Original Article

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Comparison of pretreatment gabapentin and pregabalin to control postoperative endodontic pain – a double-blind, randomized clinical trial

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Background: Postoperative endodontic pain is an enigma for the dentist. This study aimed to evaluate the analgesic effect of 300 mg gabapentin or 75 mg pregabalin in reducing postoperative endodontic pain compared with a placebo.

Methods: Ninety patients who needed root canal treatment with an initial numerical rating scale (NRS) pain score of > 4 (T0) were randomly divided into three groups (n=30). Patients were then administered either 300 mg gabapentin (group A), 75 mg pregabalin (group B), or a placebo (group C) 30 min prior to the start of endodontic treatment. A single operator performed single-visit endodontics, and pain was evaluated immediately after endodontic treatment (T1) and at 4 h (T2), 8 h (T3), 12 h (T4), 24 h (T5), 48 h (T6), and 72 h (T7) using the NRS. Ibuprofen/paracetamol (400 mg/325 mg) was administered as a rescue dose if needed.

Results: Pregabalin performed significantly better when compared with gabapentin at all time points except at 72 h after treatment (P=0.170). The placebo group showed significantly higher pain scores than the other two groups. The percentage of pain relief was maximum for pregabalin (92.1%), followed by gabapentin (87.6%) and placebo (69.1%) at 72 h after treatment completion.

Conclusion: This study showed that pretreatment with a single dose of pregabalin and gabapentin both had greater analgesic effects than a placebo. They can be effectively used to reduce postoperative endodontic pain.

Keywords: Gabapentin; Postoperative Pain; Pregabalin; Prophylaxis; Root Canal Therapy.

INTRODUCTION

Odontalgia is the most common form of orofacial pain [1]. Patients frequently experience pain during dental treatment. The fear and anxiety associated with dental treatment steers many patients to avoid dental procedures. Since its inception, the dental profession has always tried to provide a pain-free environment for patients. However, pain experienced after the completion of endodontic treatment remains a substantial issue for dentists and endodontists [2]. In patients reporting with preoperative pain, the prevalence of postoperative endodontic pain ranges from 3% to 58%, with pain levels ranging from mild to severe [3,4]. Postoperative endodontic pain most likely occurs in patients within the first 24 h following treatment [5]. Thus, it is imperative for an endodontist to alleviate the patient's pain. Preemptive analgesics are regularly used by dentists to prevent postoperative endodontic pain, as they may manage the inflammatory

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cascade following endodontic treatment [6].

Pre-emptive gabapentin (GBP) and pregabalin (PGB) have been extensively used in the medical field to control postoperative pain [7]. The idea of preemptive analgesia is to administer medications before the initiation of a pain stimulus or before the process of central sensitization. In patients who report with trauma, pain stimulus and the process of central sensitization to pain are a previous event, making the concept of preemptive analgesia controversial [8]. However, most dental operatory patients experience persistent pain; hence, the correct term is pretreatment rather than preemptive in the dental scenario. The root canal procedure can trigger prostaglandin production due to trauma from severing the pulp and irritation of the periodontal ligament after establishing patency, cleaning, and shaping [9]. After treatment, the inflammatory process in the periradicular areas of the tooth can produce postoperative pain. Postoperative endodontic pain is generally more profound and heightened in the first 48 h, progressively reduces with time, and usually disappears after 4–7 days [10]. Various pharmacological drugs have been advocated, including anti-inflammatory agents, local anesthetics (LA), and opioids, to control postoperative endodontic pain [11].

Nonsteroidal anti-inflammatory drugs (NSAIDs) have traditionally been the drugs of choice for pain control in dentistry. However, their long-term use can cause gastrointestinal mucosal damage, bleeding, renal toxicity, allergic reactions, and heart failure. Selective cyclooxygenase-2 (COX-2) inhibiting NSAIDs have prothrombotic properties and increase the risk of stroke and myocardial ischemia [7]. GBP and PGB both belong to the classes of drugs that act by modulating calcium-induced release of glutamate from activated pain-transmitting neurons [12]. PGB is a new generation of gabapentinoids that is similar in action to GBP [13]. These drugs may impede pain transmission, decrease central and peripheral sensitization, and reduce postoperative pain [14]. Reduction in central sensitization by an antihyperalgesic drug, such as GBP, may reduce acute postoperative pain [7].

This study aimed to evaluate the clinical effectiveness of prior treatment with either 300 mg GBP or 75 mg PGB before root canal treatment in reducing postoperative endodontic pain compared with a placebo. In addition, the study also aimed to investigate the elimination or reduction in the consumption of analgesics after treatment. The null hypothesis was that GBP or PGB would not help reduce postoperative endodontic pain or lead to any reduction in the consumption of analgesics after treatment.

METHODS

A total of 90 patients participated in this double-blinded, placebo-controlled, randomized study after receiving ethical clearance from the Institutional Ethical Committee. The study was conducted in a tertiary care hospital from March 2019 to January 2020 and was registered with the Clinical Trial Registry, India (Institutional review board number: ECR/786/Inst/MH/2015/RR-18). The controller, who was unblinded and independent of the treatment plan, generated the randomization code using a computer- derived permuted block. Each drug was sealed in individual packets and handed to the investigator. The patients were enrolled by a single investigator according to the following criteria. The inclusion criteria were male and female patients between 18 and 60 years of age, accepting the line of treatment, and complaining of pain of numerical rating scale (NRS) score of more than 4. The treatment was confirmed with radiographs showing pulpal involvement without any periapical abscess in single-rooted teeth with a closed apex and needing nonsurgical root canal treatment. Vitality tests were performed, and teeth with irreversible pulpitis were included in this study. Informed consent was obtained from all the included patients. Patients were excluded if they were on antibiotics one week prior or analgesics 6 h prior to their treatment. Other exclusion factors were multi-rooted teeth with the presence of an acute endodontic or periodontal abscess,

periodontal diseases, the requirement for prophylactic antibiotics, pregnancy or lactation, mental disabilities (patients with suicidal thoughts), systemic diseases that contraindicated endodontic therapy, and any known sensitivity or other adverse reactions to local anesthetics or gabapentinoids. Patients who consumed rescue medications were excluded from the study.

Based on similar studies [15], a power analysis and sample size estimation were performed before data collection. In the baseline study, 20 cases were selected for both groups, assuming that the average variation of the groups was 11.155. Power analysis showed that with a power of 0.80 and a significance level of 0.05, 23 patients were required per study group. However, considering the dropout cases, we decided to include 30 patients in each group. The statistical software used to calculate the sample size was SAS 9.1.3 (SAS Institute Inc. Cary, North Carolina, USA). The primary outcome measure was the reduction in postoperative endodontic pain after the administration of various drugs. The secondary outcome was the elimination or reduction in the consumption of analgesics after treatment.

After the final diagnosis was made on a radiographic and clinical basis, patients were randomly divided into three groups of 30 each. Age, sex, tooth vitality, and pain level of each patient were recorded (T0) and measured as baseline values. Patients were then administered the drug from the sealed packet. The drug administered was either oral 300 mg GBP (Gabapin®; Intas, India - group A), oral 75 mg PGB (Lyrica®, Pfizer, Germany; group B), or an oral placebo (group C) 30 min before the start of the endodontic treatment. A single operator at a single appointment performed the root canal procedure to eliminate any bias. The average time taken for a single-sitting root canal procedure is generally 60–75 min [16].

Patients were asked to verbally rate their perceived pain intensity on a numerical rating scale (NRS) from 0 to 10, with zero representing one extreme (e.g., no pain) and 10 representing the other extreme (e.g., the worst pain possible). A single endodontist blinded to the group allotment conducted all endodontic procedures.

An inferior alveolar nerve block was administered with 2 mL of 2% lignocaine with adrenaline. After isolation with a rubber dam, access opening was performed and the working length was determined using K-files. The working length was checked using the Root ZX II electronic apex locator (J Morita Corp. software (Osaka, Tokyo, Japan). Canals were prepared using the crown-down technique and 6% rotary protaper files. The canals were irrigated alternatively using 5% sodium hypochlorite (Vishal Dental Products, Mumbai, India) and saline. Obturation was performed with 6% gutta-percha cones using the lateral condensation technique and AH26 sealer (Dentsply, USA). The treatment was completed in a single sitting by a single endodontist.

Pain scores were reevaluated immediately (T1), at 4 h (T2), 8 h (T3), 12 h (T4), 24 h (T5), 48 h (T6), and 72 h (T7) after endodontic treatment using the NRS scale. Patients were asked to mark the pain experienced after the postoperative period on the scale. In addition, a reminder was given to the participants telephonically to note their pain readings, inform the operator, and inquire about their well-being (Fig. 1).

Patients were asked to take Tab ibuprofen 400 mg plus paracetamol 325 mg (Combiflam®, Sanofi, India) as a rescue dose if the NRS score was $\geq$ 6 after treatment completion. The patients were asked to inform of the dosage and duration of the rescue dose if taken, and it was noted. However, these patients were excluded from the study.

Data were collected in proformas and tabulated using Microsoft Excel version 2000. The significance level was set at 5% ($P < 0.05$). Statistical analyses were performed using SPSS 20.0 (Statistical Package for Scientific Studies, SPSS, Inc., Chicago, IL, USA) for Windows. Kruskal–Wallis analysis of variance was used to compare the severity of pain in the three groups at different time points. The non-parametric Mann–Whitney U test was used to compare two independent groups.

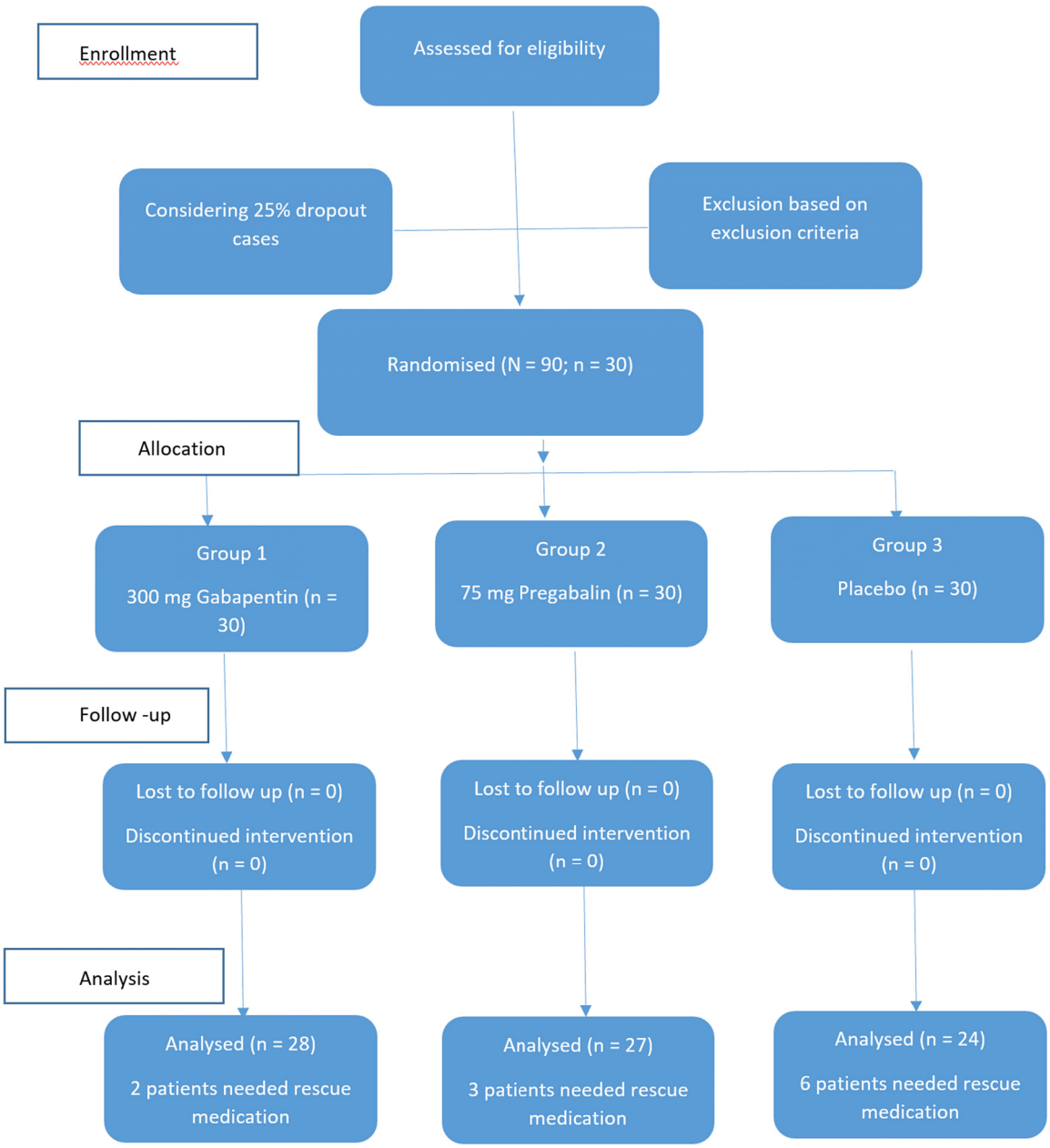

Fig. 1. CONSORT flow diagram. CONSORT, consolidated standards of reporting trials; n, number.

RESULTS

A total of 90 patients were evaluated, with 30 patients in each group. Age, sex, and baseline pain were similar in all three groups (Table 1).

Pre- and posttreatment NRS values for each group were recorded for each patient. The means and standard deviations of the NRS values after administration of various pretreatment medications are shown in Table 2. NRS values were significantly higher at T0 than at T6 and T7 in all groups. Two, three, and six patients were excluded from the GBP, PGB, and placebo groups, respectively, because of rescue medication consumption. The pain levels at T0 and T1 were not statistically significant in any group ($P = 0.140$ and $P = 0.943$, respectively). However, when comparing the three groups, the pain levels were statistically significant at all

Table 1. Demographic features of patients

Variables	Group A (Gabapentin) (N = 30) (%)	Group B (Pregabalin) (N = 30)(%)	Group C Placebo (N = 30)(%)
Age (mean ± SD)	39.40 ± 12.09	39.07 ± 8.72	37.53 ± 10.66
Sex			
Male	16 (53.3%)	14 (46.7%)	14 (46.7%)
Female	14 (46.7%)	16 (53.3%)	16 (53.3%)

N, number; SD, standard deviation.

Table 2. The NRS means in three groups concerning the time of taking the analgesics

Times (hrs)	Group A	Group B	Group C	Kruskal Wallis test†	P value	Mann Whitney U test‡	P value
T0 (Before treatment)	6.63 ± 1.13	7.13 ± 0.94	6.73 ± 1.11	3.935	0.140	1.960	0.050
T1 (immediately after treatment)	3.03 ± 1.15	2.97 ± 1.03	3.17 ± 1.23	0.118	0.943	0.294	0.769
T2 (4 hrs)	5.60 ± 1.16	3.62 ± 1.32	4.60 ± 1.00	28.026*	<0.001	4.841*	<0.001
T3 (8 hrs)	4.31 ± 1.34	2.75 ± 1.04	4.18 ± 098	25.311*	<0.001	4.133*	<0.001
T4 (12 hrs)	2.89 ± 0.96	2.33 ± 0.83	3.67 ± 0.92	24.291*	<0.001	2.503*	0.012
T5 (24 hrs)	2.25 ± 0.80	1.48 ± 0.89	3.00 ± 0.76	29.528*	<0.001	3.256*	0.001
T6 (48 hrs)	1.57 ± 0.79	0.96 ± 0.65	2.52 ± 0.87	32.771*	<0.001	3.088*	0.002
T7 (72 hrs)	0.82 ± 072	0.56 ± 0.58	2.08 ± 0.78	35.978*	<0.001	1.374	0.170

*, Significant difference (P < 0.05); †, comparing the three groups; ‡, comparing the group A with B; NRS, numeral rating scale.

Table 3. Number of patients who consumed analgesics post treatment at different time intervals

Time intervals	Group A	Group B	Group C
T0	-	-	-
T1 (immediately after treatment)	-	-	-
T2 (4hrs)	none	One	-
T3 (8hrs)	One	One	Two
T4 (12hrs)	One	One	One
T5 (24 hrs)	-	-	Two
T6 (48 hrs)	-	-	-
T7 (72 hrs)	-	-	one
Total	Two	Three	Six

other time points: T2, T3, T4, T5, T6, and T7 (P < 0.05).

When comparing the GBP group with the PGB group, statistically significant results were observed at all times except at T1 and T7 (Table 2). Furthermore, a statistically significant difference was observed at all time points when comparing the placebo group to either the GBP or PGB group (P < 0.05), except immediately after treatment at T1 and T3, that is, 8 h after treatment in the gabapentin group.

The percentage of pain relief was the highest at T7 (72 h) after the consumption of the drug in all three groups. The percentage of pain relief was calculated as follows: % Relief = (Previous NRS − New NRS/Previous NRS) × 100 [17]. Maximum pain relief was observed in the PGB group at all time intervals. Statistically, no significant difference at T7 was observed between the GBP and PGB groups. The placebo group showed a statistically significant difference compared with the other two groups. The percentage of pain relief was maximum in the PGB group (92.1%), followed by the GBP (87.6%) and placebo groups (69.1%) at T7, as shown in Fig. 2. A reduction in analgesic consumption in the GBP and PGB groups was observed when compared with the placebo group. Eleven patients used additional analgesics (ibuprofen and paracetamol) (group A: N = 2; group B: N = 3; group C: N = 6), as shown in Table 3. This shows that there was a reduction in the consumption of analgesics in the GBP and PGB groups when compared with the placebo group.

DISCUSSION

Preemptive analgesia reduces postoperative opioid

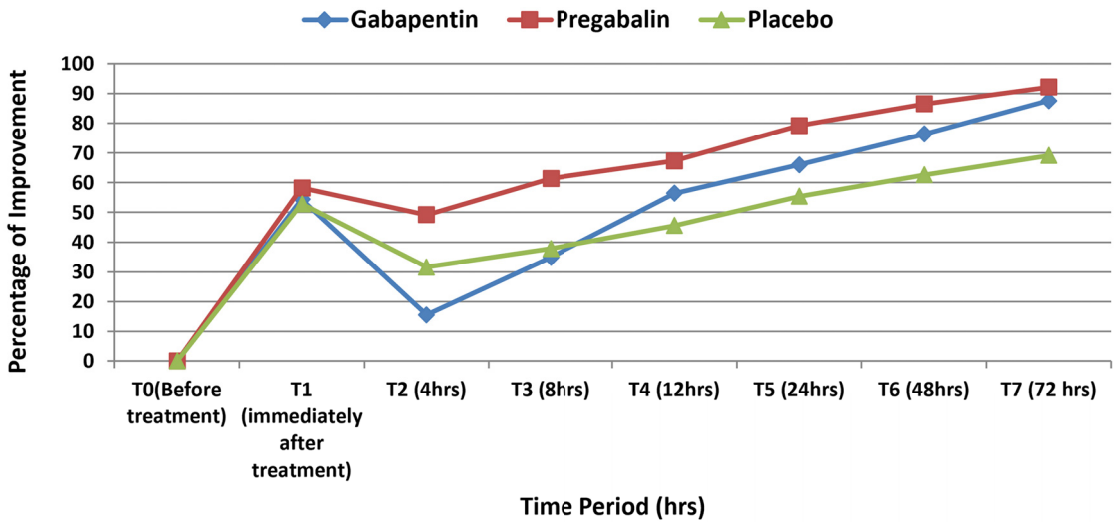

Fig. 2. Percentage of pain relieving based on the types of painkiller from the base line data

consumption and pain levels, reduces the incidence of unfavorable incidents, and enhances patient satisfaction. Several preemptive analgesic regimens, including opioids and NSAIDS, have been tested in the perioperative period [18,19]. PGB and GBP are trending imminent drugs in this field [20]. Conventionally, the medical surgical model has been used extensively to demonstrate the efficacy of GBP and PGB in reducing postoperative pain and opioid consumption and increasing patient satisfaction [7,21]. GBP and PGB have antiallodynic and antihyperalgesic properties that are helpful in treating neuropathic pain and may also be beneficial in reducing acute postoperative pain [22].

The endodontic pain model is markedly different from the oral surgery model, because inflammation and pain are usually present before treatment [23]. This can be in the form of pulpal or periapical pathologies, which contribute to pain in patients. Postoperative endodontic pain is defined as a tissue injury. Considering every traumatic interference can result in nerve injury, some neuropathic pain features may be found in postoperative pain [24]. Previous studies comparing GBP with ibuprofen [15] and lornoxicam [24] showed greater efficacy of GBP compared with other drugs or placebo. A study conducted by Narita et al. [25] showed that PGB effectively reduces pain in an acute tooth pulp inflammatory pain model in rats. However, to our knowledge, this is the first study to compare GBP and PGB with a placebo to evaluate postoperative pain in endodontic treatment.

In the current study, pain levels were not statistically significant at T0 and T1 in all groups. This can be attributed to the fact that all patients had a similar nature of pain preoperatively and thus were administered a similar quantity of local anesthetic prior to the treatment, which may be a contributory factor. In addition, the pain levels immediately after treatment were significantly lower than those at 4 h after treatment. This could be because it takes approximately 90-180 min for the local anesthetic's effect to wear off [26].

When comparing the two groups, no statistically significant difference was observed at 72 h after the procedure. The probable reason for this could be that pain is usually more severe in the first 48 h, progressively reduces with time, and usually disappears after 4–7 days [10,27]. Lesser rescue drug consumption and prolonged timing of the first rescue analgesic were observed in the GBP group (two patients; first at 8 h and second at 12 h) than in the PGB group (three patients; first at 4 h, second at 8 h, third at 12 h). This could be because orally consumed GBP achieved maximum plasma concentrations within 3–4 h, whereas PGB was absorbed more

rapidly and attained the maximum plasma concentrations within 1 h [28]. Moreover, because peak times are different, we should have administered GBP 3 h before and PGB 1 h before treatment, which would have been incorrect as we had to maintain the blinding for the patient and the dentist. These results were similar to those of studies conducted by Robertson et al. [29] and Karri et al. [30]. However, when compared to the placebo, both experimental groups showed better results.

A single dose of GBP 300 mg [31,32] and PGB 75 mg [33,34] was administered as this was a day care procedure to rule out any side effects in either group. The common side effects of gabapentinoids are drowsiness, dizziness, weight gain, peripheral edema, and fatigue, but these may occur at high doses and after prolonged usage [17]. Studies have shown that a single preoperative dose does not have negative side effects and may be beneficial in reducing postoperative pain [15,24,35].

Pain perception is exceptionally subjective and influenced by various factors. Thus, the NRS was chosen as an assessment tool because it is easy to understand and interpret and takes less time. In addition, the chance of patient dropout also decreases as communication with the patient can be performed telephonically.

The current study's limitations include the preoperative anxiety level of the patient, and the origin of the nature of the pain (pulpal or periapical in nature) was not considered. Moreover, the drugs most commonly used in dentistry to relieve pain, such as NSAIDs and COX-2 inhibitors, were not used.

In conclusion, with the limitations of the current study, the results showed that a single dose of GBP and PGB has a greater analgesic effect than placebo in single-visit root canal treatment.

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AUTHOR CONTRIBUTIONS

Jayeeta Verma: Conceptualization, Data curation, Investigation, Writing - original draft
Sidharth Verma: Conceptualization, Methodology, Writing - review & editing
Sumanthini V Margasahayam: Supervision, Writing - review & editing

CONFLICTS OF INTEREST: The authors have no conflicts of interest to declare.

PREVIOUS PRESENTATION IN CONFERENCES: The manuscript was presented at the 12th IFEA World Endodontic Congress 2020 held on July 30–31, 2021. It was a part of an online conference. The abstract of this presentation is published in the Endodontology Journal as a special issue (Special Online Supplement Issue Volume 33 Issue 5).

The trial has been registered in CTRI Clinical Trials Registry - India with number CTRI/2021/10/037572

The Institutional Review Board number is ECR/786/Inst/MH/2015/RR-18.

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