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Research article

Effect of Curcuma longa (Turmeric), as an intra-canal medicament, on inter-appointment endodontic pain in patients with symptomatic irreversible pulpitis: A randomized controlled clinical trial

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ABSTRACT

Inter-appointment pain (IAP) is a subtype of postoperative pain which occurs between endodontic appointments. It may begin within a few hours after the first appointment and may continue for several days. Apart from mechanical instrumentation and thorough irrigation, intracanal medicaments play a central role in the disinfection of root canals and thus decreasing IAP. The aim of this study was to evaluate the effect of Curcuma Longa as an intracanal medicament on IAP in patients with symptomatic irreversible pulpitis (SIP). One hundred healthy adult patients having SIP in one of their single-rooted maxillary or mandibular teeth participated in this randomized, parallel, single-blinded clinical trial. After thorough biomechanical preparation, the root canals were randomly medicated with one of the following medicaments, Control (no medicament), Calcium Hydroxide, triple antibiotic paste (TAP), and Curcuma Longa. The pain was recorded using Visual analog scale at 4 h, 24 h, and every day until the seventh day. Data were analyzed using Kruskal-Wallis, Mann-Whitney U, and Wilcoxon signed-rank tests. No statistical difference in pain scores was observed between Calcium Hydroxide, TAP or Curcuma Longa groups. It can be concluded that Curcuma Longa, Calcium hydroxide, and TAP are equally effective in controlling IAP.

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1. Introduction

The primary objective of undergoing root canal treatment from a patient's perspective is complete relief from pain. Although endodontic therapy eventually results in the elimination of pain, studies report that approximately 3–80 % of patients continue to report postoperative endodontic pain (PEP) several days afterwards [1–3]. PEP is defined as pain of any degree that occurs after the initiation of root canal treatment [1]. Inter-appointment pain (IAP) is a subtype of PEP, which occurs between endodontic appointments. It may begin within a few hours after the first appointment when the anesthetic effect wears off and may continue for several days [2]. Mild IAP often goes unnoticed or causes a slight disturbance, but moderate to severe IAP may disturb the normal activity of the patient and sometimes require an unscheduled visit to the dental office. Unfortunately, IAP may weaken the trust of some patients in their clinicians as well as endodontic procedures. Therefore, it becomes the prime responsibility of an endodontist to take steps toward minimizing IAP.

Microbial insult to pulp and peri-radicular tissues is considered as the most common cause of the development of IAP [4]. The severity of inflammation and associated symptoms is directly related to the number of bacterial cells, their virulence, and host response. In addition, endodontic iatrogenic factors such as over-instrumentation, chemical injury from irrigants, and/or intracanal medicaments may further contribute to IAP [5].

Averting factors against development of IAP include precise instrumentation, thorough debridement and whenever required, use of suitable intracanal medicament [5]. By virtue of their longer intracanal presence, root canal medicaments can further reduce intracanal microbial load and prevent reinfection of the instrumented root canal between appointments [6]. Calcium hydroxide (CH), is the most commonly used root canal medicament. The main benefits of CH include its antibacterial effect conferred by its high pH (12.5), ability to hydrolyze bacterial lipopolysaccharides and control of inflammatory exudates from the periapical region [7]. The limited antimicrobial efficacy of CH [8] and the poly-microbial nature of root canal infections has led to the use of a combination of multiple antibiotics such as Triple antibiotic paste (TAP) for effective root canal disinfection [9]. TAP consists of equal proportions of ciprofloxacin, metronidazole, and minocycline. Both CH [10] and TAP [11] have a negative impact on dentin microhardness. Furthermore, antibiotic combinations like TAP have some drawbacks like hypersensitivity, immune suppression, and the development of microbial resistance [12]. All these factors have necessitated the search for novel and effective antimicrobial compounds from natural sources like plants and herbs (phytomedicine).

Turmeric (Curcuma longa or CL), which is a common ingredient found in the Indian kitchen, is a perennial herb and a member of the Zingiberaceae family [13]. Curcumin is the main ingredient obtained from the roots of Turmeric which exhibits anti-inflammatory, antibacterial, antioxidant, and anticancer effects [14]. The U.S. Food and Drug Administration has categorized the curcumin molecule as 'Generally Recognized as Safe' (GRAS) [15]. A systematic review comprised of laboratory, animal, and human studies found curcumin to be non-mutagenic, nontoxic, and biocompatible even at high doses [16]. In endodontics, different authors have employed CL as pulpotomy medicament [13], root canal irrigant [17], or intracanal medicament [18–20], showing promising results. The systemic and/or local administration of curcumin has been shown to provide pain relief in neuropathy, burns, and other painful conditions [21–23], indicating that it has widespread analgesic properties. However, in the field of endodontics, the antinociceptive and anti-inflammatory properties of curcumin are yet to be explored clinically.

To date, no clinical study has investigated the effect of CL as an intracanal medicament in the management of IAP during multi-visit endodontics. Therefore, the purpose of this randomized clinical trial was to evaluate and compare the effectiveness of CL, CH, and TAP as intracanal medicaments in managing inter-appointment endodontic pain.

2. Material and method

2.1. Ethical approval and consent

This randomized controlled clinical trial was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of Jan Nayak Choudhary Devilal Dental College (Haryana) India with approval number **JCDV/DC/21/705**. Before patient enrollment, the clinical trial was registered with the clinical trial registry (https//ctri.icmr.org.in/) reference number CTRI/2021/09/036246. Written informed consent was obtained from all study participants after explaining to them the complete protocol, benefits, complications, and alternative procedures.

2.2. Eligibility criteria

The inclusion criteria for the study were patients, who gave informed consent, were aged 18–65 years, in good health (ASA I or II), and had moderate to severe pain [determined by Visual Analog Scale (VAS)] in any one of their single-rooted maxillary or mandibular teeth, diagnosed with symptomatic irreversible pulpitis (SIP). Clinical diagnosis of SIP was made using a history of spontaneous/nocturnal pain and sharp, prolonged painful response (>30 s) to cold (Green Endo Ice, Coltene, OH) and Electric pulp test (Digitest II, Parkell, NY). To measure pain intensity, VAS was used in the study with markings from 0 to 10, where 0–3 mm meant no to mild pain, 4 to 6 meant moderate pain and 7 to 10 meant severe pain. Each patient was trained to record their pain score using VAS. The presence of a single root and root canal was confirmed with multiple angled diagnostic periapical radiographs.

Patients were excluded from the study if they did not give consent for the study, were medically compromised (ASA category III or above), females were pregnant or lactating, had more than one root/canal in the offending tooth, had taken analgesics within 12 h of study or had an allergy to the local anesthetic solution or any of the components/materials used in the study.

2.3. Sample size calculation and randomization

The sample size was calculated on the basis of a pilot study conducted in the Department of Conservative Dentistry and Endodontics. Based on the results of the pilot study with power of 80 %, and an alpha error of 5 %, a sample size of 22 in each group was deemed sufficient for the study. Considering a 10 % dropout rate, a sample size of at least 25 per group was contemplated.

One hundred patients meeting the inclusion criteria and giving consent for the study were randomly divided into four groups with equal allocation ratios. Randomization was done by using 100 sealed envelopes containing the name of intracanal medicament (25 envelopes of each medicament). Each patient was asked to randomly choose any one envelope and hand it over to the principal investigator without opening it. Accordingly, the medicament was placed inside the root canal and the chosen envelope was then discarded. In this manner, the patient was unaware of the intracanal medicament.

2.4. Treatment procedure

All the clinical procedures were performed by the principal investigator. Each patient was anesthetized with 1.8 ml of 2 % lidocaine with 1,200000 epinephrine (Cadila Pharmaceuticals Limited, New Delhi, India). For maxillary teeth, infraorbital nerve block and for mandibular teeth, the inferior alveolar nerve block was used for anesthesia. Local infiltration with the same anesthetic solution was done if the patient had pain despite a nerve block. After confirming subjective signs of anesthesia, a rubber dam was applied, and an access cavity was prepared. The working length was determined using an electronic apex locator (Root ZX mini, J Morita, Tokyo, Japan) and confirmed radiographically. Canal shaping was done in a crown-down manner with ProTaper rotary instruments (Dentsply Maillefer, Switzerland) following the manufacturer's instructions. After enlargement with finishing file F1, the preparation was assessed with a size 20 K-file. If the instrument was snug at length, the preparation was deemed to be adequate. If the size 20 K-file was loose at length, the preparation was enlarged with size F2, and when necessary, with F3 or F4 instruments, gauging after each finishing file with the corresponding hand file until a snug fit was obtained. Throughout the procedure, irrigation was performed with 5 ml of 3 % sodium hypochlorite (NaOCL) (Hyposol, Prevest Denpro Ltd, Jammu, India). After preparation, canals were irrigated with 5 ml of 17 % EDTA (Prevest Denpro Limited) for 1 min followed by a final wash. After drying the canal with sterile absorbent points, randomly selected intracanal medicament was placed inside the canal according to the allocated group.

Group I (Control group, CG), No medicament was placed into the canal
Group II (CH), Calcium hydroxide powder (Prevest, India) was mixed in propylene glycol to form a paste and gently placed in the canal using lentulo spiral.
Group III (TAP), Triple antibiotic paste was made by mixing equal amounts of ciprofloxacin, metronidazole, and minocycline (1:1:1 ratio) with propylene glycol to obtain a creamy mix and placed in the canal with lentulospiral.
Group IV (CL), Curcuma longa powder was mixed with propylene glycol to form a paste-like consistency and was delivered into the root canal with a lentulospiral.

Curcuma Longa powder preparation – The preparation of CL powder was done in accordance with the procedure described by Prasad and Aggarwal [24]. Fresh organic Turmeric rhizomes were collected from the Agriculture research center, Sirsa, Haryana, boiled for 40–45 min, and sun-dried till the finger tapping of the rhizomes produced a metallic sound. These dried rhizomes were then ground and sifted through a fine mesh to obtain fine powder and stored in an airtight container till further use.

After placing intracanal medicaments, the access cavities were temporarily restored with Cavit (3 M ESPE Dental AG, Germany) with a minimum thickness of 4 mm to ensure a complete seal. In teeth medicated with TAP, pulp chamber walls were coated with a bonding agent (single bond universal, 3 M, ESPE, Germany) prior to temporary restoration to prevent crown discoloration.

2.5. Inter-appointment pain score recording

All study participants' were given pain evaluation sheets and instructed to record their pain scores at designated time points i.e. postoperatively at 4 h, 24 h, and then every day till the seventh day. Pain evaluation sheets had VAS (as described earlier) printed on them. In addition, an independent trained evaluator who was unaware of the intracanal medication made a telephonic call to every patient and recorded their IAP scores at designated observation time points. To prevent bias, IAP scores were kept confidential by the evaluator and were only disclosed to the principal investigator after the completion of the study. Patients were recalled after 7 days along with the evaluation sheets. At this time, pain scores obtained from the patient and values telephonically recorded by the evaluator were compared. In case of any disparity between the two readings, the worse value was recorded.

All patients were prescribed ibuprofen 400 mg tablet (Ibugesic 400, Cipla, India) and instructed to take it, if and when pain occurred and to maintain a record of tablets taken. If pain persisted or became intolerable despite taking medication, patients were told to visit the department. If any additional intervention was required or done on the tooth during the evaluation period, the patient was excluded from the study.

2.6. Statistical analysis

Statistical Package for the Social Sciences 20.0 (IBM Corp, Armonk, NY) software was used for the analysis of data. The Chi-square test was used to analyze categorical data like gender and type of teeth. One way Analysis of Variance test (ANOVA) was used for

comparing the mean and standard deviation in age. Preoperative pain scores and IAP scores were evaluated for normality using Kolmogorov – Smirnov test and were found to be non-normally distributed. Thus, these data were analyzed using non-parametric tests i.e. Kruskal-Wallis for multiple groups and Mann-Whitney for pairwise comparison. Wilcoxon signed-rank test was used to analyze the reduction in pain over days. For all tests, the p-value of <5 % was considered statistically significant.

3. Results

Total 202 patients were assessed for eligibility for the study, of which 70 didn't meet the inclusion criteria and 32 declined to participate. Therefore, 100 patients (51 females and 49 males) were included in the study (Fig. 1 study flowchart). There were no dropouts in the study and none of the patients returned for emergency treatment throughout the 7-day period. So, all patients were included in the final analysis. Statistical analysis did not reveal any significant difference between the four groups in terms of pre-operative variables i.e., age, sex, tooth type, and mean preoperative pain scores (Table 1 and Table 2).

IAP scores decreased steadily in all the groups post-treatment. The highest mean pain scores were associated with the control group (no medicament) (Table 3, Fig. 2). No statistically significant difference in pain scores was observed between Curcuma Longa, calcium hydroxide and Triple antibiotic paste groups at all designated time points. Patients in the control group consumed more ibuprofen tablets than any other group but the difference was statistically insignificant.

4. Discussion

In traditional Indian medicine (Ayurveda) and modern medicine, CL has shown medicinal benefits in the treatment of many inflammatory conditions [25]. In endodontics, it has been used as a pulpotomy agent in primary teeth [13], as a root canal irrigant [17], as an intracanal medicament in in-vitro studies [18–20] with promising results. But no clinical study so far has evaluated its effect as an intracanal medicament on IAP. The null hypothesis for the study was that there will be no difference in IAP between patients when CL, CH, or TAP is used as an intracanal medicament in case of symptomatic irreversible pulpitis. The results of our study found no significant differences in IAP between the three medicament groups. Therefore, the null hypothesis for the study was not rejected.

This is the first clinical study to use CL as an intracanal medicament and compare it with CH and TAP. In vitro studies have compared CL with CH and found its antibacterial efficacy against *E. faecalis* to be either superior to CH [18,19,26] or equivalent [20, 27] to it. In addition, it has no adverse effect on root dentin microhardness compared to CH [28]. When compared to TAP, CL was found to be more effective against *E. faecalis*[16] and demonstrated higher antibiofilm activity against *A. naeslundii* [17]. No in vitro or in

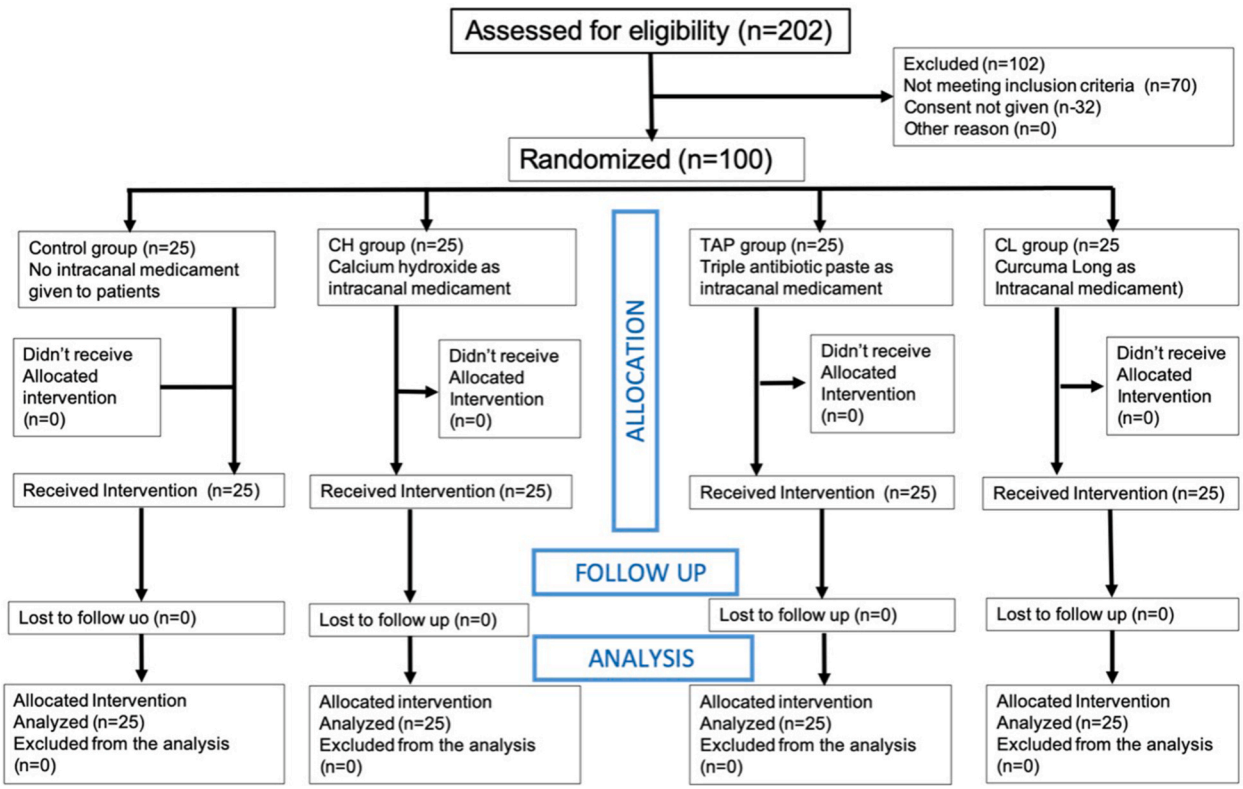

Fig. 1. Study flowchart.

Table 1
Demographic data and type of teeth in all groups.

	Placebo	Calcium hydroxide	Triple antibiotic paste	Curcuma longa	P value
Age (Mean ± SD)	33.28 ± 9.3	35.28 ± 11.4	35.16 ± 11.1	36.56 ± 10.1	0.745
Gender					
Male (%)	12 (48 %)	13 (52 %)	12 (48 %)	12 (48 %)	0.989
Female (%)	13 (52 %)	12 (48 %)	13 (52 %)	13 (52 %)	
Tooth type					
Mandibular incisor	2 (8 %)	2 (8 %)	4 (16 %)	1 (4 %)	0.533
Mandibular canine	2 (8 %)	4 (16 %)	1 (4 %)	2 (8 %)	
Mandibular premolar	12 (48 %)	8 (32 %)	10 (40 %)	12 (48 %)	
Maxillary incisor	5 (20 %)	7 (28 %)	2 (8 %)	3 (12 %)	
Maxillary canine	4 (16 %)	4 (16 %)	8 (32 %)	7 (28 %)	

Table 2
Distribution of type of teeth involved in research.

Type of teeth	Group 1	Group 2	Group 3	Group 4	P value
	n (%)	n (%)	n (%)	n (%)	
Mandibular incisor	2 (8 %)	2 (8 %)	4 (16 %)	1 (4 %)	0.533
Mandibular canine	2 (8 %)	4 (16 %)	1 (4 %)	2 (8 %)	
Mandibular premolar	12 (48 %)	8 (32 %)	10 (40 %)	12 (48 %)	
Maxillary incisor	5 (20 %)	7 (28 %)	2 (8 %)	3 (12 %)	
Maxillary canine	4 (16 %)	4 (16 %)	8 (32 %)	7 (28 %)	
Total	25 (100 %)	25 (100 %)	25 (100 %)	25 (100 %)	

SD=Standard deviation.

Table 3
Mean pain scores at different postoperative time intervals.

Time point	Placebo (Mean ± SD)	Calcium hydroxide (Mean ± SD)	Triple antibiotic paste (Mean ± SD)	Curcuma longa (Mean ± SD)	P value
4 h	3.60 ± 2.661	2.28 ± 1.487	1.80 ± 1.658	2.36 ± 1.941	0.053
Day 1	3.08 ± 2.597	1.76 ± 1.562	1.24 ± 1.451	1.64 ± 1.630	0.025*
Day 2	2.64 ± 2.177	1.52 ± 1.503	1.04 ± 1.338	0.88 ± 1.201	0.002*
Day 3	1.84 ± 1.748	1.16 ± 1.405	0.52 ± 0.823	0.56 ± 0.961	0.002*
Day 4	1.32 ± 1.626	0.76 ± 1.165	0.44 ± 0.821	0.40 ± 0.707	0.062
Day 5	0.76 ± 1.091	0.40 ± 0.913	0.56 ± 0.821	0.24 ± 0.663	0.145
Day 6	0.48 ± 0.872	0.36 ± 0.860	0.36 ± 0.757	0.12 ± 0.600	0.164
Day 7	0.32 ± 0.802	0.28 ± 0.843	0.20 ± 0.645	0.12 ± 0.600	0.547

SD=Standard deviation, *p < 0.05 significant.

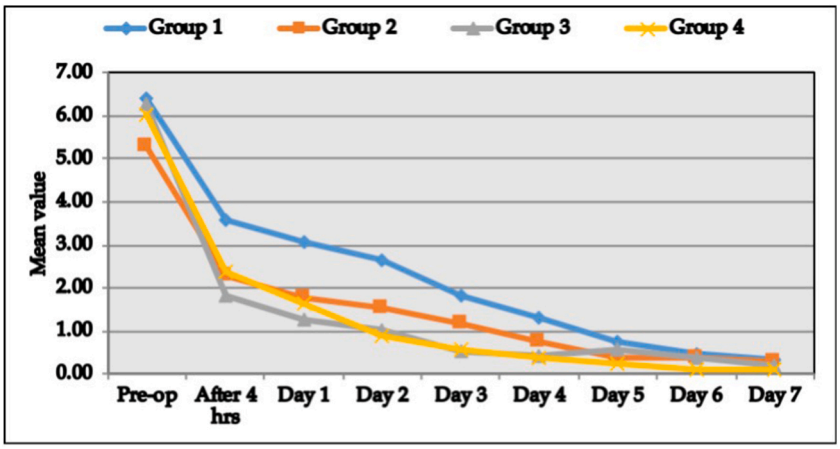

Fig. 2. Intergroup comparison of IAP pain between four treatment groups, pain intensity decreased consistently over time in each group.

vivo study has directly compared the three medicaments.

The present study suggests that the results of in vitro studies might get translated to clinical situations as well. CL was found to be as effective as CH or TAP and better than no medicament group. The promising results of CL can be attributed to its potent antimicrobial [14,29,30], anti-inflammatory [6,28,31], analgesic [32] and antioxidant activity [33]. CL acts against a number of pathogenic bacteria including *Staphylococcus aureus*, and *Enterococcus* [14,29,34]. The exact mechanism of its antibacterial activity is unknown but is suggested to be pleiotropic, a microbiological study by Tyagi et al. [34], attributed it to its active component curcumin 1, while Rai et al. [30], suggested inhibition of FtsZ protofilaments assembly and increased GTPase activity of FtsZ, which is essential for bacterial cytokinesis. Curcumin modulates the inflammatory response by downregulating the activity of cyclooxygenase-2, lipoxygenase, and inducible nitric oxide synthase enzymes, mitogen-activated and Janus kinases, and inhibits the production of inflammatory cytokines like tumor necrosis factor-α, interleukin-1, 2, 6, 8, and 12 [29,31]. In addition, curcumin inhibits pain hypersensitivity by reducing the excitability of sensory neurons and blocking TRPV1 activation [31] and decreases oxidative stress in the early phases of inflammatory hyperalgesia [33].

Our study depicted no statistical differences in IAP scores between patients medicated with CH or TAP. This is in agreement with the findings of previous clinical studies [35,36] but does not corroborate with some studies that found TAP to be significantly more effective than CH in IAP reduction [37,38]. This variability of results may be attributed to different patient inclusion criteria, as Sinhal et al. [37], involved diabetic patients with a primary endodontic lesion, whereas Prasad et al. [38], recruited patients irrespective of their pulpal or peri-radicular status.

At the first observation time point i.e., 4 h post-operatively, all patients in our study (with or without intracanal medication) exhibited similar pain scores. These findings indicate that intracanal medicaments take some time to exert their action. A recent systematic review and meta-analysis suggested that compared to no medication, CH significantly improved postoperative pain at 24 h whereas other medicaments exerted their significant antinociceptive effect at 72 h postoperatively [39]. In all groups (intragroup), IAP decreased steadily with time. On intergroup comparison, the pain reduction was significant in intracanal medicated groups till the third day after which the difference in pain scores among all groups was non-significant till the seventh day. The main pain reduction after root canal treatment is due to the elimination of microbes or irritants from the root canal system during endodontic treatment [40]. We completed the biomechanical preparation in the first visit itself, thus pain decreased in all groups compared to pre-operative levels, more so in intracanal medicaments due to their additional benefits. Over time (after 3 days) the reduction in pain among all groups became insignificant, thus overcoming any effect of intracanal medicament.

Our study was conducted in teeth with symptomatic irreversible pulpitis, i.e., vital pulp, while most previous endodontic studies on IAP were conducted in non-vital pulps [41,42]. It was considered that necrotic pulps possess a significantly higher number of microbes [43] and thus have higher chances of flare-ups or IAP, whereas root canals with irreversibly inflamed vital pulps were considered free of bacteria [44]. But recent studies based on genomic DNA analysis have shown that vital teeth with irreversible pulpitis harbor considerable bacterial loads [45]. Moreover, preoperative pain has been shown to be the most important variable that influences the prevalence of postoperative pain in studies, and the vitality of teeth was found to have no effect on postoperative pain [46]. Therefore, the current study was conducted on patients having moderate to severe preoperative pain in vital teeth with irreversibly inflamed pulps.

Another question that might arise is whether there is any need for intracanal medicament like Calcium hydroxide or Triple Antibiotic Paste in vital pulp cases as single-visit endodontics is routinely indicated in such cases. Throwing light on the recent status and future directions of intracanal medicaments, Zapata et al. [47], stated that moderate to severe preoperative pain is a strong patient variable indicating the use of an intracanal medication. They further added that performing single-visit endodontics in symptomatic patients may affect patient-centered outcomes as it precludes further evaluation by the treating dentist. Also, in a busy clinical set-up, it is often not possible to complete endodontic treatment in a single visit due to time constraints and other patient factors. In such cases, a pulpectomy is performed in an emergency visit, and a suitable intracanal medicament is placed until the further visit.

TAP was initially employed in regenerative endodontics to disinfect immature teeth where instrumentation was not always feasible due to thin dentinal walls. One prominent draw back associated with TAP could be significant tooth discoloration because of presence of minocycline. In our study, intracanal placement of TAP was followed by an adhesive coating on pulp chamber walls to prevent any tooth discoloration. None of the teeth in the current study showed discoloration but discoloration can occurs in the root dentin as well which could be aesthetically unfavorable in anteriors and premolars.

In our study, propylene glycol (PG) was used as a vehicle for all intracanal medicaments to keep uniformity among groups and due to the high solubility of CL in PG. It possesses hygroscopic properties that allow absorption of water, resulting in a sustained release of intracanal medicament for prolonged periods [48]. But using PG as a vehicle for CH might have resulted in limited effectiveness of CH in the present study [49]. Although PG itself has low surface tension and increased penetrability through dentinal tubules [50], it doesn't alter the penetration of CH and TAP when used as a vehicle [51]. Thus, using PG didn't provide any additional advantage to CH or TAP.

4.1. Limitations of the study

Our study was a single-blinded randomized controlled trial with strict inclusion criteria. However, current study evaluated only antinociceptive properties of CL and not the antibacterial effect. The study had a small sample size, and used only propylene glycol as a vehicle. The antibacterial effect of CL as an intracanal medicament is still unknown. Further clinical trials with large sample sizes, using different vehicles, including multirooted teeth, different preoperative diagnoses and evaluation of antibacterial effectiveness are recommended to draw definitive clinical conclusions.

5. Conclusion

Within the limitations of this study, it can be concluded that Curcuma longa as an intracanal medicament is as effective as calcium hydroxide and triple antibiotic paste in managing inter-appointment pain.

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Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Rakesh Singla: Funding acquisition, Formal analysis, Data curation, Conceptualization. **Charu Gupta:** Funding acquisition, Formal analysis, Data curation. **Gurdeep Singh Gill:** Resources, Project administration, Formal analysis, Data curation, Conceptualization. **Namita Jain:** Validation, Supervision, Software, Resources, Project administration. **Suraj Arora:** Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Youssef A. Algarni:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software. **Mohammed Abdul Kader:** Supervision, Software, Resources. **Marco Cicciù:** Visualization, Validation, Supervision, Software. **Giuseppe Minervini:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e33797.

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