



# Effect of pre-operative medication with paracetamol and ketorolac on the success of inferior alveolar nerve block in patients with symptomatic irreversible pulpitis: a double-blind randomized clinical trial

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**Background:** The efficacy of local anesthesia decreases in patients with symptomatic irreversible pulpitis. Therefore, it was proposed that the use of premedication with an anti-inflammatory drug might increase the success rate of pulpal anesthesia in mandibular posterior teeth with vital inflamed pulp.

**Methods:** One hundred thirty-four patients who were actively experiencing pain willingly participated in this study. The Heft Parker (HP) visual analog scale (VAS) was used to record the initial pain intensity. Patients were randomly allocated to receive a placebo, 10 mg of ketorolac, and 650 mg of paracetamol. The standard inferior alveolar nerve block (IANB) was administered to all patients using 2% lidocaine with 1:200,000 adrenaline after one hour of medication. After 15 min, the patient was instructed to rate the discomfort during each step of the treatment procedure, such as access to remaining dentin, access to the pulp chamber, and during canal instrumentation on the HP VAS. IANB was considered successful if the patient reported no or mild pain during access preparation and instrumentation. Moderate or severe pain was classified as a failure of IANB and another method of anesthesia was used before continuing the treatment.

**Results:** The rate of successful anesthesia in the placebo, paracetamol, and ketorolac groups was 29%, 33%, and 43%, respectively, and no statistically significant difference was found between the groups.

**Conclusion:** Preoperative administration of paracetamol or ketorolac did not significantly affect the success rate of IANB in patients with irreversible pulpitis. No significant difference was observed between the paracetamol and ketorolac groups.

**Keywords:** Inferior Alveolar Nerve; Ketorolac; Nerve Block; Paracetamol; Placebos; Pulpitis.

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## INTRODUCTION

Pain control is an important aspect of dentistry, particularly during endodontic management of dental

emergencies. Achieving successful anesthesia in patients with acute pulpalgia is a continuous challenge in dentistry. Successful pulpal anesthesia during root canal treatment benefits not only the patient but also the dentist by preventing iatrogenic mishap due to sudden movement

Received: July 13, 2021 • Revised: August 28, 2021 • Accepted: September 14, 2021

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or reactions of the patient [1,2]. The inferior alveolar nerve block (IANB) is one of the most common techniques for achieving pulpal anesthesia during endodontic treatment of mandibular posterior teeth. However, despite good knowledge of human anatomy and anesthetic agents the failure of pulpal anesthesia may be unavoidable, especially during the management of vital inflamed pulp [3-5]. In dentistry, anesthetic failures occur in 13% of cases, and almost 88% of these are experienced following IANB. The failure rate of IANB is higher due to anatomical variations in the position of the mandibular foramen and accessory innervation of the mandibular teeth by other nerves. Moreover, the success rate of IANB is < 30% in patients with symptomatic irreversible pulpitis as compared to 85% to 90% in patients without pulpal inflammation [1,3,6,7]. Various theories have been proposed to explain the mechanism of failure of IANB in patients with symptomatic irreversible pulpitis, but the most valid explanation is the activation of nociceptors by inflammatory mediators such as prostaglandins (PGs) [8]. To increase the efficacy of primary IANB in symptomatic teeth, many strategies have been attempted, such as repeat IANB, increasing the volume of local anesthetic administered using supplemental injection techniques, and preoperative medication with nonsteroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, and anxiolytic agents [9]. In dentistry, NSAIDs are the most commonly administered analgesics. NSAIDs block PGs, that act on voltage-gated sodium channels present in nociceptor neurons and make them highly sensitive to inflammatory mediators such as bradykinin and histamine, thus facilitating pain, hyperalgesia, and decreased anesthesia [10-11].

The effects of premedication with NSAIDs and other drugs during endodontic treatment of patients with symptomatic irreversible pulpitis have been widely studied and mixed results have been reported. Oleson et al. [12] evaluated the efficacy of premedication with ibuprofen 800 mg in patients administered IANB for mandibular teeth and found no statistically significant difference with that of placebo. Noguera-Gonzales et al.

[13] reported a significant improvement in the efficacy of IANB after premedication with 600 mg ibuprofen. In another study, the success of IANB in patients with irreversible pulpitis was compared 1 h after administration of ketorolac and ibuprofen and no significant effect was reported [14].

Potential side effects of long-term use of NSAIDs include bleeding, gastrointestinal ulceration, renal dysfunction, and impaired postoperative bone healing. However, low complication rates with good analgesic effects been reported in several studies with the short-term use of NSAIDs such as ketorolac. Ketorolac is a pyrrolo-pyrrole derivative NSAID that inhibits the conduction in C fibers, which are more resistant than A-delta fibers to local anesthesia, thereby increasing the pulpal anesthesia success rate. Paracetamol is an NSAID with a central analgesic effect and fewer side effects [15-16]. Thus, in patients with irreversible pulpitis, paracetamol as preoperative pain medication may increase the effectiveness of the IANB. Therefore, our study aimed to compare the effects of paracetamol and ketorolac on the success rate of IANB in anesthetizing teeth with vital inflamed pulp, that required endodontic treatment.

## METHODS

This study was designed and conducted with an allocation ratio on a sample of 138 patients of both sexes; aged between 21 and 45 years; voluntarily reporting to the clinics at our institution from January 2018 to January 2019 with the chief complaint of moderate to severe pain in the mandibular first or second molars; and selected using convenience sampling. The sample size was calculated considering an  $\alpha$  level type I error of 0.05, and a  $\beta$  level type II error of 0.20. The power analysis revealed that a sample size of 134 subjects would provide 80% power to detect a 20% difference in the success rates of the three test groups. The study was approved by the institutional ethical committee (No. INT/IEC/2018/

000883). Written informed consent was obtained from all participants. The entire procedure, premedication, and its experimental role at this stage were explained to all patients in their language. Data confidentiality was ensured.

Only patients in good health with no history of taking any medication for at least 12 h before the procedure were selected. Pregnant patients and patients with known allergies to NSAIDs or lignocaine were excluded from the study. We attempted to include patients with similar height and weight (Body Mass Index ranging from 21 to 26 kg/m<sup>2</sup>). Teeth in which root canal treatment was previously attempted, teeth found to be necrotic/partially necrotic during access opening, and teeth indicated for extraction were excluded from the study. Teeth fulfilling the inclusion criteria were subjected to cold testing (Roeko Endo- Frost, Coltene/Whaledent Inc. , Germany) for 10 s, and the intensity of pain felt by the patient was evaluated using the Heft Parker Visual Analog Scale (HPVAS). The HPVAS score is recorded using a 170 mm long line, the extreme left of which depicts no pain, extreme right depicts maximum pain that could ever be experienced, and the midpoint signifies moderate pain [17]. This was explained to the participants and they were told to mark the pain experienced during the cold test on the scale. The HPVAS score was determined as follows: 0, no pain; 1–54, weak or mild pain; 55–114 mm, moderate pain; >114 mm, severe pain. Patients with moderate to severe pain were selected for the study [14]. To ensure masking of drugs, 138 capsules of the same size and color were emptied by a trained dental assistant and divided into three dark bottles, which were randomly allocated three-digit alphanumeric codes and assigned to three groups of 46 patients each: placebo (PLAC), paracetamol (PARA), and ketorolac (KETO) groups. In the PLAC, PARA, and KETO groups, capsules were filled with starch, 650 mg of paracetamol and 10 mg of ketorolac, respectively. To blind the trial, only the alphanumeric code was recorded on the date sheets by a trained assistant who was not operating the patients. Sample selection, diagnostic testing, briefing of the

patient, administration of oral medications, and recording responses were performed by another investigator. This was done to blind the procedure and eliminate bias. Both the operator and patients were blinded to the group allocation. One investigator randomly distributed the selected patients into any of the three groups: PLAC group (placebo), PARA group (650 mg paracetamol), and KETO group (10 mg ketorolac). Patients in the PLAC, PARA, and KETO groups ingested an starch (placebo), 650 mg paracetamol, and 10 mg ketorolac, respectively. After one hour, IANB was administered by another trained and calibrated investigator using a cartridge containing 1.8 ml of 2% lignocaine with 1:80,000 adrenaline (Lignospan special, Septodont, France) and a metallic syringe with a 27-gauge, 35 mm long needle (Septoject; Septodont, France). After 15 min of IANB administration, patients were evaluated for signs/symptoms such as profound lip numbness and tingling sensation. Patient without any signs/symptoms were excluded from the study and were transferred to another trained dentist for management. In patients with profound lip numbness, the involved tooth was isolated under a rubber dam, and a two-step evaluation was performed. The operator subjected the isolated tooth to a second cold test to check the effect of IANB prior to performing an endodontic access opening. The pain response during both steps was recorded using HPVAS. No pain or mild pain response was recorded as successfully anesthetized. Patients complaining of moderate to severe pain during any of the steps were managed using intrapulpal supplemental injection techniques prior to performing subsequent endodontic steps. The tooth was thoroughly debrided chemically and mechanically during the same visit, and a closed calcium hydroxide dressing was placed. The incidence of pain at any point in time during the procedure was recorded using HPVAS and was categorized as within the dentin, within the pulp space, or during instrumentation [14]. Figure 1 shows the Consolidated Standards of Reporting Trials (CONSORT) diagram detailing patient recruitment and follow-up.

The data were recorded on a Microsoft Excel sheet

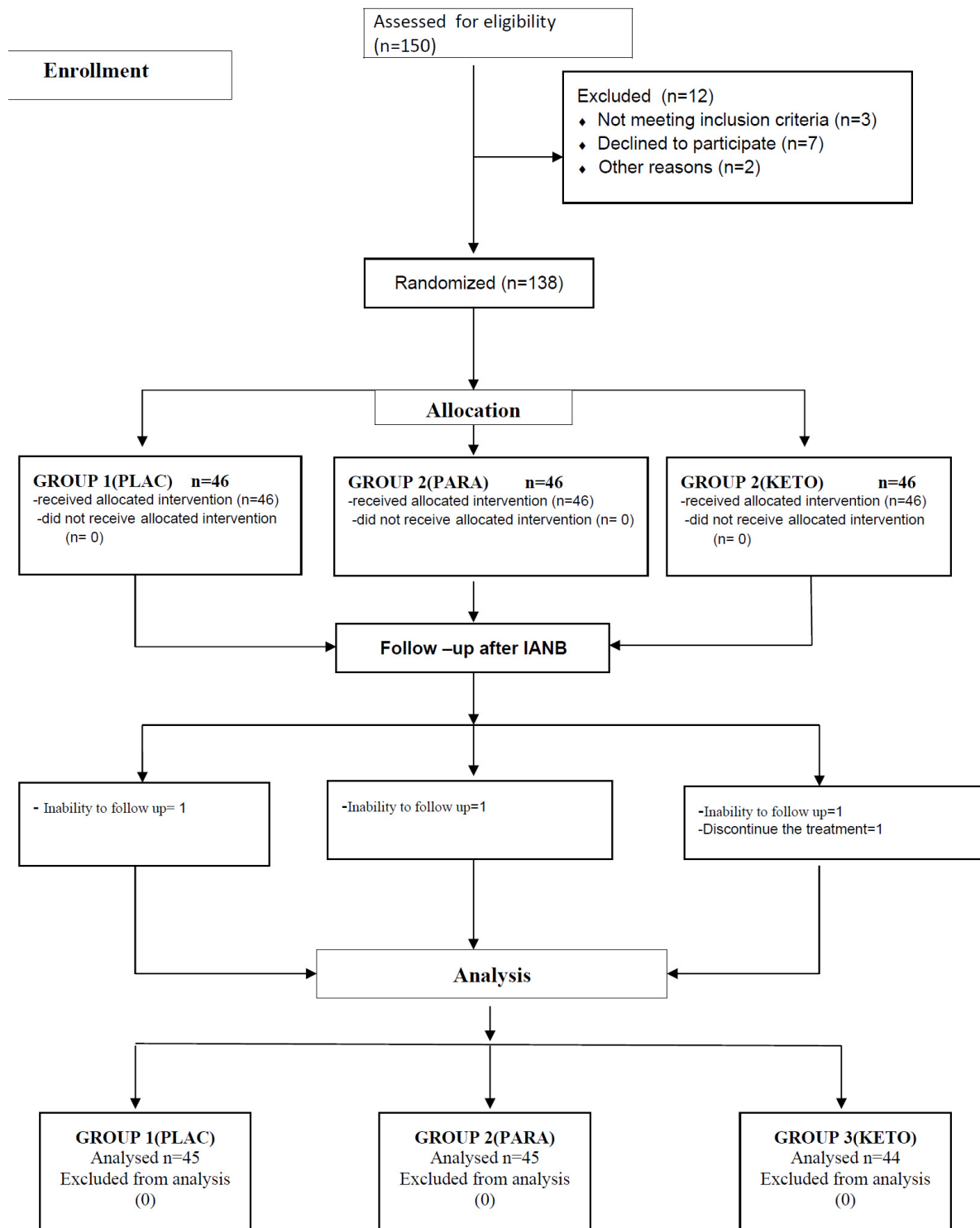


Fig. 1. The Consolidated Standards of Reporting Trials (CONSORT) diagram detailing patient recruitment and follow-up. IANB, inferior alveolar nerve block.

(Microsoft Office Excel 2019) for statistical evaluation using IBM SPSS statistics, (version 25.0; IBM Corp, Armonk, NY: ). Age and pre-and post-injection pain of the patients were summarized using means and standard

deviations. Multiple comparison analyses of variance and post hoc tests were used to determine significant differences at  $P < 0.05$ . The anesthetic success rates of the three groups (PARA, KETO, and PLAC) groups were

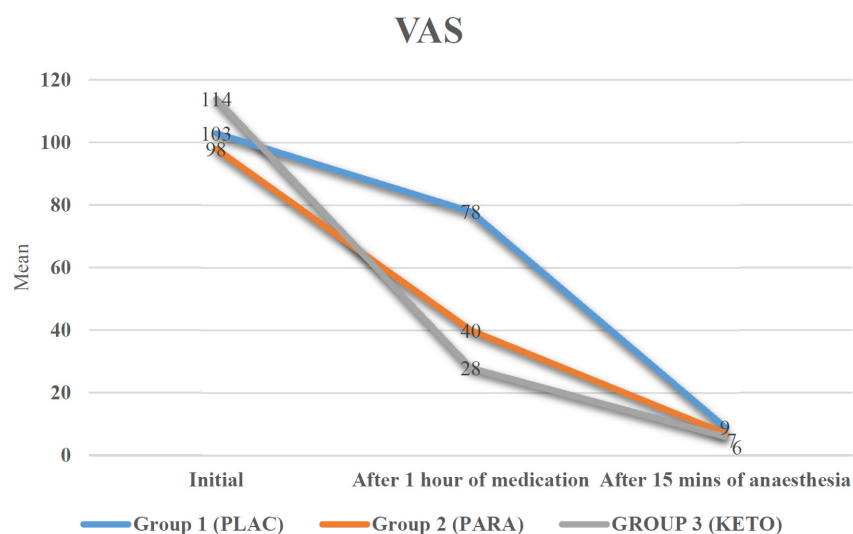
**Table 1.** Comparison of baseline characteristics among the three groups

Characteristics	Group 1 (PLAC) N=45	Group 2 (PARA) N=45	Group 3 (KETO) N=44	P-value
Age	30 ( $\pm$ 8) 22-37	29 ( $\pm$ 7) 24-37	28 ( $\pm$ 9) 21-35	0.18
Gender				0.97
Male	26 (58%)	24 (53%)	24 (55%)	
Female	19 (42%)	21 (47%)	20 (45%)	
Initial pain	103 $\pm$ 38	98 $\pm$ 42	114 $\pm$ 27	0.132
After 1 hr. of medication	78 $\pm$ 15	40 $\pm$ 10	28 $\pm$ 14	0.001
After 15 min. of anaesthesia	9 $\pm$ 3	7 $\pm$ 5	6 $\pm$ 3	0.001

**Table 2.** Comparison of percentage of successful & failure (< &gt; 54 HP VAS) is among the three groups

Anaesthesia	Group 1 (PLAC) N=45	Group 2 (PARA) N=45	Group 3 (KETO) N=44
Failure	32 (45) 71%	30 (45) 67%	25 (44) 57%
Successful	13 (45) 29%	15 (41) 33%	19 (44) 43%

HPVAS, Heft Parker visual analog scale.

**Fig. 2.** Comparison of different mean VAS scores at different periods. VAS, visual analog scale.

analyzed using Chi-square tests.

## RESULTS

One hundred thirty-eight adult patients participated in this double-blind, prospective, randomized clinical trial. Four patients, one, one, and two from the PLAC, PARA, and KETO groups, respectively, were excluded because they did not show subjective symptoms after 15 min of IANB administration. Among the 134 adult patients

included in the study, there were 60 women and 74 men, and the average age was 29 years. Baseline characteristics, such as age and sex, of all the groups are presented in Table 1. No undesirable effect was observed during or after the procedure in any patient ( $P > 0.05$ ). A significant decrease in active pain was observed in all patients after the administration of IANB ( $P < 0.05$ ) (Figure 2).

The overall percentage of successful anesthesia in the PLAC, PARA, and KETO groups was 29%, 33%, and 43%, respectively, as presented in Table 2. However, the

**Table 3.** Comparison of the number of unsuccessful /failure (>54 HP VAS) in control and test groups

VARIABLES	Group 1 (PLAC) n=32	Group 2 (PARA) n=30	Group 3 (KETO) n=25
Within dentin*	(18)	(15)	(13)
HP VAS 54-114	12	09	08
HP VAS > 114	06	06	05
Within pulpal space*	(10)	(09)	(07)
HP VAS 54-114	03	06	05
HP VAS > 114	07	03	02
During instrumentation *	(04)	(06)	(05)
HP VAS 54-114	03	04	03
HP VAS > 114	01	02	02

\*P  $\geq$  0.05; HP VAS, Heft Parker visual analog scale.

difference in successful anesthesia among the three groups was not statistically significant. None of the techniques yielded a 100% success rate. The HPVAS scores for unsuccessful anesthesia (> 54) and the level at which the painful episode occurred are summarized in Table 3. The difference in the incidence of failed anesthesia among the three groups was not statistically significant (P > 0.05).

## DISCUSSION

The most commonly used pharmacological inhibitors of inflammatory pain are NSAIDs. The inhibition of cyclooxygenases (COX) is the main mechanism of action that produces prostanoids (prostaglandins, prostacyclins, and thromboxanes). The potent booster of inflammatory pain which activates neuronal EP1-EP4 receptors and sensitizes nociceptor neurons to other painful stimuli is PGE2. PGE2 acts on proximal ion channels and sensitizes the activity of nociceptors. Through the activation of NF $\kappa$ B in DRG neurons, PGE2 also induces hyperalgesia, which is persistently mediated via PKA and PKC [8,10,18]. These responses mediated by PGE2 are blocked by NSAIDs, which is thought to increase the depth of anesthesia in an inflamed tooth. TTX-r sodium channels (Nav 1.8 and 1.9) have increased expression in the inflamed dental pulp and are resistant to the action of local anesthetics. This is another reason for the failure of the IANB in the inflamed dental pulp tissue. This increased expression of Nav 1.8 and 1.9 is sensitized by

PGs. The effect of NSAIDs on PGs is well known and can potentiate the effect of lignocaine in the presence of inflammation [19-21]. All patients who participated in the present study had active pain before medication, and inflammatory mediators had activated the nociceptors. It is not known whether the anti-nociceptive effects of NSAIDs are limited to new nociception or whether they can revert to activated nociceptors.

The ability of NSAIDs to potentiate the effect of local anesthesia in patients with irreversible pulpitis has been explored previously. Various NSAIDs such as ibuprofen, piroxicam, ketorolac, naproxen sodium, diclofenac, indomethacin, lornoxicam, acetaminophen, and other drugs including steroids and benzodiazepines have been tested in various combinations and dosages. The results are mixed and inconclusive, and no consensus has been reached regarding oral premedication before IANB in patients with irreversible pulpitis [12-15,22]. Noguera-Gonzalez et al. [13] administered 600 mg ibuprofen orally in 25 patients one hour before IANB using 2% mepivacaine with 1: 100000 epinephrine and achieved success in 72% of patients as compared to 36% success in the placebo group. Wali et al. [22] found that oral premedication with 20 mg piroxicam, 50 mg diclofenac potassium, and 550 mg naproxen sodium was effective in 90%, 75%, and 35% of patients, respectively, whereas the placebo, was effective in only 10% of patients. The effects of ibuprofen have been studied more widely, perhaps because ibuprofen is the most commonly used analgesic worldwide [12-14]. Ketorolac is a potent NSAID



and is as effective as morphine and meperidine for pain relief. It inhibits conduction in C-fibers, which are more resistant to local anesthesia than A-delta fibers. Other advantages of ketorolac over other NSAIDs include the lesser likelihood of alteration of bleeding time, acute renal failure in patients with pre-existing renal impairment, and interaction with other drugs and single-dose administration [15-16]. The potential of oral premedication with ketorolac to augment the effects of IANB in patients with irreversible pulpitis has not been well explored. Yadav et al. [23] used 10 mg ketorolac as an oral premedication and found significant results. They studied not only oral premedication but also other variables, such as anesthetic used (lignocaine and articaine) and simultaneous buccal and lingual infiltration with and without 10 mg oral ketorolac. Since this study was not placebo-controlled, it is difficult to directly extrapolate the effects of oral premedication and make a definite statement as to whether it was the premedication or the other variables that specifically influenced the overall result. In a placebo-controlled study by Saha et al. in 2016 [24], oral premedication with 10 mg ketorolac resulted in significantly better anesthesia than 50 mg diclofenac or placebo. In a systematic review and network meta-analysis conducted by Pulikkotil et al. [25], oral premedication with 10 mg ketorolac was found to be the most effective among all NSAIDs. Jena et al. [26] also found that 10 mg ketorolac was significantly more effective than placebo and other experimental drugs. Praveen et al. [27] compared ketorolac with prednisolone and the latter drug was observed to have a more persistent effect than ketorolac or placebo. In contrast, adjuvant ketorolac with nitrous oxide has not been shown to have an additive analgesic effect in patients with symptomatic pulpitis [28].

Paracetamol is the preferred drug for pain in pregnant patients and those allergic to NSAIDs [29]; therefore, its usability as a premedication was also tested in the present study. The potential of paracetamol as a premedication before IANB has been tested mostly in combination with other NSAIDs such as ibuprofen, aceclofenac, and etodolac. Premedication with paracetamol in combination

with other NSAIDs demonstrated efficacy similar to that of the respective NSAIDs alone [25]. Ianiro et al. [30] compared paracetamol alone and in combination with ibuprofen and found no significant difference (71.4% and 75.9% success rate, respectively). However, both medication groups fared better than the control group (46.2% success rate). Contrary results were obtained in the studies by Simpson et al. [31,32], wherein oral premedication with 325 mg paracetamol did not significantly improve the quality of anesthesia after IANB. In their study, the wait time between oral premedication and IANB was 30 min. compared with 60 min. in most other studies. The low dose of paracetamol (325 mg) used and a shortened wait time could have affected the results. On evaluating the studies on the topic, it was found that there is no standardization concerning the anesthetic solution used, although in the majority of studies 2% lidocaine was used as the anesthetic agent. In studies using lidocaine, varying concentrations of epinephrine (1:80000, 1:100000, or 1:200000) were used. We used 10 mg ketorolac and 650 mg paracetamol in this study for the reasons cited above and 2% lignocaine with 1:200000 adrenaline for IANB because it is most widely used at this concentration. Preoperative medications were administered one hour before local anesthesia as the onset of action of most NSAIDs is within an hour. Most patients reported lip numbness 15–20 min after IANB; therefore, a second cold test was performed after 15 min of IANB administration.

In conclusion, both ketorolac and paracetamol improved the success rate of IANB, but the results were not statistically significant. Their role as premedication is not well defined and requires more research with different parameters, such as dosage, time, or combination of drugs.

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**Akhil Rajput:** Formal analysis, Validation, Writing - original draft

**Nidhi Rani:** Investigation, Methodology, Writing - original draft

**Pragnesh Parmar:** Investigation, Methodology

**Amandeep Kaur:** Investigation, Methodology, Writing - original draft

**Vivek Aggarwal:** Conceptualization, Writing - review & editing

**DECLARATION OF INTERESTS:** The authors have no conflicts of interest to declare.

**FUNDING:** None.

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