International Journal of Medical and Pharmaceutical Research

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Available online on: https://ijmpr.in/

Original Article

A Randomized, Controlled, Assessor Blind, Comparative Study to Evaluate Efficacy and Safety of Polmacoxib and Ibuprofen+ Paracetamol in Endodontic Pain

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Received: 22-12-2025
Accepted: 15-01-2026
Available online: 31-01-2026

ABSTRACT

Background: NSAIDs are effective in endodontic pain, but they have many gastrointestinal adverse effects. Polmacoxib is a novel COX-2 inhibitor with carbonic anhydrase inhibitory activity that has potential benefits.
Objectives: The primary objective was to compare the analgesic efficacy, and the secondary objective was to compare the safety of Polmacoxib with the combination of Ibuprofen and Paracetamol.
Methods: This was a prospective, randomized, assessor-blind, parallel-group, active-controlled study conducted in adult patients with endodontic pain. Eligible patients (n=221) were allocated in a 1:1 ratio to either Polmacoxib 2 mg once daily (Group A; n=109) or a combination of Ibuprofen and Paracetamol 400/325 mg three times daily (Group B; n=109) for two days. Patients who adhered to the protocol were analyzed (Group A: n=105; Group B: n=105). The primary endpoint was to evaluate the changes in the Visual Analogue Scale (VAS) and Numerical Rating Scale (NRS) at 6, 12, 24, and 42 hours from baseline 0 hours. The secondary endpoint was evaluating the number of treatment emergent adverse event (TEAE).
Results: Pain scores expressed as mean and standard deviation were comparable between groups at baseline 0 hours (Group A= NRS: 4.57 ± 2.05, VAS: 4.08 ± 2.06; Group B= NRS: 4.53 ± 2.21, VAS: 4.06 ± 2.40). Analysis of variance (ANOVA) showed a statistically significant reduction in NRS and VAS scores over time in both groups [Group A= NRS: 38.39 (p-value < 0.0001), VAS: 36.80, (p-value < 0.0001); Group B= NRS: 51.98, (p-value < 0.0001), VAS: 50.50, (p-value < 0.0001)]. However, no statistically significant differences were observed between groups at any time point [independent t-test value for NRS at 6 hours: 0.12 (p-value=0.89), 12 hours: 0.28 (p-value=0.77), 24 hours: 0.48 (p-value=0.62), 42 hours: 0.10 (p-value=0.91); independent t-test value for VAS at 6 hours: 0.6 (p-value=0.95), 12 hours: 0.22 (p-value=0.82), 24 hours: 0.49 (p-value=0.69), 42 hours: 0.16 (p-value=0.87)]. The TEAE were 11.4% in Group A and 14.3% in Group B, with gastrointestinal events being the most common. No serious adverse events were reported.
Conclusion: Polmacoxib and the combination of Ibuprofen and Paracetamol demonstrated comparable efficacy and safety in the short-term management of endodontic pain.

Keywords: *Acute pain, Dental pulp disease Endodontic pain, Ibuprofen, Paracetamol, Polmacoxib.*

INTRODUCTION

Endodontic pain refers to pain originating from pulp tissue. It can be an inflammatory reaction to dental caries, irritants, trauma, or infection. (J.R et al., 2024)

Oral diseases affect more than 3.7 billion people globally; the most prevalent is untreated dental caries, affecting 2.3 billion individuals, which is one of the main cause for endodontic pain.(WHO Oral Health Factsheet, n.d.) (WHO Global Strategy and Action Plan on Oral Health 2023–2030, n.d.)

In India the prevalence of untreated caries is 28.8%. (World Health Organization. Oral Health Country Profile: India. Geneva: World Health Organization; 2022., n.d.)

To alleviate the pain Non-steroidal anti-inflammatory drugs (NSAIDs) are the first line of treatment. They exert their therapeutic effect by inhibiting cyclooxygenase enzyme and thereby reducing prostaglandin (PG). Non-selective COX inhibitors (COX-1 & 2) Ibuprofen and paracetamol in a fixed-dose combination are commonly used for treating endodontic pain.(González-Barnadas et al., 2020)

However, there is a high risk of adverse events, including GI bleeding and ulcers, impaired renal function and hypertension, and bleeding tendency because of the inhibition of constitutive COX-1 that is involved in physiological functions.(Lee et al., 2017)

To reduce the gastrointestinal side effects of nonselective COX inhibitors, selective COX-2 inhibitors (aka coxibs) were developed. They have a longer half-life, hence they require once daily dosing. They inhibit the inducible COX-2 without affecting COX-1 but several studies have reported a higher risk of heart attack, stroke, hypertension, and myocardial infarction. (Kim et al., 2015; Lee et al., 2017)

The dose-dependent inhibition of COX-2 leads to inhibition of production of cardioprotective prostaglandin- I2 (PGI2) without reduction in thromboxane A-2 (TXA2). This eicosanoid imbalance causes platelet dependent thrombosis. Due to this, Valdecoxib and Rofecoxib were removed from the market.(Huber & Terezhalmy, 2006; Kim et al., 2016)

There was a need for a COX-2 inhibitor with fewer cardiovascular side effects. The recently approved drug Polmacoxib exhibits a dual inhibitory action on COX-2 and carbonic anhydrase (CA).

It has negligible effect on overall CA functioning but at sites where CA and COX-2 coexist, Polmacoxib has higher affinity for CA than COX-2. There is abundant CA in the cardiovascular system, which reduces the COX-2 inhibiton and hence the cardiovascular side effects. Whereas in the inflamed tissue CA levels are not high but it has increased levels of COX-2 that is inhibited by the drug completely, resulting into reduction in pain.(Kim et al., 2016; Lee et al., 2017)

There are few studies showing the efficacy of Polmacoxib in osteoarthritis but in our knowledge there is no data available regarding its efficacy in endodontic pain.

Although multiple studies have compared the analgesic efficacy of various coxibs with other NSAIDs and opioid–paracetamol combinations in dental pain, and a few have evaluated Polmacoxib in osteoarthritis, there is currently no evidence regarding its effectiveness in endodontic pain. (Huber & Terezhalmy, 2006). Hence, here we hypothesize that Polmacoxib provides better efficacy and safety compared to the combination of Ibuprofen and Paracetamol in the treatment of endodontic pain.

METHODOLOGY

Study design:

In this prospective, randomized, assessor-blind, parallel-group, active comparator-controlled study to compare the efficacy and safety of Polmacoxib vs the Combination of Ibuprofen and Paracetamol in patients suffering from endodontic pain. The study was done to compare Polmacoxib and the combination of Ibuprofen and Paracetamol in terms of efficacy and safety.

The study was conducted in accordance with the Good Clinical Practice guidelines of the International Conference on Harmonisation and the ethical principles of the Declaration of Helsinki.

The study was conducted as a part of an academic project. The study protocol was reviewed, and it was approved by the Institutional Ethics Committee of the tertiary care hospital(approval number). The study was conducted from 08/01/2024 (first patient enrolled) to 27/02/2025 (follow-up visit of last patient). Informed consent was taken before enrollment of every patient.

There was no public or patient involvement in designing, conducting, or reporting during the study. There were no changes in the original protocol after the study was initiated.

Study setting:
Patients were recruited from the dental OPD in a tertiary care hospital on an outpatient- basis by dentists after diagnosing their pain to be of endodontic origin.

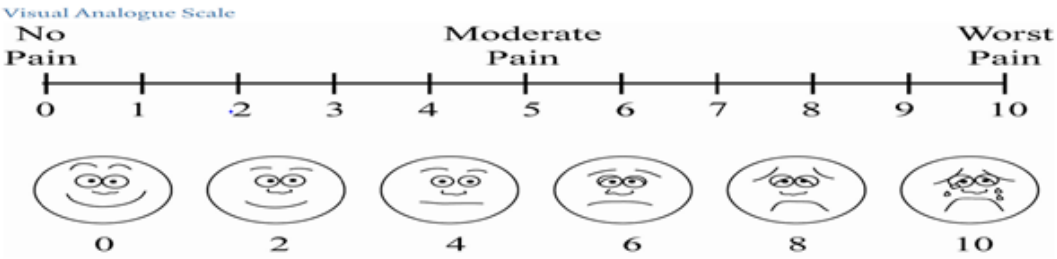
Participant eligibility:
Adult patients aged 18- 60 years with endodontic pain and willing to give consent were included.

Patients were excluded if they met any of the following criteria during the screening: were pregnant or lactating females, were allergic to the drug, presented with gastritis, had a history of smoking/alcohol addiction/recreational drug use, were undergoing a cardiac procedure within 6 months, had systemic steroid use, or had any major systemic illness that could interfere with results.
Patients were withdrawn from analysis if they met any of the following criteria during follow-up: didn't take the study medication, used any analgesic other than the study medication, and loss to follow-up.

Intervention and comparator:
Patients who met the eligibility criteria and gave consent for participation were prescribed either Capsule Polmacoxib 2 mg per oral once daily for 2 days or Tablet Ibuprofen + Paracetamol 400/325 mg per oral thrice daily for two days according to their randomization group. Use of analgesics other than the study drugs and systemic steroids was prohibited. In case of any untoward side effect/ medical situation patients were advised to report and appropriate treatment was provided by the dentist.

Outcome:
The primary objective was to compare the analgesic efficacy of Polmacoxib and the combination of Ibuprofen and Paracetamol by evaluating the changes in Visual analogue scale (VAS) (Yale School of Medicine, n.d.) and Numerical rating scale (NRS) (Breivik et al., 2008) at 6, 12, 24, and 42 hours from baseline (0 hour) in both the groups.

VAS (modified with the Faces Pain Rating Scale- FPRS): the 11-point scale contained 6 facial expressions. The patient chose the face that best described his pain intensity. Each facial expression corresponded to a number on the scale of 0 to 10, where 0= no pain, 2= mild pain, 4= moderate pain, 6= severe pain, 8= very severe pain, and 10= worst pain possible.



NRS score: the 11-point scale contained whole numbers from 0 to 10, where 0= no pain, 1-3= mild pain, 4-6= moderate pain, 7-9= severe pain, and 10= worst pain ever.

0	1	2	3	4	5	6	7	8	9	10
No pain	Mild pain			Moderate pain			Severe pain			Worst pain ever

The NRS score is easy for repeated use, and one can also verbally describe the pain but it requires numerical understanding, whereas the VAS modified with the FPRS score relies on visual and emotional recognition. The mode of assessment by patient is different, and using them together increases the reliability of pain assessment.

The secondary objective was to compare the safety of Polmacoxib and the combination of Ibuprofen and Paracetamol by evaluating the number of treatment emergent adverse drug events.

Sample size:
The sample size was calculated according to the 28.8% expected prevalence of dental caries, 95% confidence level, absolute precision of 6%, the required sample size calculated using the standard formula for single-proportion estimation was 212. The formula used for calculation was

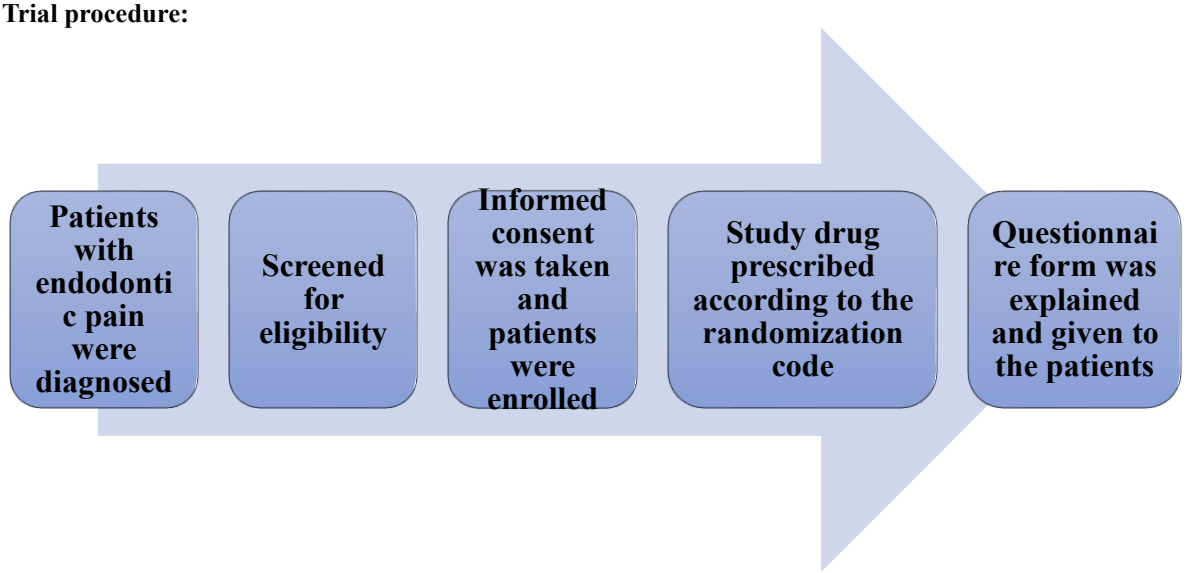
$$n = \frac{Z^2 * p * q}{d^2}$$

n= required sample size, Z= 1.96 (95% confidence interval), p= prevalence/ proportion, q= 1-p (proportion without outcome), d= absolute precision

Randomization:
The patients were randomized into Group A (Capsule Polmacoxib 2mg) (n= 105) and Group B (Fixed-dose combination tablet of Ibuprofen and Paracetamol 400/325 mg) (n=105) in a 1:1 ratio.

Block randomization sequence (fixed block size: 4) (no stratification) was generated with the help of computer-generated randomization code using a web-based platform Sealed envelope.(Sealed Envelope Ltd., 2026)

Trial procedure:



The form included
1) Visual Analogue Scale (VAS) and Numerical Rating Scale (NRS) for pain assessment at 0, 6, 24, and 42 hours.
2) Checklist for side effects.

When the patient reported back for follow-up after 2 days, their questionnaire forms were collected and the readings and were recorded.

The adverse events reported by the patient during the treatment period or as recorded in the questionnaire form collected during the follow-up (passive surveillance) were assessed.

The dentist was responsible for diagnosing and prescribing the study drug. The assessor was responsible for enrollment of the patients, collecting the questionnaire forms during the follow-up visit and analyzing the data. Further use of analgesics was decided by the dentist.

How adherence of participants was evaluated:
Adherence was assessed during the follow-up visit by direct patient interview. Patients were asked questions regarding compliance with the dosing schedule and duration of drug intake. Self-reported adherence was recorded for the per-protocol analysis.

Allocation concealment:
To make sure that the dentist was unaware of the group assignment prior to the drug prescription, the randomization sequence datasheet was locked in a secure place by an independent person. Details of the group assigned was provided on a one-by-one basis to the dentist via telecommunication, thereby ensuring manual allocation concealment.

Blinding:
The assessor was blinded. There were no breaches or emergency unblinding until the data was analyzed.

Statistical analysis:
The data were analyzed on a per protocol basis using SPSS version 29.0 software. The quantitative variables (VAS and NRS) were expressed as mean and standard deviation. The categorical variables (adverse drug reactions) were compared using frequency and percentage.

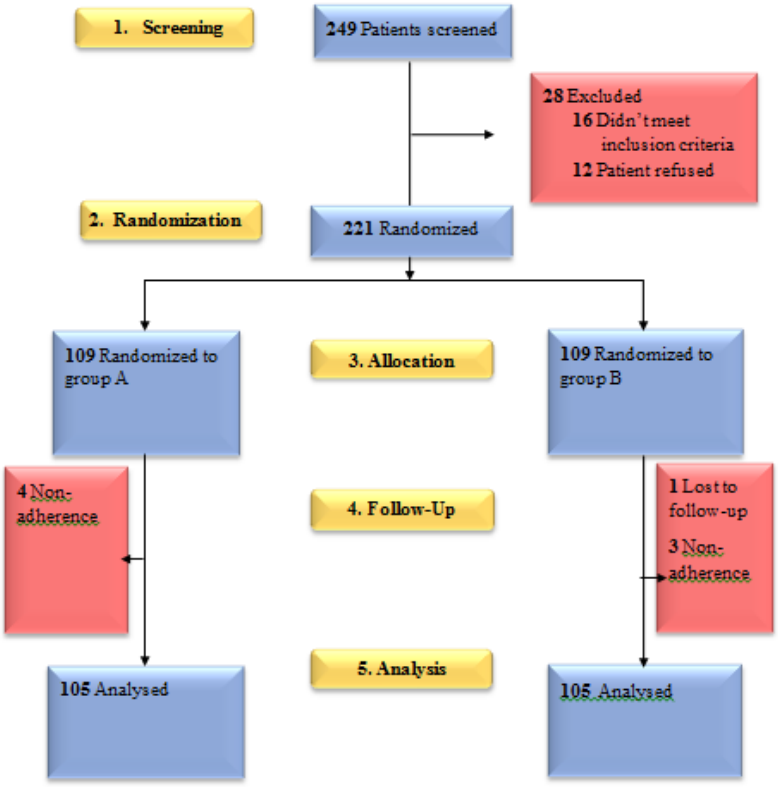
The changes in VAS and NRS within each group over time were analyzed using repeated-measures analysis of variance (ANOVA), with time as within subject factor.

For primary efficacy analysis, changes in VAS and NRS score between two groups were compared using an independent (unpaired) t-test.

For secondary safety analysis, frequency and percentage of adverse drug reactions in both the groups were compared. Missing data were handled by excluding the patients who were lost to follow-up. The analysis also excluded the patients who failed to take the study medication or consumed prohibited medication.

RESULTS

1. Patient Flow Diagram



2. Baseline demographic data: The data is given in Table 1.

Table 1: Patient baseline demographic data

Baseline characteristic	Group A	Group B
Age	37.96	37.82
Gender		
Male	41 (39.05%)	41 (39.05%)
Female	64 (60.95%)	64 (60.95%)
Medical condition		
Diabetes mellitus	3 (2.86%)	3 (2.86%)
Hypertension	6 (5.71%)	7 (6.67%)
Hyperlipidemia	0	1 (0.95%)
Hypothyroidism	4 (3.81%)	4 (3.81%)
Baseline score		
NRS score	4.57 (± 2.05)	4.53 (± 2.21)
VAS score	4.08 (± 2.06)	4.06 (± 2.40)

3. **Primary objective:** comparison of efficacy between group A and group B

a. **Change in NRS score over time:** The variable and analytic test details of the graphical presentation in figure 1 is given in the table 2.

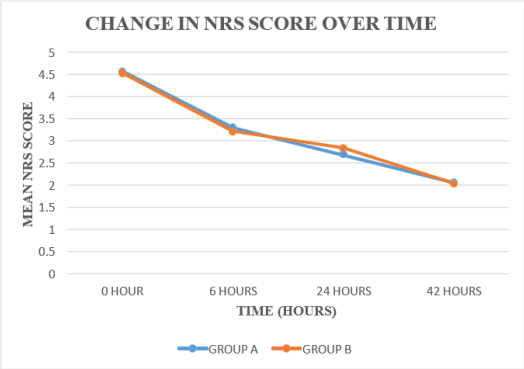


Figure 1: Change in NRS score over time.

Table 2: Comparison of NRS score at different time points in group A and group B

	Group A			Group B			
Time (hour)	Mean	SD	Repeated ANOVA (p value)	Mean	SD	Repeated ANOVA (p value)	Independent t test value (p value)
0	4.57	2.05	38.39 (<0.0001)	4.53	2.21	51.98 (<0.0001)	0.12 (0.89)
6	3.30	2.06		3.22	2.43		0.28 (0.77)
24	2.70	1.89		2.84	2.32		0.48 (0.62)
42	2.07	1.97		2.04	2.04		0.10(0.91)

b. **Changes in VAS score over time**: The variable and analytic test details of the graphical presentation in Figure 2 is given in the Table 3.

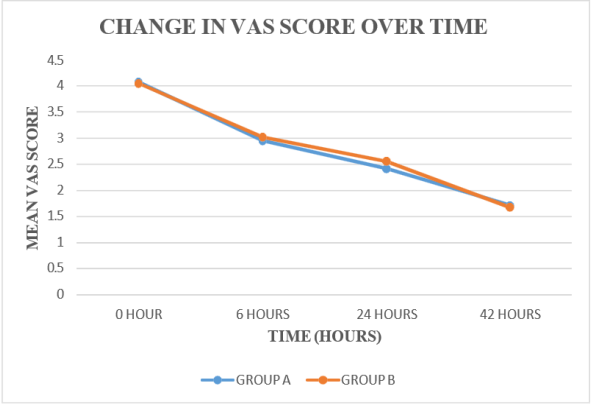


Figure 2: Change in VAS score over time.

Table 3: Comparison of VAS score at different time points in group A and group B

	Group A			**Group B**			
Time (hour)	Mean	SD	Repeated ANOVA (pvalue)	Mean	SD	Repeated ANOVA (pvalue)	Independent t test value (p value)
0	4.08	2.06	36.80 (<0.0001)	4.06	2.40	50.50 (<0.0001)	0.6 (0.95)
6	2.95	2.02		3.02	2.37		0.22 (0.82)
24	2.42	1.92		2.56	2.09		0.49 (0.61)
42	1.71	1.97		1.67	1.82		0.16(0.87)

4. **Secondary objective:** comparison of safety between group A and group B: The data is given in Table 4

Table 4: Comparison of safety between group A and group B

	Group A (n=105)			**Group B (n= 105)**	
Adverse event	f	%	f	%	Total
Treatment emergent adverse event (TEAE)	12	11.43%	15	14.29%	27
Details of all the TEAE					
Gastritis	3	2.86%	5	4.76%	8
Diarrhea	1	0.95%	3	2.86%	4
Vertigo	1	0.95%	2	1.90%	3

Headache	0	-	2	1.90%	2
Itching	2	1.90%	0	-	2
Nausea	2	1.90%	0	-	2
Abdominal pain	0	-	1	0.95%	1
Dizziness	1	0.95%	0	-	1
Drowsiness	0	-	1	0.95%	1
Early menstruation	0	-	1	0.95%	1
Numbness/ tingling in leg	1	0.95%	0	-	1
Rhinitis	1	0.95%	0	-	1

DISCUSSION

The randomized, controlled trial was conducted to assess the efficacy and safety of Polmacoxib compared to the combination of Ibuprofen and Paracetamol using the NRS and VAS scores over a period of 42 hours.

The baseline NRS (Group A: 4.57 ± 2.05, Group B: 4.53 ± 2.21) and VAS (Group A: 4.08 ± 2.06, Group B: 4.06 ± 2.40) scores were comparable in both groups. This indicates that the randomization process was effective, ensuring both groups are well balanced at baseline with respect to confounding factors, including baseline pain perception. This also reduces the likelihood of subsequent pain reduction being confounded by differences in pain perception; hence, it strengthens the validity of efficacy compared during follow-up.

There was a significant reduction in NRS score in both the treatment arm (Group A: 6 hours-3.30 ± 2.06, 24 hours-2.70 ± 1.89, 42 hours-2.07 ± 1.97; Group B: 6 hours-3.22 ± 2.43, 24 hours-2.84 ± 2.32, 42 hours-2.04 ± 2.04). The within-group analysis by repeated measures ANOVA (Group A: ANOVA- 38.39, p value- < 0.0001; Group B: ANOVA- 51.98, p value- < 0.0001) showed that both the treatments were effective in reducing NRS score over time.

There was a significant reduction in VAS score in both the treatment arm (Group A: 6 hours- 2.95 ± 2.02, 24 hours- 2.42 ± 1.92, 42 hours- 1.71 ± 1.97; Group B: 6 hours- 3.02 ± 2.37, 24 hours- 2.56 ± 2.09, 42 hours- 1.67 ± 1.82). The within-group analysis by repeated measures ANOVA (Group A: ANOVA- 36.80, p value- <0.0001; Group B: ANOVA- 50.50, p value- <0.0001) showed that both the treatments were effective in reducing VAS score over time.

The pain reduction in Group B, treated with the combination of Ibuprofen and Paracetamol is 25.6%, 36.9%, and 58.9% at 6, 24, and 42 hours, which is consistent with the previous reports.(Saroj et al., 2022) In that study the pain reduction was 33%, 54%, 70%, and 92% compared to baseline at 6, 24, 48, and 72 hours.

When the two studies are compared, the pain reduction observed in this study appears to be lower. It can be explained by differences in these studies. In this study the patients were included based on the diagnosis of endodontic pain, irrespective of the etiology. Here, most of the patients were of preoperative status or they didn't require tooth extraction for their etiology, whereas the previous study (Saroj et al., 2022) included patients who experienced pain after tooth extraction, where the offending agent leading to the dental problem had been removed.

To the best of our knowledge, there are no published studies about the use of Polmacoxib in endodontic pain, this limits the discussion regarding the efficacy of Polmacoxib in comparison to the previous studies.

The pharmacological action of both the drugs targets the prostaglandin synthesis and leads to symptomatic relief. The repeated ANOVA ensures that the effect observed at different timepoints is systematic and not random. It strengthens the evidence of treatment efficacy.

The between-group analysis done by independent t-tests showed that there was no significant difference between two treatments at any time point for NRS score (p value at 6 hours- 0.77, 24 hours- 0.62, 42 hours- 0.91) as well as VAS score (p value at 6 hours- 0.82, 24 hours- 0.61, 42 hours- 0.87). This reflects that both the treatments are effective in producing sustained and meaningful reduction in pain; however, there is no treatment that is superior to the other in terms of efficacy. The comparable efficacy despite the different targets can be explained by the likelihood that there is convergence at the level of the prostaglandin-mediated pain pathway.

The safety analysis shows that there was similarity in frequency and type of TEAE. The incidence was 11% in group A and 14% in group B. The gastrointestinal adverse events were the most common TEAE in both groups. COX-2 inhibitors were thought to have less gastric toxicity but indeed have sufficient COX-1 inhibition to cause gastrointestinal toxicity. (K. & G., 2016) This hypothesis explains why mild gastrointestinal side effects were seen in this study and is consistent with the previous reports (M. J. Kim et al., 2015, p. 1). The nature of TEAE was mild, and they were tolerable. It can be because of the short duration of treatment and excluding all the high-risk patients.

No serious adverse events were reported in any group, suggesting that there is no clinically significant toxicity.

The limitations of this study are that the sample size calculated was 212, yet only 210 patients were evaluated in the study due to exclusion during screening and withdrawal of loss to follow-up patients. Yet the final sample size provides a comparable level of precision of 6.1% and is sufficient to meet the study objectives.

Secondly, it was done for a short duration that limits the assessment of long-term efficacy and safety. The treatment response and adverse event profile are likely to be different with long-term treatment, and also short-term follow-up cannot cover reporting of the delayed adverse events.

Additionally, even though the scales used for pain assessment are validated, they are subjective in nature and can be influenced by patient pain perception, leading to bias. However, the similar baseline pain score and repeated assessment at multiple timepoints reduce the likelihood of the reports being influenced by reporting bias.

In conclusion, the Polmacoxib demonstrates non-inferior efficacy and safety compared to the combination of Ibuprofen and Paracetamol in the context of short-term treatment. This study adds the evidence supporting the potential of Polmacoxib to be used as an analgesic for endodontic pain.

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