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ORIGINAL ARTICLE

Efficiency of Immediate and Controlled release of Aceclofenac on Post-instrumentation Pain in Root Canal Treatment – A Triple Blind Randomized Controlled Trial

Jothi Latha SUNDARAMURTHY,[1] Velmurugan NATANASABAPATHY,[2] Kavitha MAHENDRAN,[1] Srinivasan NARASIMHAN,[3] Sandhya RAGHU,[4] Anna Ravi CHERIAN,[2] Murugadoss VAANJAY,[5] Jogikalmat KRITHIKADATTA[2]*

[1]Department of Conservative Dentistry and Endodontics, Tamil Nadu Government Dental College and Hospital, The Tamil Nadu Dr. M.G.R. Medical University, Chennai, India
[2]Department of Conservative Dentistry and Endodontics, Meenakshi Ammal Dental College and Hospital, Meenakshi Academy of Higher Education and Research University, Chennai, India
[3]Department of Endodontics, Hamad Dental Center, Hamad Medical Corporation, Doha, Qatar
[4]Department of Conservative Dentistry and Endodontics, Saveetha Dental College and Hospital, Chennai, India
[5]Department of Conservative Dentistry and Endodontics, CSI College of Dental Sciences, Madurai, India

**The current affiliation of the author: Department of Cariology, Saveetha Dental College and Hospital, Chennai, India*

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Address for correspondence: Velmurugan Natanasabapathy Department of Conservative Dentistry and Endodontics, Meenakshi Ammal Dental College and Hospital, Meenakshi Academy of Higher Education and Research University, Chennai, India
E-mail: vel9911@yahoo.com

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ABSTRACT

Objective: Patients with moderate to severe preoperative pain have a high incidence of postoperative pain. The objective of this trial was to evaluate the efficiency of oral premedication with Aceclofenac (immediate release and controlled release) in the management of post-instrumentation pain in root canal treatment, in patients with moderate to severe preoperative pain.

Methods: Three-arm parallel, triple blinded randomized controlled trial was planned. Patients with moderate to severe endodontic pain, requiring primary endodontic treatment were enrolled. Aceclofenac 100mg- immediate release (Aceclofenac-IR), Aceclofenac 200mg- controlled release (Aceclofenac-CR), and Ibuprofen 400mg were compared. The tablets were given one hour before the root canal treatment. Postoperatively, patients rated their pain at various time points. The duration of pain relief (primary outcome), the intensity of post-instrumentation pain, and the need for additional medicine were calculated. Statistical analysis was done using Kruskal-Wallis followed by Dunn post-hoc, Chi-square tests, and Binominal logistic regression.

Results: Aceclofenac-CR had a statistically significant longest duration of pain relief when compared to Ibuprofen (p=0.037) and Aceclofenac-IR (p=0.026). The intensity of post-instrumentation pain was lowest in Aceclofenac-CR, followed by Aceclofenac-IR and Ibuprofen. Additional medicine was required for only 8% of patients in Aceclofenac-CR group; whereas for 32% in each of Aceclofenac-IR and Ibuprofen groups. The odds of taking additional medicine were reduced to 0.16 in Aceclofenac-CR; increased to 1.05 with age.

Conclusion: Aceclofenac-CR had the longest duration of pain relief compared to Aceclofenac-IR and Ibuprofen.

Keywords: Aceclofenac, controlled-release, Ibuprofen, NSAIDs, post-instrumentation pain, premedication

HIGHLIGHTS

- All the three premedications (Aceclofenac-IR, Aceclofenac–CR and Ibuprofen) used were effective in reducing post-instrumentation pain.
- Aceclofenac-CR resulted in the longest duration of pain relief compared with Aceclofenac-IR and Ibuprofen.
- Premedication with Aceclofenac-CR reduced the need for additional medicine in the post-operative period.

INTRODUCTION

Endodontic pain is an unpleasant experience often necessitating immediate treatment. Patients expect the pain to be reduced after the root canal therapy. Though there is an expectation of pain relief, the incidence of post–endodontic pain ranges from 3% to 58% (1). Post-instrumentation pain occurs because of complex multi-factorial reasons. Periapical tissue injury caused by improper instrumentation, extrusion of irrigants/debris, diffusion of caustic medicaments and occlusal discrepancies are some of the common reasons for the initiation of post-instrumentation pain. Patient-related factors, type of tooth involved and clinician's expertise are other factors that can influence the post-instrumentation pain. The presence of moderate to severe preoperative pain was reported as one of the main factors influencing postoperative pain (2, 3).

Clinicians use orally administered premedication (4) and postoperative nonsteroidal anti-inflammatory drugs (NSAIDs) (5), corticosteroids (6, 7), centrally acting analgesics, or inhalation of NSAID (8) or injection of steroids/local anesthetics to reduce the post-instrumentation pain (9, 10). Among these, premedication given orally is one of the simplest and easiest methods to control post-instrumentation pain. Thus far, medications such as Ibuprofen, Ketorolac, Diclofenac, centrally acting drugs and Corticosteroids have been used for managing endodontic pain. In assessing the relative safety/efficacy relationship, NSAIDs outrank steroids and are considered the first choice of drug in post-instrumentation pain management (11).

Aceclofenac is a phenylacetic acid derivative and a potent NSAID. It has a superior safety profile amongst NSAIDs, leading to better patient acceptance and compliance (12). Aceclofenac has a longer duration of action in comparison with Ibuprofen. The controlled-release formulation of Aceclofenac allows the drug to be effective over an extended period. It also reduces repeated administration of the drug and allows for better patient compliance (13, 14). Logically, an analgesic premedication with an extended duration of action could be more effective because of the prolonged anti-inflammatory action in managing post-instrumentation pain. However, there is a lack of evidence for the efficiency of oral premedication with controlled-release Aceclofenac on post-instrumentation pain.

Hence, the aim of this randomized clinical trial was to evaluate the efficiency of oral premedication with Aceclofenac (immediate release and controlled release) in the management of post-instrumentation pain. The research question was framed using PICO format as, 'Will oral premedication with Aceclofenac (immediate release and controlled release) before endodontic treatment (Intervention) increase the duration of post-instrumentation pain relief (Primary outcome) when compared to oral premedication with Ibuprofen (Control) in patients with moderate to severe pre-operative endodontic pain (Population)?' The null hypothesis formulated was that there is no difference in duration of pain relief among oral premedication with Aceclofenac (immediate release and controlled release) or Ibuprofen on post-instrumentation pain.

MATERIALS AND METHODS

A three-arm parallel design randomized controlled trial was planned to answer the research question. The trial was conducted in two institutional hospitals in the city of Chennai, and the protocol was approved by the respective institutional ethical committee and review board (IRB reference numbers: 4/IRB/2018; MADC/IRB-XXVIII/2019/449). The trial was registered in the national trial registry (CTRI registration number: CTRI/2019/09/021074) and was conducted in accordance with the Declaration of Helsinki. The reporting of the trial followed CONSORT (Consolidated Standards of Reporting Trials) guidelines. The sample size was calculated based on a pilot study, with α error set at 5%, power at 80%. Adult patients aged 18 years or above with moderate to severe pain [categorized using a 10 point numeric rating scale (NRS)], with any endodontic diagnosis requiring primary endodontic treatment and consenting to participate were recruited and enrolled in the trial by the Principal Investigators (PI) in the corresponding institutions. Patients with a history of allergy to any of the drugs used in the trial, gastric or peptic ulcer, bronchial asthma, blood dyscrasias, hepatic/renal impairment, pregnant women, lactating mothers, with more than one tooth requiring endodontic intervention, and on any current analgesic medication were excluded. The demographic details as age, gender, and tooth-related details as tooth type (single/multi-rooted), pulpal (vital/pulpal necrosis), and periradicular status (normal periapex/symptomatic periradicular disease /asymptomatic periradicular disease) were recorded for all the patients.

The three groups studied were, Aceclofenac 100mg- immediate release (Aceclofenac-IR) [Zerodol, Ipca laboratories ltd., Mumbai, India], Aceclofenac 200mg- controlled release (Aceclofenac-CR) [Zerodol - CR, Ipca laboratories ltd., Mumbai, India] and Ibuprofen 400mg [Brufen 400 - Abbot India ltd., Goa, India]. The three groups were coded at random as A, B, and C by a staff nurse who was not involved in the treatment, outcome assessment, or data analysis. The tablets were wrapped and coded as A, B and C by the same person. The patients were randomly assigned to one of the three intervention groups using computer-generated permuted block randomization, with an allocation ratio of 1:1:1. Allocation concealment was done by sealing the allocation note in an opaque envelope. The drug was given one hour before the endodontic procedure. The intake of the drug by the patient was monitored by a nursing assistant. Endodontic treatment was done by two calibrated senior post-graduate students of the respective departments, trained by two senior Endodontists using a standard operating protocol. Endodontic treatment was carried out in multiple-visits for all the cases. In the first visit, local anesthetic (2% lignocaine with 1:80,000 adrenaline) was administered by infiltration or inferior alveolar nerve block (IANB) injection, depending on the tooth type; cleaning and shaping was completed using MtwoNiTi rotary files (VDW, Munich, Germany), with minimum apical enlargement of 30 size or more, depending upon the canal size. Copious irrigation with 3% sodium hypochlorite was done throughout the procedure and final irrigation was

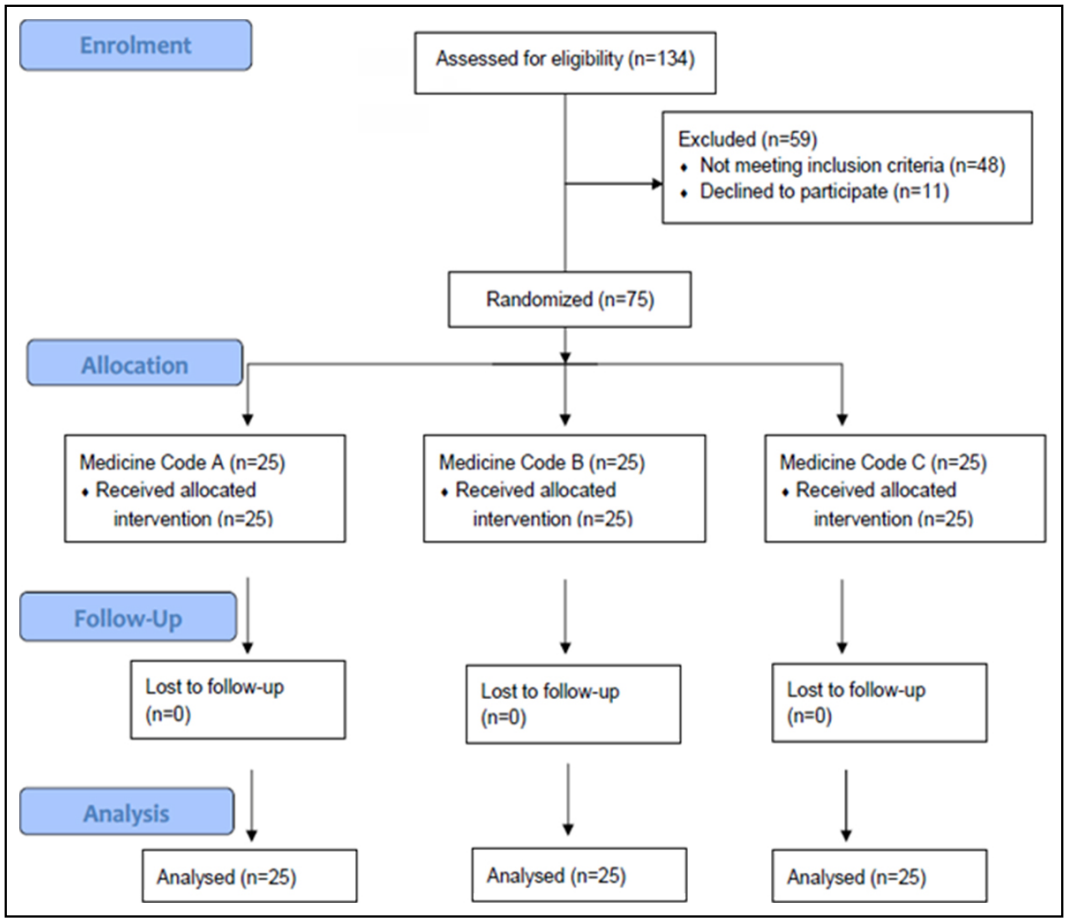

Figure 1. A Flow of patients through the trial (CONSORT flow chart)

done with 17% EDTA, followed by 3% sodium hypochlorite, using 30-gauge side-vented needles. The canals were dried with absorbent paper points; calcium hydroxide intracanal medicament paste (Apexcal, IvoclarVivadent, Schaan, Liechtenstein) was placed and access cavity was temporized with IRM (Dentsply Sirona, York, PA).

The patients were requested to rate their pain immediately after treatment and then at 6hrs, 12hrs, 24hrs, 48hrs, and 72hrs post-operatively. The scores were made in a pain diary handed over to the patients. In addition, the PI contacted the patients over the phone at regular intervals to ensure that the pain rating was done and made a note of it, to minimize the chance of any missing data. All the patients were provided with rescue medicines for the event of any post-instrumentation pain (Acetaminophen 650mg). The patients were instructed to make a note of the time at which they took the rescue medicine in the pain diary, to estimate the duration of pain relief. The duration of pain relief was calculated as the time interval between the completion of the first visit and the time of need of rescue medicine or endpoint of the postoperative assessment. The patients were requested to return the pain diary when they reported for the next visit. All teeth were root canal filled using lateral compaction technique with gutta-percha and zinc-oxide eugenol sealer. The data analysis was done by the statistician blinded to the treatment groups. The patients, the principal investigators who enrolled the patients and performed outcome assessment, the operators, and the statistician were blinded in this trial. Hence, the trial followed a triple blinding strategy. As the study was of 'low-risk behaviour' and short duration, only Data Safety and Monitoring Plan (DSMP) was needed. The patients were given an emergency contact number to call for any emergency, during the trial period. The PI held the responsibility for monitoring all the subjects for safety, data accuracy and protocol compliance.

Statistical Analysis

The age of the patients and pre-operative pain scores were analyzed using the Kruskal-Wallis test; distribution of gender, pulpal and periradicular status, and tooth type were analyzed using the Chi-square test to assess for comparability of the groups at the baseline. The primary objective i.e. the duration of pain relief was analyzed using Kruskal-Wallis, followed by Dunn Post-hoc test. The secondary objectives, i.e. intensity of pain (represented by the pain scores) at different time points and the need for additional medicine post-operatively were given as descriptive data for the groups. A binomial logistic regression was performed to ascertain the effects of various predictor variables as age, gender, pre-operative pain score, medicine code, pulp status, and tooth type, on the odds of taking additional medicine. The reference category used in the categorical predictor variables namely gender, medicine code, pulp status, and tooth type were female, Ibuprofen, non-vital, and single-rooted respectively. The statistical analyses were performed using IBM SPSS Statistics for Windows, (IBM Corp., USA). The

TABLE 1. Baseline demographic characteristics and preoperative details

Variables	Aceclofenac-IR (medicine code C) (n=25)		Aceclofenac-CR (medicine code A) (n=25)		Ibuprofen (medicine code B) (n=25)		Level of significance (p)
	n	%	n	%	n	%	
Age (years)							
Mean±SD	36±15.7		32.2±11		32.2±9.8		
Median (IQR)	30 (24)		30 (12.5)		32 (14)		0.89
Gender							
Male	16	64	14	56	11	44	
Female	9	36	11	44	14	56	0.36
Preoperative pain score							
Mean±SD	6.8±1.8		6.8±2.1		6.9±1.8		
Median (IQR)	7 (3)		7 (3)		7 (3)		0.94
Tooth type							
Single-rooted	6	24	5	20	6	24	
Multi-rooted	19	76	20	80	19	76	0.93
Pulpal status							
Vital	16	64	15	60	14	56	
Non-vital	9	36	10	40	11	44	0.85
Periradicular status							
Normal	2	8	2	8	1	4	
Symptomatic	21	84	22	88	23	92	
Asymptomatic	2	8	1	4	1	4	0.91

IR: Immediate release, CR: Controlled release, p: Probability value, SD: Standard deviation, IQR: Interquartile range

TABLE 2. Comparison of duration of pain relief among the groups

Duration of pain relief (in hours)	Aceclofenac-IR (medicine code C) (n=25)	Aceclofenac-CR (medicine code A) (n=25)	Ibuprofen (medicine code B) (n=25)	Level of significance (p)
Mean±SD	51.3±30.8	67.8±14.7	51.4± 30.6	
Median (IQR)	72 (63.5)	72 (0.0)	72 (64.1)	0.045

IR: Immediate release, CR: Controlled release, p: Probability value, SD: Standard deviation, IQR: Interquartile range

groups were decoded only after completion of the analysis. Medicine codes A, B and C were later identified as, Aceclofenac-CR, Ibuprofen and Aceclofenac-IR respectively.

RESULTS

A total of 134 patients were assessed for selection criteria among which 59 were excluded. 75 patients who met the inclusion criteria were enrolled in the trial and analyzed. Each patient was followed for a period of 72 hours during the trial. The flow of patients through the trial was as in Figure 1. There was no significant difference among the groups concerning the baseline data (Table 1). There was a significant difference in the duration of pain relief among the groups (p=0.045). Aceclofenac-CR had the longest duration of pain relief, which was statistically significant in comparison with Aceclofenac-IR (p=0.026) and Ibuprofen (p=0.037) (Table 2). There was no significant difference between the other groups. The descriptive statistics for the intensity of pain at various time points for the groups were as shown in Figure 2 and Figure 3. In the Aceclofenac-CR group, only 8% of the patients required additional medicine; in Aceclofenac-IR and ibuprofen groups 32% of the patients in each required additional medicine. The logistic regression model was statistically significant, χ^2 (7) = 16.55, p=0.021, and the model correctly classified 78.7% of cases. Of the six predictor variables, only medicine code and age were statistically significant (Table 3). On comparing with the Ibuprofen (control), the odds of taking additional medicine were reduced to 0.16 times in Aceclofenac-CR. An increase in age was associated with increased odds of taking additional medicine to 1.05 times. No adverse effects were reported in any of the groups in the trial.

DISCUSSION

Pain management is an integral part of endodontic treatment. Development of post-instrumentation pain after root canal therapy is usually due to acute inflammatory response in the periapical tissue, induced by chemical, mechanical or microbial injury (15–17). Various factors that can potentially influence post-instrumentation pain namely age, gender, tooth type, clinician's experience, and preoperative pain have been studied earlier. Among these, preoperative pain is reported to be the strong

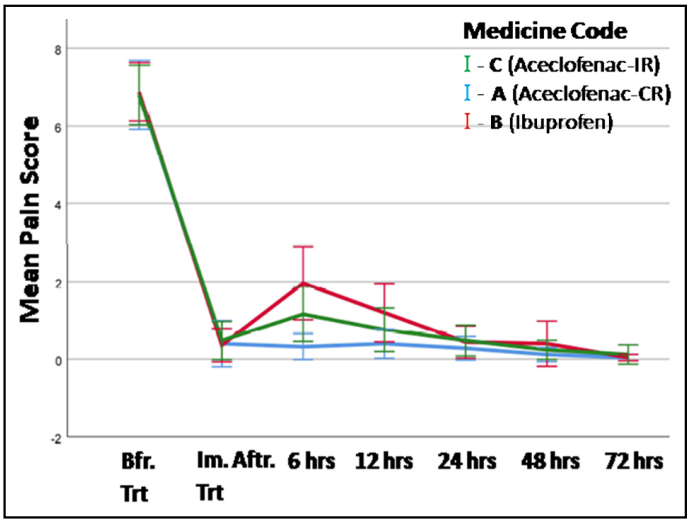

Figure 2. Mean pain scores at various time points for the groups (data inclusive of patients taken rescue medicine)

IR: Immediate release, CR: Controlled release

and consistent predictor of post-instrumentation pain in most of the studies. Patients with moderate to severe preoperative pain were reported to have a high incidence of postoperative pain (3, 18–20). The plausible reason for this could be an exacerbation of the preexisting inflammatory responses and peripheral sensitization. Hence, additional strategies for the management of post-instrumentation pain, in these classes of patients may be beneficial, which influenced the selection criteria in this trial.

NSAIDs continue to be the mainstay for pain management in dentistry (21, 22). Whenever there is tissue damage, arachidonic acid (AA) is released from plasma membrane phospholipids by phospholipases. AA is metabolized by the sequential action of Prostaglandin G/H synthases [colloquially known as cyclooxygenases (COXs)] to Prostaglandin H2 (PGH2) (23, 24). The subsequent cascade of inflammatory reactions leads to peripheral sensitization of nociceptors. NSAIDs act by inhibiting the COX pathway (23). The inhibition of cyclooxygenase-2 (COX-2) mediates antipyretic, analgesic, and anti-inflammatory actions of NSAIDs, while the simultaneous inhibition of cyclooxygenase-1

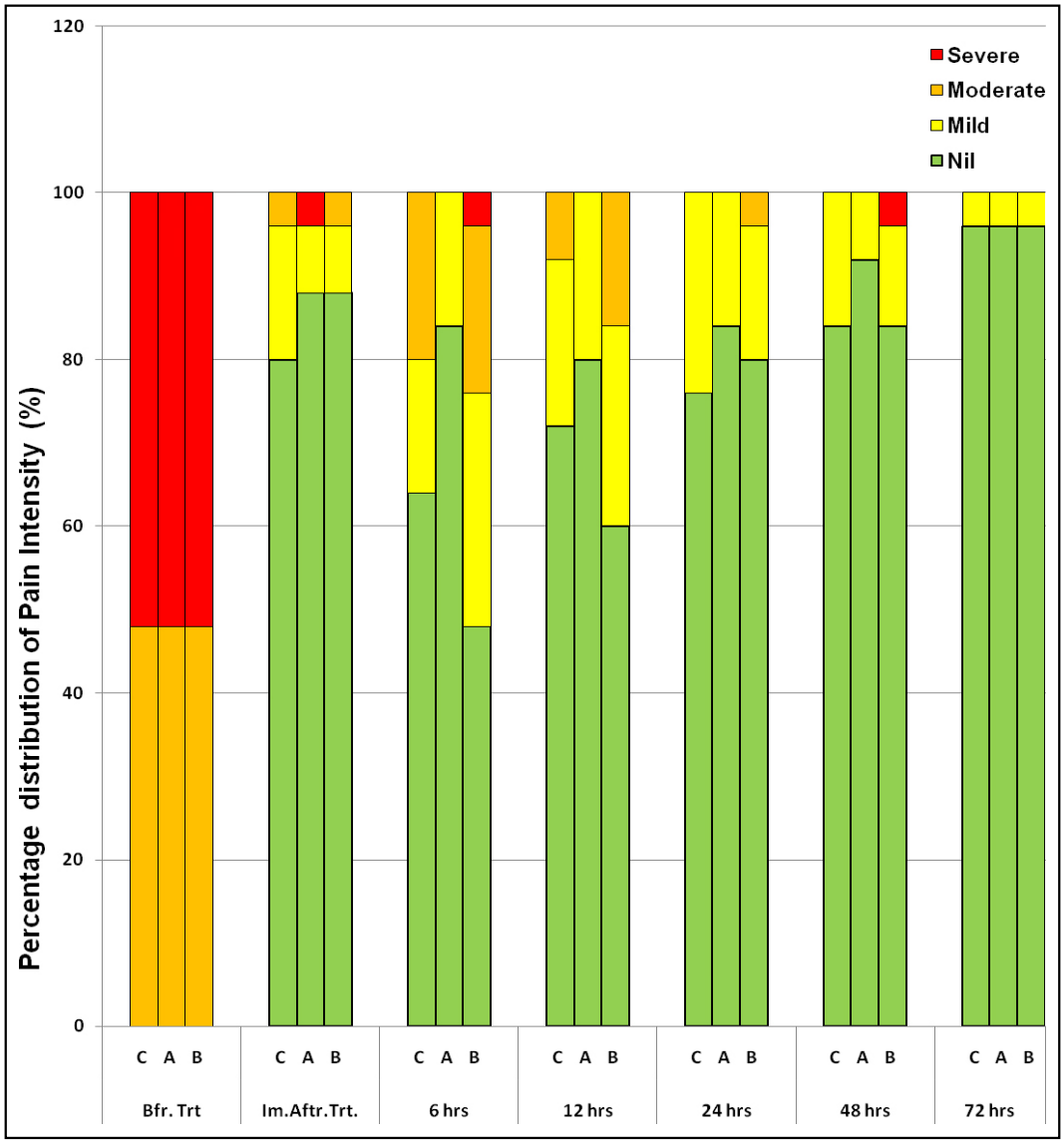

Figure 3. Percentage distribution of pain intensity among the patients at various time points

Data inclusive of patients taken rescue medicine. C: Aceclofenac-IR, A: Aceclofenac-CR, B: Ibuprofen

TABLE 3. Binomial logistic regression model depicting the effect of various predictor variables on additional medicine need

Predictor variables	Co-efficient	S.E.	Wald	p	Odds ratio	95% CI for odds ratio	
						Lower	Upper
Age	0.052	0.025	4.537	**0.033**	1.054	1.004	1.105
Gender (male)	–0.373	0.673	0.307	0.58	0.689	0.184	2.575
Medicine code (Ref: Ibuprofen)		4.274	0.118				
Medicine code (Aceclofenac-IR)	–0.122	0.695	0.031	0.861	0.886	0.227	3.46
Medicine code (Aceclofenac-CR)	–1.826	0.924	3.901	**0.048**	0.161	0.026	0.986
Preoperative pain score	–0.106	0.185	0.327	0.568	0.9	0.626	1.293
Pulpal status (vital)	–0.563	0.635	0.785	0.375	0.569	0.164	1.978
Tooth type (multi-rooted)	–0.985	0.699	1.986	0.159	0.373	0.095	1.47

The reference category used in the categorical predictor variables namely gender, medicine code, pulp status and tooth type were female, Ibuprofen, non-vital and single rooted respectively. S.E.: Standard error, p: Probability value, CI: Confidence interval, IR: Immediate release, CR: Controlled release

(COX-1) mainly accounts for unwanted adverse effects in the GI tract. Ibuprofen is a propionic acid derivative and a non-selective COX inhibitor. Aceclofenac is a phenylacetic acid derivative. It causes preferential inhibition of COX-2 and PGE2 synthesis in blood mononuclear and polymorphonuclear cells (25). This makes Aceclofenac a well-tolerated NSAID with a lower incidence of gastrointestinal adverse effects(12). Ibuprofen is the most commonly prescribed NSAID. It is available in doses of 200 to 800mg. It has a half-life of 1.8 to 2 hours, necessitating dosing every 6 to 8 hours (TID or QID) (26). Aceclofenac has a half-life of approximately 3.5–6.2 hours, necessitating dosing every 12 hours (BD) to maintain adequate analgesia. Recently once-daily (OD) controlled release formulation of Aceclofenac 200mg was introduced, which produces biphasic Aceclofenac release (13).

Understanding the neurobiological basis of acute pain made it vivid that pain is a dynamic experience and prior nociceptive inputs act peripherally and centrally, resulting in intensifying the pain produced by subsequent noxious stimuli. This has resulted in the concept of premedication analgesia, which aims at initiating the analgesic intervention prior to the expected subsequent nociceptive stimuli as in operative intervention (27). Patients with continued symptoms after root canal treatment had proved to be less satisfied with the treatment received. Appropriate post-instrumentation pain management before it peaks can positively influence patient satisfaction level and quality of life after endodontic treatment (28, 29). Various premedication analgesics had been studied in mitigating postoperative pain in oral surgery (30, 31) and root canal treatment (21, 32–34). The role of Ibuprofen as a premedication analgesic had been proved in a recent systematic review and meta-analysis (21). The need for additional trials in post-operative pain management to increase the level of evidence had been highlighted in recent systematic reviews and meta-analyses (21, 35). This randomized controlled trial aimed at evaluating the efficiency of the commonly used analgesics as Ibuprofen 400mg, Aceclofenac-IR 100mg, and Aceclofenac-CR 200mg with different durations of action as 6-8 hrs, 12 hrs, and 24 hrs respectively as a premedication analgesic; with the speculation that when peripheral sensitization is mitigated for an extended duration, this may positively influence post-instrumentation pain management.

The computer-generated permuted block randomization, allocation concealment, and the triple blinding followed in this trial ensured the elimination of any biases during the selection and allocation of participants, measurement of the dependent variable, and data analysis. These measures along with the operator calibration strengthened the internal validity of the trial. Distribution of various confounding factors as age, gender, preoperative pain, pulpal and periradicular status, and tooth type amidst the groups at the baseline were analyzed and found to be similar, to rule out their potential influence on results. The broader inclusion criteria used in this trial extends the generalizability to all patients with preoperative pain requiring primary root canal therapy, irrespective of the diagnosis. The results of the primary outcome in this trial revealed that all the three premedications had a longer period of pain relief than the actual duration of action of the drugs. This suggests that the practice of routine use of NSAIDs for a few days after endodontic treatment should be revisited to using it only if pain resurfaces when premedication analgesic is used. Aceclofenac-CR exhibited the longest duration of pain relief, which was significantly higher than the other groups. This could be attributed to its extended duration of anti-inflammatory action aiding in modulation and mitigation of peripheral sensitization, which had clinically reflected with the longest duration of pain relief, well beyond the duration of action of the drug.

Most often post-instrumentation pain had been reported to occur mainly on the first day after treatment and found to reduce thereafter with resolution of inflammation by the treatment rendered (19). The recent standards suggest follow-up of the patients for at least three days as severe post-instrumentation pain was reported to reduce to tolerable levels within 72 hrs (19, 21). The results of the secondary outcome of this trial are in accordance with that. The frequency distribution of pain at various time points reveals that the majority of patients in all the groups remained pain-free at various time points. Among the patients with post-instrumentation pain, the Aceclofenac-CR group had only mild pain at various time points postoperatively. The pain of greater intensity mainly occurred within the first 24 hrs in the Ibuprofen and Aceclofenac-IR group, which gradually reduced thereafter, and at 72 hrs all patients were devoid of moderate or severe pain (Fig. 2).

The need for additional medicine in only 8% of the patients in the Aceclofenac-CR group, underscores the fact that 92% of the patients in this group had good pain control and did not require any additional postoperative medication. Moreover, the odds were significantly reduced to 0.16 times in the Aceclofenac-CR group. In Ibuprofen and Aceclofenac-IR groups, the percentage of patients without any need for post-operative medication reduced to 68% in each group. Age was found to play a significant role in the need for additional medicine; the odds were found to increase to 1.05 times with each year of increase in age. This reveals that the need for additional medicine may be higher in elderly patients, irrespective of the premedication analgesic taken.

The fact that Aceclofenac-CR had the longest duration of pain relief with least post-instrumentation pain scores and least need of additional medication will give an edge over in successful clinical management of post-instrumentation pain. Patients have better compliance with OD drug dose than to multiple dosing (36). When the same is given as a premedication medicament under direct monitoring, post-instrumentation pain management will not be dependent on the patients' compliance. This can potentially increase patients' convenience and quality of life in the postoperative period. Placebo group was not considered in this trial intentionally, as there was some pre-existing evidence in favour of premedication use of Ibuprofen for post-instrumentation pain (21, 32). Hence, Ibuprofen was considered as an active control in this trial. But this is a limitation for any comparisons to be inferred with standard endodontic treatment alone without premedication analgesic. However, a recent trial also proved the superiority of all the premedications tested in comparison to placebo (7).Patient anxiety scale to negate the influence of anxiety in pain perception and quality of life after endodontic treatment can be considered for future trials.

CONCLUSION

Post-instrumentation pain relief was best with Aceclofenac-CR among the three groups studied. Aceclofenac-CR provided the longest duration of pain relief when compared to Aceclofenac-IR and Ibuprofen. Aceclofenac-CR can be preferred as an oral analgesic premedication, before primary root canal treatment in patients with moderate to severe preoperative pain, for efficient management of post-instrumentation pain. Patients can be instructed to take NSAIDs postoperatively only in case of symptoms and not otherwise.

Disclosures

Conflict of interest: The authors deny any conflict of interest.

Ethics Committee Approval: This study was approved by The Institutional Ethical Committee and Review Board (Date: 14/11/2018; 25/6/2019, Number: 4/IRB/2018; MADC/IRB-XXVIII/2019/449).

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REFERENCES

1. Sathorn C, Parashos P, Messer H. The prevalence of postoperative pain and flare-up in single- and multiple-visit endodontic treatment: a systematic review. Int Endod J 2008; 41(2):91–9.
2. Glennon JP, Ng YL, Setchell DJ, Gulabivala K. Prevalence of and factors affecting postpreparation pain in patients undergoing two-visit root canal treatment. Int Endod J 2004; 37(1):29–37. [CrossRef]
3. Sadaf D, Ahmad MZ. Factors associated with postoperative pain in endodontic therapy. Int J Biomed Sci 2014; 10(4):243–7.
4. Praveen R, Thakur S, Kirthiga M. Comparative evaluation of premedication with ketorolac and prednisolone on postendodontic pain: a double-blind randomized controlled trial. J Endod 2017; 43(5):667–73.
5. Elzaki WM, Abubakr NH, Ziada HM, Ibrahim YE. Double-blind randomized placebo-controlled clinical trial of efficiency of nonsteroidal anti-inflammatory drugs in the control of post-endodontic pain. J Endod 2016; 42(6):835–42. [CrossRef]
6. Suneelkumar C, Subha A, Gogala D. Effect of preoperative corticosteroids in patients with symptomatic pulpitis on postoperative pain after single-visit root canal treatment: a systematic review and meta-analysis. J Endod 2018; 44(9):1347–54. [CrossRef]
7. Suresh N, Nagendrababu V, Koteeswaran V, Haritha JS, Swetha SD, Varghese A, et al. Effect of preoperative oral administration of steroids in comparison to an anti-inflammatory drug on postoperative pain following single-visit root canal treatment - a double-blind, randomized clinical trial. Int Endod J 2021; 54(2):198–209. [CrossRef]
8. Turner CL, Eggleston GW, Lunos S, Johnson N, Wiedmann TS, Bowles WR. Sniffing out endodontic pain: use of an intranasal analgesic in a randomized clinical trial. J Endod 2011; 37(4):439–44. [CrossRef]
9. Yavari HR, Jafari F, Jamloo H, Hallaj-Nezhadi S, Jafari S. The effect of submucosal injection of corticosteroids on pain perception and quality of life after root canal treatment of teeth with irreversible pulpitis: a randomized clinical trial. J Endod 2019; 45(5):477–82. [CrossRef]
10. Aksoy F, Ege B. The effect of pretreatment submucosal injections of tramadol and dexamethasone on post-endodontic pain in mandibular molar teeth with symptomatic irreversible pulpitis: a randomized controlled clinical trial. Int Endod J 2020; 53(2):176–85. [CrossRef]
11. Nagendrababu V, Duncan HF, Bjørndal L, Kvist T, Priya E, Jayaraman J, et al. PRIRATE 2020 guidelines for reporting randomized trials in Endodontics: a consensus-based development. Int Endod J 2020; 53(6):764–73. [CrossRef]
12. Legrand E. Aceclofenac in the management of inflammatory pain. Expert Opin Pharmacother 2004; 5(6):1347–57. [CrossRef]
13. Bae SK, Kim SH, Lee HW, Seong SJ, Shin SY, Lee SH, et al. Pharmacokinetics of a new once-daily controlled-release formulation of aceclofenac in Korean healthy subjects compared with immediate-release aceclofenac and the effect of food: a randomized, open-label, three-period, crossover, single-centre study. Clin Drug Investig 2012; 32(2):111–9. [CrossRef]
14. Sanjay SS, Shruthi B, Sarvesh, Rama Smriti P, Zaranappa. Sustained release formulations of aceclofenac: a brief review. J Chem Pharm Res 2017; 9(3):302–7.
15. Genet JM, Hart AA, Wesselink PR, Thoden van Velzen SK. Preoperative and operative factors associated with pain after the first endodontic visit. Int Endod J 1987; 20(2):53–64. [CrossRef]
16. DiRenzo A, Gresla T, Johnson BR, Rogers M, Tucker D, BeGole EA. Postoperative pain after 1- and 2-visit root canal therapy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002; 93(5):605–10. [CrossRef]
17. El Mubarak AH, Abu-bakr NH, Ibrahim YE. Postoperative pain in multiple-visit and single-visit root canal treatment. J Endod 2010; 36(1):36–9.
18. O'Keefe EM. Pain in endodontic therapy: preliminary study. J Endod 1976; 2(10):315–9. [CrossRef]
19. Genet JM, Wesselink PR, Thoden van Velzen SK. The incidence of preoperative and postoperative pain in endodontic therapy. Int Endod J 1986; 19(5):221–9. [CrossRef]
20. Siqueira JF Jr, Rôças IN, Favieri A, Machado AG, Gahyva SM, Oliveira JC, et al. Incidence of postoperative pain after intracanal procedures based on an antimicrobial strategy. J Endod 2002; 28(6):457–60. [CrossRef]
21. Smith EA, Marshall JG, Selph SS, Barker DR, Sedgley CM. Nonsteroidal anti-inflammatory drugs for managing postoperative endodontic pain in patients who present with preoperative pain: a systematic review and meta-analysis. J Endod 2017; 43(1):7–15. [CrossRef]

22. Abbott PV, Parirokh M. Strategies for managing pain during endodontic treatment. Aust Endod J 2018; 44(2):99–113. [CrossRef]
23. Ochroch EA, Mardini IA, Gottschalk A. What is the role of NSAIDs in pre-emptive analgesia? Drugs 2003; 63(24):2709–23. [CrossRef]
24. Ricciotti E, FitzGerald GA. Prostaglandins and inflammation. Arterioscler Thromb Vasc Biol 2011; 31(5):986–1000. [CrossRef]
25. Cho JY. Immunomodulatory effect of nonsteroidal anti-inflammatory drugs (NSAIDs) at the clinically available doses. Arch Pharm Res 2007; 30(1):64–74. [CrossRef]
26. Bushra R, Aslam N. An overview of clinical pharmacology of Ibuprofen. Oman Med J 2010; 25(3):155–61. [CrossRef]
27. Katz J. Pre-emptive analgesia: evidence, current status and future directions. Eur J Anaesthesiol Suppl 1995; 10:8–13.
28. Dugas NN, Lawrence HP, Teplitsky P, Friedman S. Quality of life and satisfaction outcomes of endodontic treatment. J Endod 2002; 28(12):819–27. [CrossRef]
29. Hamasha AA, Hatiwsh A. Quality of life and satisfaction of patients after nonsurgical primary root canal treatment provided by undergraduate students, graduate students and endodontic specialists. Int Endod J 2013; 46(12):1131–9. [CrossRef]
30. Presser Lima PV, Fontanella V. Analgesic efficacy of aceclofenac after surgical extraction of impacted lower third molars. Int J Oral Maxillofac Surg 2006; 35(6):518–21. [CrossRef]
31. La Monaca G, Pranno N, Annibali S, Polimeni A, Pompa G, Vozza I, et al. Comparative analgesic effects of single-dose preoperative administration of paracetamol (acetaminophen) 500 mg plus codeine 30 mg and ibuprofen 400 mg on pain after third molar surgery. J Evid Based Dent Pract 2021; 21(4):101611. [CrossRef]
32. Gopikrishna V, Parameswaran A. Effectiveness of prophylactic use of rofecoxib in comparison with ibuprofen on postendodontic pain. J Endod 2003; 29(1):62–4. [CrossRef]
33. Mokhtari F, Yazdi K, Mahabadi AM, Modaresi SJ, Hamzeheil Z. Effect of premedication with indomethacin and ibuprofen on postoperative endodontic pain: a clinical trial. Iran Endod J 2016; 11(1):57–62.
34. Al-Rawhani AH, Gawdat SI, Wanees Amin SA. Effect of diclofenac potassium premedication on postendodontic pain in mandibular molars with symptomatic irreversible pulpitis: a randomized placebo-controlled double-blind trial. J Endod 2020; 46(8):1023–31. [CrossRef]
35. Nagendrababu V, Pulikkotil SJ, Jinatongthai P, Veettil SK, Teerawattanapong N, Gutmann JL. Efficacy and safety of oral premedication on pain after nonsurgical root canal treatment: a systematic review and network meta-analysis of randomized controlled trials. J Endod 2019; 45(4):364–71.
36. Srivastava K, Arora A, Kataria A, Cappelleri JC, Sadosky A, Peterson AM. Impact of reducing dosing frequency on adherence to oral therapies: a literature review and meta-analysis. Patient Prefer Adherence 2013; 7:419–34. [CrossRef]