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ORIGINAL ARTICLE

Evaluation of the Anaesthetic Efficacies of Three Different Formulations of Intraligamentary Injections for Hypertensive Patients with Symptomatic Irreversible Pulpitis: A Randomised Controlled Trial

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ABSTRACT

Objective: This double-blinded randomised clinical trial aimed to compare the efficacy of lignocaine hydrochloride, diclofenac sodium, and ketorolac tromethamine as supplemental intraligamentary injections for intra-appointment pain in normotensive and hypertensive patients with moderate to severe symptomatic irreversible pulpitis.

Methods: Ethical clearance was obtained, and the trial was registered on the Clinical Trial Registry India (CTRI/2020/09/027635; registered on 07/09/2020). A total of 198 patients were divided into two groups: the hypertensive group (Group HYP; n=99) and the normotensive group (Group NOR; n=99). After computerised randomisation and double blinding, participants were subdivided into three subgroups HYPLIG and NORLIG: (lignocaine hydrochloride n=33), HYPDIC and NORDIC: (diclofenac sodium n=33), and HYPKET and NORKET: (ketorolac tromethamine n=33). The preoperative visual analogue scale (VAS) scores were recorded. For the group HYP, blood pressure was recorded, and an inferior alveolar nerve block (IANB) comprising 1.8ml of 2% lignocaine hydrochloride without adrenaline was administered. For the group NOR, IANB with 1.8mL of 2% lignocaine hydrochloride with adrenaline was administered. A supplemental intraligamentary injection comprising one of the experimental drugs was injected into both groups. Endodontic access was gained, and the intraoperative VAS score was recorded. As part of the statistical analysis, paired t tests, Tukey's post hoc test, and ANOVA were performed using SPSS software version 20.

Results: Supplemental intraligamentary injections of diclofenac sodium and ketorolac tromethamine showed a statistically significant difference ($p<0.05$) compared to lignocaine hydrochloride in the reduction of intraoperative pain with no side effects in hypertensive and healthy individuals.

Conclusion: Supplemental injections of both NSAIDs performed better than lignocaine hydrochloride in *reducing intraoperative pain* among healthy and hypertensive individuals.

Keywords: Hypertension, intra-operative pain, intraligamentary injection, ketorolac tromethamine, symptomatic irreversible pulpitis

HIGHLIGHTS

- Conventional local anaesthetic nerve blocks pose a challenge when it comes to the management of hot teeth.
- Supplemental intra-ligamentary injection with the use of NSAIDS reduces the intraoperative pain, and side effects and can be preferred over oral pre-medications.
- Diclofenac sodium and ketorolac tromethamine performed better than lignocaine hydrochloride in reducing intra-operative pain among healthy and hypertensive individuals.

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INTRODUCTION

The primary reason for seeking dental treatment is to eliminate pain. For patients, justifiably, the eradication of twinge takes priority over all other aspects. "Pain is a complex phenomenon, and dental pain, a multifactorial or multi-dimensional experience, involves sensory responses and emotional, conceptual, and motivational aspects." Pulpal pain and periradicular pain are two factors for patients seeking dental care (1). Among teeth with pulpal pain, those with symptomatic, irreversible pulpal inflammation are the most prevalent and challenging to treat and anaesthetise. When a tooth is diagnosed with symptomatic irreversible pulpitis and spontaneous severe pain, it is referred to as a "hot tooth" (2).

Conventional local anaesthetic nerve blocks pose a challenge when it comes to an inflamed pulp. The decline in the success rate of anaesthesia may be due to the formation of lactic acid near inflamed tissues, altered resting membrane potential, or tetrodotoxin-resistant channels (TTXR) (3). TTXR channels are the latest and most accepted reason for the decline in the efficacy of anaesthesia. TTXR channels are present on the inflamed pulp's C fibers, which are 4 to 5 times more resistant to lignocaine hydrochloride (2, 4–7). Various authors have reported that the failure rate of a single inferior alveolar nerve block (IANB) block injection in patients with hot teeth ranges between 30% and 90% (8–10). Buffered (Local Anaesthetic) LA can manage the difficulty of accomplishing anaesthesia in such cases by using other anaesthetics, such as articaine and supplemental injections, such as intraosseous and intraligamentary injections, and by administering medicines preoperatively (2, 11, 12).

The advantages of using VC in dental settings are clear, but its use in hypertensive patients remains controversial (13). Risks associated with VC in the hypertensive population include an increased probability of acute hypertensive or hypotensive episodes, angina pectoris, arrhythmias, and myocardial infarction (13).

Hypertensive patients suffering from hot teeth receive lignocaine hydrochloride without VC (adrenaline), which makes endodontic therapy even more challenging (13). The minimal effect of anaesthesia tends to increase blood pressure and pain due to increased sympathetic activity directly acting on the muscle sympathetic nerve activity controlled by baroreceptors (14).

Alternative pulpal pain management approaches include premedication with nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids (15). The most frequently used NSAIDs in dentistry are aspirin, diclofenac sodium, ketorolac, ibuprofen, and paracetamol, which act by selective or nonselective cyclo-oxygenase1 (COX1) and COX2 inhibitory mechanisms. However, the oral administration of NSAIDs causes gastrointestinal problems (16).

One way to overcome the gastrointestinal disturbances caused by NSAIDs is to administer the drug through the intraligamentary route (16). Intraligamentary injection helps bypass first-pass metabolism in the liver, thus ensuring 100% availability of the drug in the odontogenic region (17, 18). However, a significant amount of solution redirects into the surrounding cancellous bone through the fenestrations in the dental socket rather than being driven down the PDL to the tooth apex (19) A study by Bangerter (20) reported that the periodontal ligament injection continues the foremost widely taught and used supplemental technique.

Although one study investigated the use of prophylactic intraligamentary injection of piroxicam (Feldene) for the management of post-endodontic pain in molar teeth with irreversible pulpitis (16). Various agents like lignocaine hydrochloride and diclofenac sodium have been clinically tried as intra-ligamentary injections, while ketorolac is only used by oral or long buccal injections (21). Since ketorolac was not yet tested by the intraligamentary route, it was selected as one of the experimental groups. Additionally, no study has been conducted thus far to investigate the same in hypertensive patients.

VAS scores are based on self-reported measures of symptoms that are recorded with a single handwritten mark placed at one point along the length of a 10 cm line that represents a continuum between the two ends of the scale "no pain" on the left end (0 cm) of the scale and the "worst pain" on the right end of the scale (10 cm)" (19).

Therefore, the present study aimed to compare the anaesthetic efficiency of adjuvant intraligamentary injection of lignocaine hydrochloride, diclofenac sodium, and ketorolac tromethamine on the reduction of intra-appointment pain in healthy and hypertensive patients with symptomatic irreversible pulpitis following the failure of IANB.

The null hypothesis was that there are no differences between the anaesthetic efficiencies of IANB and the adjuvant intraligamentary injection of lignocaine hydrochloride, diclofenac sodium, and ketorolac tromethamine in the reduction of intra-appointment pain in normotensive and hypertensive patients with symptomatic irreversible pulpitis.

MATERIALS AND METHODS

Protocol Registration and Study Design

The study was conducted by the Declaration of Helsinki. Ethical approval was obtained from the Institutional Ethics Committee (SVIEC/ON/DentBNPG18/D19020) and registered in Clinical Trial Registry India (CTRI/2020/09/027635), and written informed consent was obtained from each participant. This study was a randomised, controlled, single-centre clinical trial with parallel experimental groups.

Patient Selection

Inclusion criteria were normotensive individuals and patients with stage 1 hypertension (systolic pressure 130 to 139 mmHg or diastolic pressure of 80 to 89 mmHg) and stage 2 hypertension (systolic pressure of 140 mmHg or higher or a diastolic pressure of 90 mmHg or higher) for hypertension group (22); between 18 to 60 years of age showing deep caries; patients having spontaneous and postural pain concern-

ing mandibular molars with preoperative visual analog scale (VAS) scale of 5 or more on one to 10 point scale, and teeth having delayed response on electric pulp testing. Patients in whom IANB failed to achieve pulpal anaesthesia. Patients with known hypersensitivity to diclofenac sodium, ketorolac tromethamine, and lignocaine hydrochloride; with a history of cardiac surgery in the last six months; pregnant or lactating females; tooth with any fracture or visible crack; developmental anomalies; pathology or open apex related to study teeth; subjects who were taking analgesics or non steroidal anti inflammatory medicines that could change their pain perception were excluded from the study.

Sample Size Estimation

The recruitment of patients for this trial lasted for two years; an average of 2150 individuals with pain were screened. Among these, 198 were selected to participate in this study depending on inclusion and exclusion criteria. The total sample of 198 patients (99 patients per group and 33 per subgroup) with a Standard Deviation (SD) of 0.5 at 95% confidence interval and 80% power was calculated.

Randomisation

After selection, 198 patients were divided into two groups namely hypertension (GROUP HYP;(n=99)) and Normotensive (GROUP NOR; (n=99)) individuals. Further, the co-investigator allocated the subjects into three subgroups using computer randomisation (www.randomizer.org) software. Intraligamentary subgroup: HYPLIG and NORLIG: lignocaine hydrochloride (n=33). HYPDIC and NORDIC: diclofenac sodium (n=33) and HYPKET and NORKET: ketorolac tromethamine (n=33). Allocation concealment was done using sequentially numbered opaque sealed envelopes with an allocation ratio of 1:1:1.

Blinding

The entire procedure was double-blinded to avoid bias. The operator and the patient were both blinded by subgroups. The operator received a syringe loaded with the cartridge of either lignocaine hydrochloride, diclofenac sodium, or ketorolac tromethamine with a 27gauge needle attached to the unit's tip.

Preparation of Customised Cartridge

Customised preparation of cartridges for sodium diclofenac (GCLAM laboratories, Maharashtra, India) and ketorolac tromethamine (Dr. Reddy's, HP, India) was done. Empty cartridges were procured, autoclaved, and a sterile rubber stopper was placed. NSAID drug vials of 30mg/ml were taken and broken from the tip. The sterile 2.5 mL syringe drug was injected into the autoclaved cartridge from the back end (rubber stopper). All aseptic precautions, and voids, if any, were aspirated with a syringe.

A VAS was taken as a parameter to evaluate the pain. It consists of a 10 point scale from no pain (VAS 0) to severe pain (VAS 10). Patients were explained about the same, and pre-operative VAS score was recorded.

Inferior Alveolar Nerve Block

In Group HYP, blood pressure was recorded. A conventional nerve block with 1. 8 mL of 2% lignocaine hydrochloride without adrenaline (Septodont, Lancaster, United States) was injected. In Group NOR, a conventional nerve block with 1.8 mL of 2% local anaesthetic agent 1:200000 lignocaine hydrochloride with adrenaline (X-Cain ADR, GALPHA Lab, Mumbai, Maharashtra) was injected. Patients were asked to wait till subjective or objective symptoms like tingling and numbness of the lower lip, buccal and lingual mucoperiosteum, followed by tongue. The profoundness of IANB was confirmed by electric pulp testing (Gentle pulse, Parkell Inc., Farmingdale, NY, USA), and those showing positive responses on pulp testing even after the IANB block were given supplemental injection from either of the three groups.

Supplemental Injection

A co-investigator loaded the intraligamentary drug of both groups into the intraligamentary unit (Paroject, Septodont, Lancaster, PA, USA). The intraligamentary syringe loaded with the cartridge of lignocaine hydrochloride with adrenaline (1:200000), diclofenac sodium (30mg/ml), or ketorolac tromethamine (30mg/mL) with 27 gauge needle attached to the tip of the unit. The needle was inserted into the periodontal ligament through the gingival sulcus, between the root surface of the tooth and the alveolar crest, until resistance was encountered. A total of four sites, i.e., axial corners, were selected as the site of injection. Per click, 0.06mL amount of the drug was delivered into the tissues. Approximately 0.4 mL of the drug was injected per tooth. Successful delivery was considered when blanching of the tissue was noticed. A Time interval of 5 minutes post-injection was given after intraligamentary to act to its full potential. Later, excavation of caries and access cavity preparation was performed. As soon as the initial drop was achieved in the pulp chamber, again, the intra-operative VAS score was recorded.

Statistical Analysis

Paired t-test was used to compare two groups before and after the VAS scale, while one-way ANOVA and Tukey's Post Hoc test were used to compare the subgroups of group HYP and group NOR. Statistical analysis was performed using SPSS software version 20 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) The level of significance was set at $p \leq 0.05$.

RESULTS

The patients enrolled in the clinical trial are presented on the CONSORT flow diagram. Table 1 describes the demographic data of the patients. Of the 198 patients treated, 93 were male, while 105 were female. The age of 27 patients was between 51–60 years, 35 patients were between 41–50yrs, 52 patients were 30–40yrs, and the rest 83 patients were between 18–29 yrs. mandibular molars with symptomatic irreversible pulpitis were selected.

IANB nerve block with intraligamentary injections of lignocaine hydrochloride, diclofenac sodium, and ketorolac tromethamine was statistically highly significant in reducing the intra-operative pain in NOR and HYP group with symptomatic irreversible pulpitis (p=0.025) (Table 2).

TABLE 1. Comparison of demographic data among both groups

	Age group (years)				Total
	≤30	31–40	41–50	51–60	
Group					
Group-HYP					
Male- 44	40	27	17	15	99
Female- 55	40.4%	27.3%	17.2%	13.1%	100.0%
Group-NOR					
Male -49	43	25	18	13	99
Female -50	43.4%	25.3%	18.2%	13.1%	100.0%
Total	83	52	35	28	198
	41.9%	26.3%	17.7%	13.1%	100.0%

HYP: Hypertensive, NOR: Normotensive

VAS_DIFF is the Visual analog scale pain difference between the preoperative and intraoperative scores of the patient. It shows the statistically significant difference between the pre-operative and intraoperative scores of Group HYP and Group NOR respectively (Table 2).

Statistical analysis of one-way ANOVA and Paired t-test showed all three intraligamentary injecting solutions were highly effective in reducing intra-operative pain in both groups (Fig. 1).

Post hoc Tukey's test was used to evaluate sub-group comparison, which showed no statistically significant differences between the diclofenac sodium and ketorolac tromethamine intra group in NOR and HYP groups (HYPDIC and HYPKET p=0.761) and (NORDIC and NORKET p=0.970). However, a statistically significant difference was seen between lignocaine hydrochloride and diclofenac sodium (HYPLIG and HYPDIC Group p=0.013) (NORLIG and NORDIC Group p=0.037) / ketorolac tromethamine (HYPLIG and HYPKET Group p=0.001) (NORLIG and NORKETGroup p= 0.045) (Table 3).

TABLE 2. Independent T-test showing a pre and intraoperative comparison of pain scores among (Group HYP) and (Group NOR) patients

	Group	N	Mean	SD	t	p
VAS-Pre	Group-HYP	99	8.1515	1.38773	0.105	0.917
	Group-NOR	99	8.1313	1.32208		
VAS-Post	Group-HYP	99	2.0707	1.85303	2.288	0.023
	Group-NOR	99	1.5051	1.61860		
VAS_Diff	Group-HYP	99	6.0808	1.79385	-2.257	0.025
	Group-NOR	99	6.6263	1.60093		

SD: Standard deviation

TABLE 3. Post hoc Tukey's test Comparison of intra-operative VAS score in all the subgroups

Dependent variable	Sub group		Mean difference	p
VAS Group HYP	HYPLIG	HYPDIC	1.242	0.013
		HYPKET	1.545	0.001
	HYPDIC	HYPKET	0.303	0.761
VAS Group NOR	NORLIG	NORDIC	0.969	0.037
		NORKET	0.878	0.045
	NORDIC	NORKET	-0.090	0.970

VAS: Visual analogue scale

DISCUSSION

Statement of Principal Findings

The present clinical trial investigated the effect of supplemental intraligamentary injection on intra-operative pain using NSAIDs and local anaesthesia in healthy and hypertensive patients. Since there was a significant difference between the anaesthetic efficiency of IANB and adjuvant intraligamentary injection of lignocaine hydrochloride, diclofenac sodium, and ketorolac tromethamine on reduction of intra-appointment pain in healthy and hypertensive patients, the null hypothesis was rejected.

Strengths and Weaknesses of the Study

This study provides important insights into the comparative effectiveness of intra-ligamentary NSAID injections versus conventional lignocaine hydrochloride in managing postoperative endodontic pain. A major strength of the study is the use of a validated pain assessment tool—Visual Analogue Scale (VAS)—which has been shown to yield consistent and reliable measures of pain intensity in short time intervals (23). Additionally, the choice to evaluate the effects in hypertensive patients, given the known cardiovascular effects of adrenaline-containing anaesthetics (24).

However, the study has several limitations. Only two NSAIDs—diclofenac sodium and ketorolac tromethamine—were assessed, both sharing a similar mechanism of action. Although ketorolac has greater analgesic potency, its anti-inflammatory effect is not proportionally superior to diclofenac, potentially limiting therapeutic diversity. Furthermore, commercial availability of NSAIDs in cartridge form is limited, posing practical challenges to broader clinical implementation. Systemic conditions were limited to hypertension, and patients with other chronic illnesses were not included, which could have provided more generalizable insights. Also, subjective variability in patient responses to VAS and the potential for non-normal distribution in pain scores present additional methodological limitations.

Strengths and Weaknesses in Relation to Other Studies, Discussing Particularly Any Differences in Results

The success rate of supplemental injections in endodontic therapy has varied widely in previous literature, ranging from 50% to 96% (4, 25). Walton and Abbott reported a success rate of 71% with supplemental injections, increasing to 92% upon reinjection (26), which aligns with the present findings and supports the use of repeated injections for pain control. Similarly, Smith et al. (12) reported improved outcomes after a second periodontal ligament (PDL) injection, and Cohen et al. (9) observed an initial success rate of 74% with supplemental intraligamentary injections, which rose to 96% after reinjection.

Contrary to some of these findings, Moore et al. (26) demonstrated that anaesthetic success is not dependent solely on the technique but on the pharmacological agent itself, as saline in-

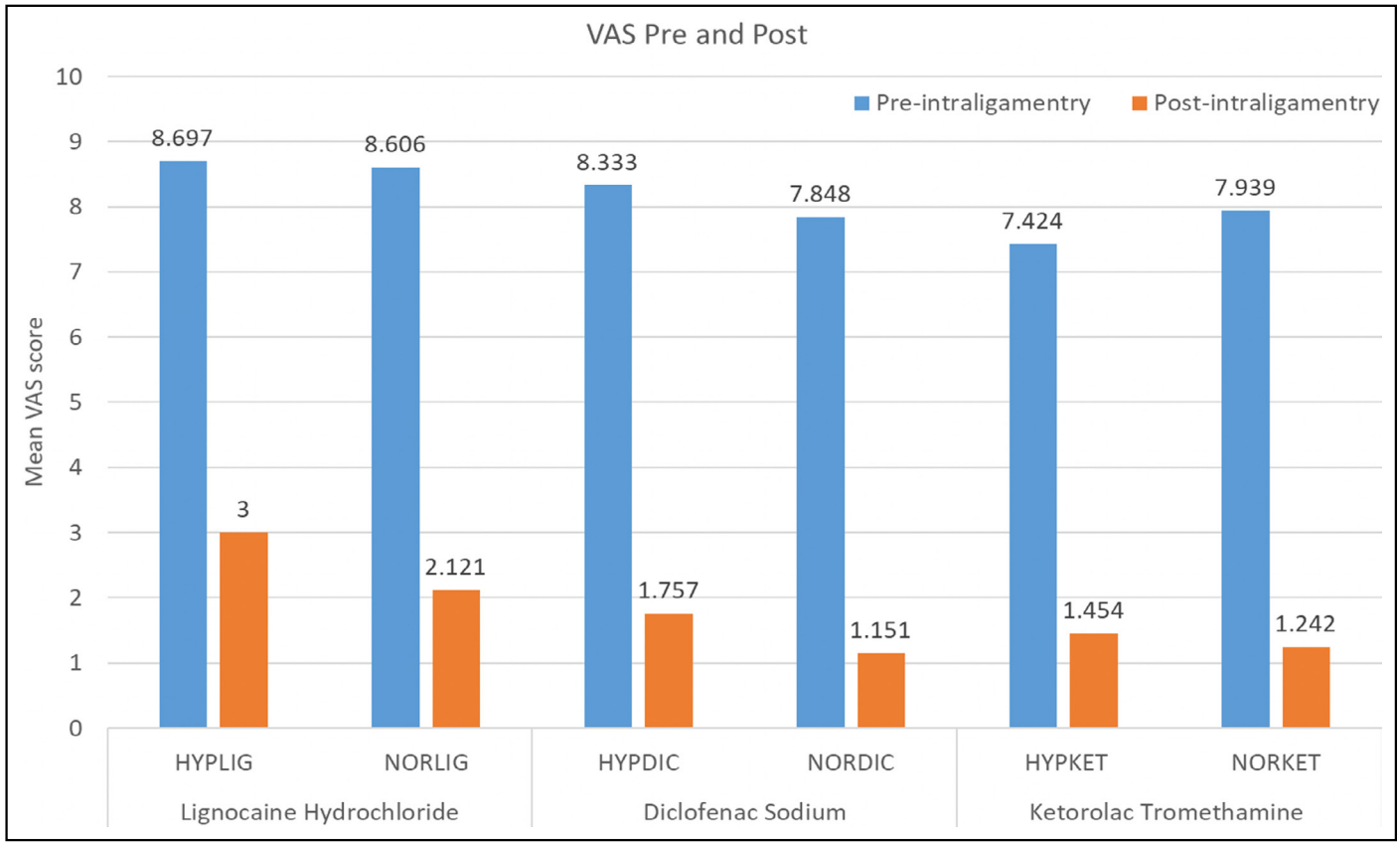

Figure 1. Comparison of VAS at preoperative and intra-operative scores among both groups

VAS: Visual analogue scale

jections failed to provide anaesthesia. This supports the current study's approach in emphasizing drug efficacy over technique.

In terms of patient selection, the study included hypertensive participants based on evidence that adrenaline-containing local anaesthetics can affect blood pressure regardless of baseline values (24). While this adds clinical relevance, it also limits comparisons with studies that included broader populations

VAS was chosen for pain measurement due to its ability to reflect real changes in pain levels and its strong correlation with other self-report tools (27). Bijur et al. (28) also emphasized the reliability of repeated VAS assessments within short intervals, which justifies its use over other scales, such as the numeric rating scale.

Meaning of the Study: Possible Mechanisms and Implications for Clinicians or Policymakers

Findings suggest that locally administered NSAIDs via intraligamentary injections could serve as an effective alternative to systemic administration in the management of postoperative endodontic pain. Jenarthanan and Subbarao et al. (29) found that diclofenac sodium administered through this route provided more effective and prolonged pain relief compared to lignocaine hydrochloride. This is attributed to the complete bioavailability and extended half-life of the drug when delivered locally, with tissue persistence exceeding 11 hours (29).

Although ketorolac tromethamine showed similar analgesic potential to diclofenac, no statistically significant difference was noted between the two in the present study. Mellor et al. (30), however, found no added benefit of intraoral ketorolac in managing irreversible pulpitis, indicating that results may vary depending on the delivery method and clinical context.

Other studies have supported the efficacy of NSAIDs in enhancing anaesthesia. Aggarwal et al. (31) reported modest improvements in IANB success when ketorolac or ibuprofen was used as premedication. Saha et al. (32) documented a 76% success rate for IANB with 10 mg oral ketorolac.

Furthermore, meta-analyses by Pope et al. and Johnson et al. (33, 34) emphasized the that nonselective COX-1 inhibitors like ibuprofen and naproxen are associated with gastrointestinal complications, impaired renal function, and reduced efficacy of antihypertensive. Consequently, localized delivery of NSAIDs via intraligamentary injection may help mitigate these systemic side effects, making it a promising alternative for pain control, especially in medically compromised patients.

Unanswered Questions and Future Research

While the study provides valuable insights, several areas remain to be explored. Future research should expand the range of NSAIDs examined via the intraligamentary route to assess their comparative efficacy and safety. Given the pharmacological differences among NSAIDs, broader evaluations may identify more effective agents suited for this method of administration.

Additionally, the development and commercialization of various NSAIDs in cartridge form would support clinical feasibili-

ty. The current study focused solely on hypertension as a systemic factor, excluding patients with other chronic conditions such as diabetes, cardiovascular disease, or renal impairments, which limits the generalizability of the findings.

To improve data reliability, future studies might incorporate both subjective (e.g., VAS) and objective clinical measures. Larger-scale, multicenter trials would enhance the statistical power of findings and aid in the establishment of standardized treatment protocols for intraligamentary NSAID use in endodontic practice.

CONCLUSION

To conclude, supplemental anaesthesia effectively reduced intra-operative pain in patients with symptomatic irreversible pulpitis. Diclofenac Sodium and Ketorolac Tromethamine performed better than lignocaine hydrochloride in reducing intra-operative pain among healthy and hypertensive individuals.

Disclosures

Ethics Committee Approval: The study was approved by the Faculty of Dental Sciences, Sumandeep Vidyapeeth University, Pipariya, Vadodara, Gujarat, India Ethics Committee (no: SVIEC/ON/DentBNPG18/D19020, date: 15/02/2019).

Informed Consent: Informed consent was obtained from all participants.

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