and those with pulp necrosis, were excluded from this study.

Using the drawing lots method to achieve randomisation, patients were allocated to Group 1 which has nitrofurantoin as an intracanal medicament, Group 2 which has Calcium Hydroxide Paste, and Group 3 which acted as a control group, respectively. Those who did not fulfil the inclusion criteria were excluded from the study including non-compliance with treatment visits and non-willingness to participate in the study. The diagnostic criteria were confirmed by clinical and radiological examination. Patients included in this study were those with a history of severe pain with visual and radiographically presence of a carious lesion. Patients who were not suitable for conventional root canal treatment and multirouted teeth were excluded. Demographic data such as age, gender, and Outpatient Department (OPD) number were taken from the patients. Diagnosis of symptomatic irreversible pulpitis was based on: Clinical examination, Pulp Vitality Tests (Cold test), and Radiographs (Periapicals).

After administration of local anesthesia (Septodont- 2% Lidocaine, epinephrine 1:100000), the tooth under treatment was isolated using a rubber dam. Using a high-speed handpiece, an access cavity was prepared where the carious lesion was present (this step is called as Access Opening). After locating the orifices of the root canals, manual hand K files (Mani- K Files) were used to perform pulpectomy using watch winding movement. Now, the working length was taken approximately 1mm short of the apex as confirmed by both tactile sensation and radiographs. In this same appointment, chemomechanical preparation was also completed. After determining the working length, preparation of the canals was started, that is cleaning and shaping using the Step Back Technique. Irrigation was performed frequently to flush out all the debris using 3% sodium hypochlorite (Tehnodent -Antiseptic Liquid - Sodium Hypochlorite). To avoid the accumulation of smear layer, 17% EDTA (PD -EDTA 17% Gel) was used and after a minute the canal was flushed using normal saline solution. Before placement of intracanal medicaments, the canals were dried using paper points (Meta BioMed - Absorbent Paper Points). Now the intracanal medicaments were placed in the root canals and temporary restoration material with cotton pellet placed on the access cavity.

In this study, patients assigned to Group 1 were allotted Nitrofurantoin as the intracanal medicament in their root canal treatments, Group



**Fig. 1. Visual Analogue Pain Scale**  
 0= No pain, 1-3= Mild Pain, 4-6= Moderate Pain, 7-10=Severe Pain

2 was allotted Calcium Hydroxide Paste (Meta BioMed -Metapex- Calcium Hydroxide with Iodoform), and Group 3 was Control (No intracanal medicament). Nitrofurantoin in the powdered form was mixed and then normal saline was mixed in this powder (liquid: powder 1ml:100mg) to prepare 100mg/ml Nitrofurantoin paste [6]. The paste formed was carried in the root canals of the patients using Lentilospiral. For Calcium hydroxide, a preformed paste in the injection form was used and carried in the root canals of the patients using Lentilospiral. Now on the second visit, the patients were evaluated for their pain, which was noted down on the proforma. The temporary restoration (3M- Cavite G Temporary Filling Material) placed on the first visit was removed and the root canals were irrigated using sodium hypochlorite to flush out the intracanal medicament.

To determine the level of pain in the patients, the predetermined intervals were as follows: Before Treatment (pre-operative), and then post-operative at 12 hours, 24 hours, 48 hours, and 72 hours, respectively. A numeric pain scale was used, according to which the pain was categorised as follows: 0= No pain and 10= Severe pain [14] It was further subdivided into categories as follows: 0= No pain, 1-3= Mild Pain, 4-6= Moderate pain, and 7-10= Severe pain, as shown in Fig. 1. As the score of the pain increases, so does the severity with which the patient is experiencing the pain. Patients were instructed to fill this pain scale form in the respective time periods mentioned and bring it with them in their next visit with the Endodontist.

### 2.1 Statistical Analysis

All of the clinical steps in this study were performed by a single endodontist. For data analysis, Statistical Packages for Social Sciences (SPSS) version 25.0 was used. Mean and Standard deviation was calculated for age.

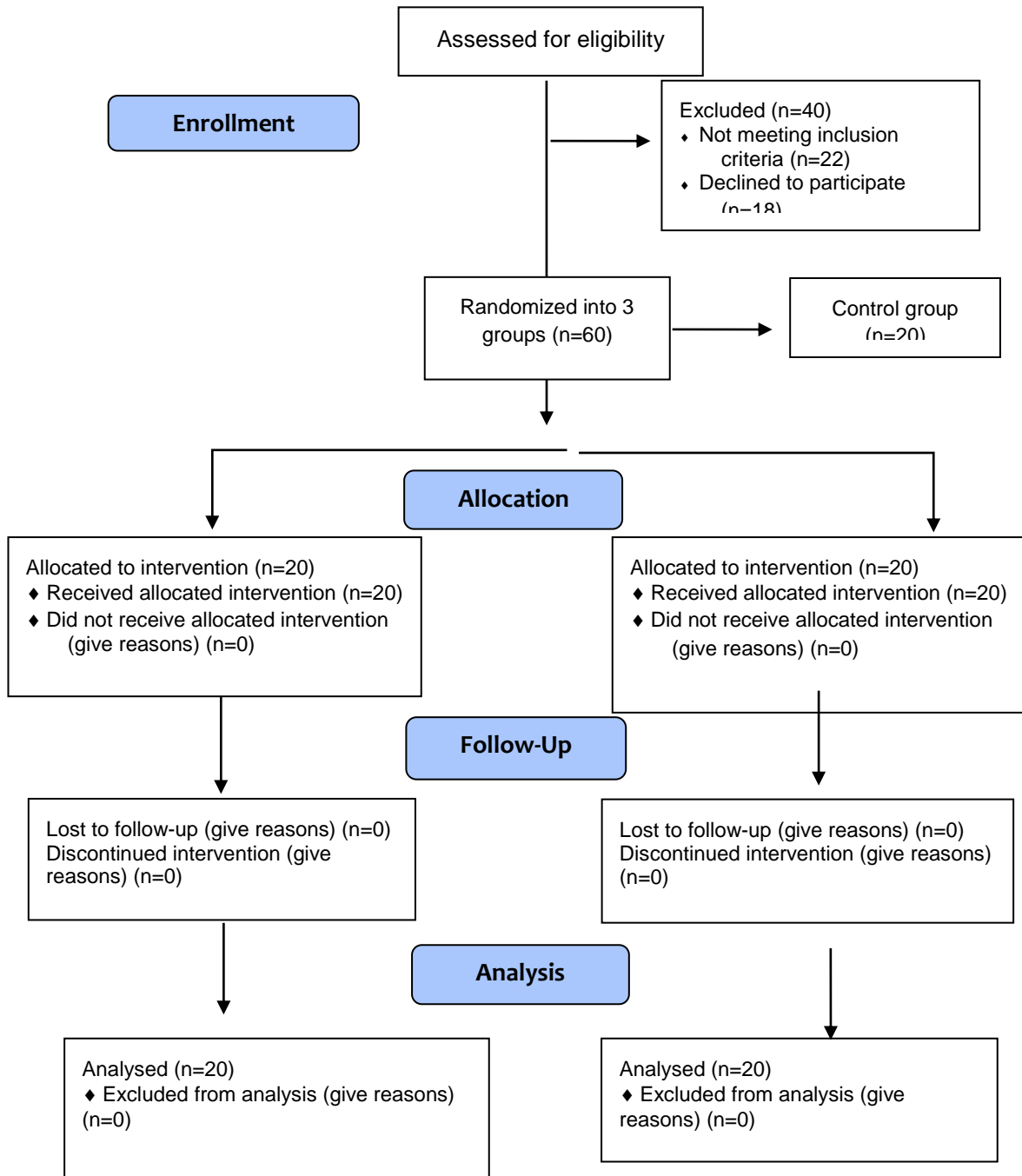
For comparison of pain scores between the two groups (Group 1 and Group 2), the Mann-Whitney U test was applied. Friedman test was performed to test for significance between the 5 time periods within each group. Linear Regression test was used for the association of age and gender with pain scores. Kruskal-Wallis test was used for comparison of pain scores among the three groups. A p-value of  $\leq 0.05$  was considered to be statistically significant.

### 3. RESULTS

In this study, a total of 60 patients were included as shown in the CONSORT flow diagram Fig. 2. The mean age of patients is as follows: Group 1 (Nitrofurantoin):  $43.9 \pm 7.92$ , Group 2 (Calcium Hydroxide):  $41.9 \pm 11.52$ , and Group 3 (Control):  $43.05 \pm 13.9$  as shown in Table 1. The distribution of males and females in each group was Group 1: 11 and 9, Group 2: 14 and 6, and Group 3: 9 and 11.

Incidence of post-operative pain review showed a marked difference in pain score between the three groups. In comparison with post-operative pain at different intervals, a significant difference (p-value= 0.00) was found between Group 1 (Nitrofurantoin) and Group 2 (Calcium Hydroxide). The initial pain with which the patient came to the dental Operative Department was high in all of the 3 groups. Majority of the patients belonging to Group 1 gradually had their pain scores decreased from severe pain to no pain after 72 hours. However, up till 48 hours, the majority of the patients belonging to Group 2 had moderate to severe pain, which started to subside after 72 hours. For the control group, most of the patients reported to have severe pain up to 48 hours post-operatively, which started to decrease after 72 hours but the effect was not that significant as compared to Groups 1 and 2, as presented in Table 2.

**CONSORT Flow Diagram**



**Fig. 1. CONSORT Flow Diagram for the study**

**Table 1. Demographic characteristics of the different groups**

Groups	Variables	Mean and Standard Deviation
Nitrofurantoin	Age	43.9 ± 7.92
Calcium Hydroxide	Age	41.9 ± 11.52
Control	Age	43.05 ± 13.9

**Table 2. Categorical representation of pain scores in different groups**

Pain	Group 1 (n=20)	Group 2 (n=20)	Group 3 (n=20)
<b>Initial Pre-operative Pain</b>			
No pain	0 (0%)	0 (0%)	0 (0%)
Mild pain	0 (0%)	0 (0%)	0 (0%)
Moderate pain	9 (45%)	4 (20%)	4 (20%)
Severe pain	11 (55%)	16 (80%)	16 (80%)
<b>Pain at 12 Hours</b>			
No pain	0 (0%)	0 (0%)	0 (0%)
Mild pain	0 (0%)	0 (0%)	0 (0%)
Moderate pain	16 (80%)	6 (30%)	1 (5%)
Severe pain	4 (20%)	14 (70%)	19 (95%)
<b>Pain at 24 Hours</b>			
No pain	0 (0%)	0 (0%)	0 (0%)
Mild pain	3 (15%)	0 (0%)	1 (5%)
Moderate pain	15 (75%)	9 (45%)	6 (30%)
Severe pain	2 (10%)	11 (55%)	13 (65%)
<b>Pain at 48 hours</b>			
No pain	0 (0%)	0 (0%)	0 (0%)
Mild pain	13 (65%)	1 (5%)	1 (5%)
Moderate pain	6 (30%)	10 (50%)	2 (10%)
Severe pain	1 (5%)	9 (45%)	17 (85%)
<b>Pain at 72 Hours</b>			
No pain	10 (50%)	1 (5%)	1 (5%)
Mild pain	8 (40%)	15 (75%)	10 (50%)
Moderate pain	1 (5%)	4 (20%)	9 (45%)
Severe pain	1 (5%)	0 (0%)	0 (0%)

**Table 3. Comparison of pain scores among the 3 groups using Friedman Test**

Pain Groups		Preoperative Pain	Postoperative Pain (Hours)			
			12	24	48	72
Nitrofurantoin Paste	Median	7	6	5	3	0.5
	Min	4	4	3	1	0
	Max	9	7	8	8	7
	Mean Rank	1.83	1.28	1.35	1.18	1.48
	Median	8	7	7	6	2
Calcium Hydroxide	Min	4	5	4	3	0
	Max	10	9	8	8	5
	Mean Rank	1.93	2.10	2.23	2.20	2.05
	Median	8	8	7	8	3
Control	Min	5	5	3	1	0
	Max	10	10	9	9	6
	Mean Rank	2.25	2.63	2.43	2.63	2.48
	P-value (P≤0.05)	0.318	0.000	0.001	0.000	0.002

Overall, the pain score at 12 Hours was significantly less in Group 1, as compared to Group 2 and Group 3. Whereas pain score at 24 Hours for Group 1 further decreased, with Group 2 and Group 3 not showing any significant difference. At 48 hours, patients belonging to Group 1 reported minimal pain, with Group 2 patients now reporting to have a decrease in

their pain intensity. No significant change in pain score was reported by the patients in Group 3. Lastly, at 72 Hours, majority of the patients belonging to Group 1 were pain-free, for Group 2 the pain score kept on decreasing, whereas patients belonging to Group 3 still had pain, as shown in Table 3.

**Table 4. Comparison of Age with Pain Scores among different groups using Linear Regression Test**

Groups	Variables	P-value
Group 1 (Nitrofurantoin)	Age	0.648
	Gender	0.131
Group 2 (Calcium Hydroxide)	Age	0.764
	Gender	0.883
Group 3 (Control)	Age	0.870
	Gender	0.210

**Table 5. Comparison of mean pain scores among the 3 groups using Kruskal-Wallis Test**

Groups	Mean Rank	Kruskal-Wallis	P-value
Group 1 (Nitrofurantoin)	14.45	28.407	0.000
Group 2 (Calcium Hydroxide)	33.80		
Group 3 (Control)	43.25		

Patients in all of the three groups were prescribed analgesics in case the pain was more than they could tolerate. In Group 1, none of the patients required the need to take any of the prescribed painkillers. However, on the other hand, patients in both Group 2 (51.2%) and Group 3 (81.5%) had to take painkillers prescribed to them in order to get relief from the pain.

In comparison to pain perceived at different age groups, no statistically significant relationship was found of age with Group 1 ( $P= 0.648$ ), Group 2 ( $P= 0.764$ ) and Group 3 ( $P= 0.870$ ). Similarly, gender also had no significant association with pain scores of Group 1 ( $P=0.131$ ), Group 2 ( $P= 0.883$ ) and Group 3 ( $P=0.210$ ), as shown in Table 4.

By comparison of the mean pain score amongst the three groups, a statistically significant relation ( $P < 0.001$ ) was noted, as shown in Table 5

#### 4. DISCUSSION

Multiple treatment options are available for patients presenting with symptomatic irreversible pulpitis, with pulpectomy (root canal treatment) being one of the most important treatment modalities for such patients. Usually, patients with such condition present with severe pain which physically and psychologically debilitates them until and unless the pain subsides. For such cases, the use of intracanal medicaments has emerged as practically the most beneficial tool for the endodontist as these medicaments act as analgesics to relieve the pain of the patients.

Most of the time, the intensity of the pain is so severe that although the teeth which can be easily saved with root canal treatment, patients opt for extraction of such salvageable teeth [15]. For such a scenario, endodontists and dental surgeons should play a key role in counselling the patients to help them understand how their pain would eventually subside with the root canal treatment.

Elimination of the bacterial load in the canals of the teeth under root canal treatment is the prime factor to relieve the pain of the patients, and this role is played by the intracanal medicaments, which determines its success rate and patient comfort [16]. Anatomy of the root canal also plays an important role in complete elimination of bacteria, as complex anatomy such as apical deltas have reported having some bacteria which is visible on post-obturation radiograph [17].

Calcium hydroxide has been used as a standard intracanal medicament recently and literature states its efficacy in reducing post-operative pain in patients undergoing root canal treatment [18,19]. In this study, when calcium hydroxide was used in patients, the pain did not significantly subside until after 72 hours post-operatively, thereby mandating patients to take prescribed analgesics to them by their endodontists. Several studies do report *Enterococcus faecalis* to be resistant to Calcium hydroxide mainly because of bacterial factors such as high pH tolerance and surviving in food deprived states [20,21]. However, some studies do report that the use of calcium hydroxide and no intracanal medicaments in patients showed no significant reduction in pain scores of the patients [22,23]. Calcium hydroxide has been

known to have its pain preventive properties by being an antimicrobial as well as having tissue altering properties as well [24]. This contrasts with the results of our study as patients perceived a considerable amount of pain up to 72 hours post-operatively.

At times, a positive medical history also plays a vital role in the intensity of pain present in such patients. Although not part of this study, but some studies do report that patients who suffer from diabetes mellitus are more likely to have severe endodontic pain and interappointment flare-ups as compared to non-diabetic patients [25]. Although this could be due to decreased immunity in patients suffering from this pathology thereby being more susceptible to have infections and their related pain.

Nitrofurantoin is a very well-known drug that is primarily used to treat urinary tract infections because of its high efficacy against anaerobic bacteria that are abundant in such infections. Considering the flora of anaerobic bacteria predominant in the root canals of patients suffering from irreversible pulpitis, this drug has been shown to be effective in its antimicrobial action, especially against *Enterococcus faecalis* as well as pain-relieving capabilities according to a recent study in literature [6]. A study reports *Enterococcus faecalis* to be 80.32% susceptible to Nitrofurantoin [26]. In our study, patients who underwent root canal treatment with nitrofurantoin as the intracanal medicament reportedly got the maximum relief in pain immediately post-operatively after the effects of the local anesthesia subsided. The majority of the patients were pain-free by the end of 72 hours post-operatively. Furthermore, none of the patients reported any side effects when they visited for the next scheduled appointment.

In our study, age and gender, both had no relationship with pain scores in all of the 3 groups. However, some studies conclude children to experience an increased level of dental pain as compared to adults [27,28]. Moreover, literature states that females tend to experience increased intensity of dental pain as compared to males, which contrasts with the results of our study [29,30].

To our knowledge, no study has been carried out to report the use of nitrofurantoin in alleviating post-operative pain in patients undergoing root canal treatment for symptomatic irreversible pulpitis. Furthermore, no studies have been carried to compare the efficacy of nitrofurantoin

with other standard and currently used intracanal medicaments such as Calcium Hydroxide, Double Antibiotic Paste (DAP), and Triple Antibiotic Paste (TAP). Therefore, this study provides significant findings of the use of nitrofurantoin as a possible intracanal medicament in adjunct to the available ones. Despite the strengths of this study, first limitation is that more studies need to be carried out to evaluate the pain-relieving properties of nitrofurantoin, along with its comparison with other intracanal medicaments as well. Moreover, this study can be carried out on a larger scale to further evaluate the effects of Nitrofurantoin. Lastly, few limitations of the drawing lots method include difficulty to be used in large populations and inclusion of biasness in selection.

## 5. CONCLUSION

Although at the present moment, Calcium Hydroxide is being used as the standard intracanal medicament for patients with symptomatic irreversible pulpitis, Nitrofurantoin has been shown to be a possible substitute to it considering the immediate post-operative pain-relieving properties of it

## DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

## CONSENT

All authors declare that 'written informed consent was obtained from the patient preserved'.

## ETHICAL APPROVAL

This study was approved by ethical review committee of Sir Syed College of Medical Sciences Ref no: (2021/067)

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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