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Evaluation Of The Efficacy Of Analgesics In Patients With Symptomatic Apical Periodontitis In Terms Of Number Needed To Treat: A Double Blind Randomized Controlled Trial

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Abstract
Aim:
The study aimed to evaluate the efficacy of analgesics in patients with acute apical periodontitis (AAP) using the Number Needed to Treat (NNT) model.
Material and Methods:
Patients diagnosed with AAP without periapical lesions, with or without periodontal ligament (PDL) widening, and those who rated their pain at the 4 cm or above level on the Visual Analogue Scale (VAS) were selected for this study at the dental institute. The patients were randomly divided into four groups, each consisting of 50 individuals.
- ***Group B*** *received Ibuprofen 400 mg*
- ***Group C*** *received Ketorolac 10 mg*
- ***Group D*** *received Diclofenac Sodium 100 mg*
- ***Group A*** *(Control) received a placebo following the completion of the first dental appointment*

A questionnaire containing the Numerical Rating Scale (NRS) was administered to each patient to record their pain intensity at intervals of 6, 12, 24, 48, and 72 hours after administration of the medication.
Results:
The Kruskal-Wallis test was employed to analyze the data. The NNT values were:
- ***Group B (Ibuprofen):*** *2.17*
- ***Group C (Ketorolac) and Group D (Diclofenac Sodium):*** *1.85 each, both of which were more effective than the control group (Group A).*

Conclusion:
Ibuprofen 400 mg had an NNT of 2.17, which was slightly higher than Ketorolac 10 mg and Diclofenac Sodium 100 mg (both with an NNT of 1.85), indicating that both Ketorolac and Diclofenac Sodium were more effective than Ibuprofen. The highest percentage of pain reduction was observed in the Ketorolac and Diclofenac Sodium groups at the 72-hour mark.
Keywords: *Analgesics, Number Needed to Treat (NNT), NSAIDs.*

INTRODUCTION

Dental pain is a multifaceted process influenced by biological, environmental, biochemical, and psychogenic factors. Postoperative discomfort following root canal therapy is a significant concern for endodontists, dental staff, and patients alike. It has been reported that 25% to 40% of all endodontic patients experience such discomfort post-treatment [1]. The discomfort primarily arises from inflammation of the pulp tissue, which may be either reversible or irreversible. Several factors, outlined below, may influence the decision-making of healthcare providers when prescribing analgesics to manage postoperative pain in these patients.

Endogenous chemical mediators, particularly PGs, play a crucial role in inflammation and associated pain [2]. PGs, specifically the E series (PGE2), are involved in various aspects of the inflammatory process, including vascular dilation, vascular stasis, bone resorption, and pain [3]. These lipids are derived from arachidonic acid and are enzymatically released from cell membrane phospholipids [2].

The first enzyme in the biosynthetic pathway that converts arachidonic acid into prostacyclin and PGs is cyclooxygenase (COX). COX exists in two distinct isoforms: a constitutive form, COX-1, and an inducible form, COX-2, which is notably linked to inflammation and pain [4,5]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed analgesics in endodontics for several reasons. Firstly, pulpal inflammation and necrosis, as well as alterations in the periradicular tissues, lead to the production of inflammatory mediators, such as PGs, which are directly implicated in pain modulation [6]. Consequently, the rationale for pharmacological management of post endodontic pain revolves around the reduction of chemical inflammatory mediators that activate or sensitize peripheral nociceptors, thus affecting pain perception.

Specific treatment strategies include NSAID inhibition of PGs, steroid inhibition of various inflammatory mediators, local anesthetic inhibition of sodium channels, and opioid suppression of central nociceptive processing [7]. PGs' suppression is particularly important since PGs decrease the pain threshold (i.e., induce allodynia) and sensitize nociceptors to other pain mediators [8]. Additionally, while PGs represent only one of many pro-nociceptive inflammatory mediators, it is essential to note that their tissue concentrations correlate with the intensity of pain perceived by patients [6,9], suggesting that NSAIDs may be particularly effective in managing inflammatory pain. Furthermore, NSAIDs are widely available over the counter, and several studies have demonstrated their efficacy in controlling endodontic pain [10,11]. Due to their therapeutic benefits stemming from the suppression of PGs synthesis, NSAIDs are often referred to as a "double-edged sword" [5].

The increasing demand for accessible information on analgesics has led to the development of analgesic league tables, which evaluate the efficacy and side effects of various analgesics [12]. According to the literature, the effectiveness of an analgesic is defined by the proportion of patients who experience at least a 50% reduction in pain compared to a placebo [13]. The relative benefit of an analgesic is quantified using the number needed to treat (NNT), which represents the number of patients who must be treated with an analgesic to achieve one additional beneficial outcome compared to a placebo group [14]. To date, no studies have utilized the NNT model to evaluate the analgesic efficacy in the context of endodontic pain management.

Therefore, the study aimed to use the NNT model to evaluate the efficacy of analgesics in the Indian subpopulation of patients with acute apical periodontitis (AAP).

METHODOLOGY

The study was approved by the Institutional Ethics Committee (Ref no IEC/Cons/31/23) and registered with the Clinical Trials Registry India under registration number CTRI/2024/03/063846. This was a randomized, double-masked, placebo-controlled clinical trial involving four treatment groups. The study was conducted at a dental institute in Greater Noida, where patients were screened based on their baseline pain intensity, which was measured using a Numerical Rating Scale (NRS) prior to sample selection.

Random sequences were generated by an individual not participating in the trial, ensuring allocation concealment. Permuted block randomization was employed, generated using randomization software. Allocation concealment was further ensured by placing the drugs in sequentially numbered, sealed, opaque envelopes, with the randomization code written on the envelope. Once a patient was assigned to a treatment group by final-year postgraduate students, the corresponding number was recorded on the patient's case sheet. The code was decoded only at the conclusion of the trial.The inclusion criteria for the study were patients presenting with symptoms of AAP, without periapical lesions, and with or without periodontal ligament (PDL) widening, provided that they marked a pain level of 4 cm or higher on the NRS. The patients were required to undergo root canal treatment for pain originating from either anterior or posterior teeth.The exclusion criteria included patients under 16 or over 65 years of age, those who had consumed any analgesic within 6 hours prior to their visit, those with a history of allergy to NSAIDs, peptic ulcer disease, renal or hepatic disorders, hemorrhagic conditions, pregnancy, breastfeeding, prior endodontic treatments, or acute apical abscess.Patients meeting the inclusion criteria were informed about the study's nature and invited to participate in the study. A total of 200 patients provided written consent, acknowledging the procedures and potential risks associated with them. The patients were randomly allocated into four groups of 50 each, using balanced block random allocation:

- Group B: Ibuprofen 400 mg
- Group C: Ketorolac 10 mg
- Group D: Diclofenac sodium 100 mg
- Group A (Control): Placebo

The analgesics were administered after the first appointment, and pain intensity was measured using the NRS scale. Root canal treatment was performed in two appointments. The first appointment involved cleaning and shaping the canals using standard aseptic techniques under local anesthesia. The crown-down technique was employed, with sodium hypochlorite and saline used as irrigants. After completing the cleaning and shaping, the canals were dried with paper points, and a calcium hydroxide dressing was placed. The teeth were then sealed with a sterile cotton pellet and an intermediate restorative material. The designated NSAID treatment for the group was given before the patient left the surgery on the first day.

Postoperative pain intensity was assessed at 6, 12, 24, 48, and 72 hours after surgery. Each patient was provided with an "escape" drug, Tramadol, in case they experienced severe pain (7-10 on the NRS) even after taking the test medication. The patients were instructed to report if they required the additional medication, including the time it took to alleviate their pain. At the conclusion of the study (72 hours), the NNT was calculated. The NNT is the inverse of the absolute risk difference (ARD): NNT = 1/ARD. A lower NNT indicates higher analgesic efficacy, which is taken to provide relief. At the end of the procedure (72 hours), the NNT was calculated, which is the inverse of the absolute risk difference (ARD):NNT = 1/ARD. The lower the NNT, the greater the analgesic efficacy.

Sample Size Derivation

The sample size calculation was based on the following parameters:

- Level of significance: 5%
- Power: 80%
- Type of test: Two-sided

The formula for calculating the sample size for clinical trials, assuming the outcome variable is on a ratio scale and testing the null hypothesis (M1 = M2 = M3 = M4) across four intervention groups, was applied. Based on these parameters, the estimated sample size for each group was approximately 50 subjects, resulting in a total of 200 participants across the four study groups.

Statistical Analysis

Data analysis was conducted using the Statistical Package for the Social Sciences (SPSS) version 21 for Windows (Armonk, NY: IBM Corp). Descriptive statistics, including mean and standard deviation (SD), were used to summarize quantitative data. A significance level of $p < 0.05$ was considered statistically significant, with an alpha error of 5% and a 95% confidence interval. The power of the study was set at 80%, with a beta error of 20%.

The normality of data was assessed using the Shapiro-Wilk test. The p-value from the Shapiro-Wilk test was greater than 0.05, indicating that the null hypothesis, which posits that the data does not follow a normal distribution, was accepted. As a result, non-parametric tests, specifically the Kruskal-Wallis test, were applied to analyze skewed data.

RESULTS

Out of 50 subjects in the control group (Group A), 27 (54%) experienced pain at the 72-hour mark. In contrast, only 4 (8%) subjects in Group B (Ibuprofen) had pain at the end of 72 hours, while no subjects in Group C (Ketorolac) or Group D (Diclofenac) reported pain at the same time point. Consequently, the NNT scores were 2.17 for Group B (Ibuprofen), and 1.85 for both Group C (Ketorolac) and Group D (Diclofenac) when compared to Group A (Control). This indicates that both Ketorolac and Diclofenac were slightly more effective than Ibuprofen, as reflected by their lower NNT values (Table 1, Figure 1).

Table 1: Comparison of NNT among different study groups in relation to NRS pain score

	Subjects with pain at End of 72 hours	Absolute Risk Difference (ARD)	NNT
Group A (Control)	27/50 (54%)		
Group B (Ibuprofen)	4/50 (8%)	46%	2.17
Group C (Ketorolac)	0/50 (0%)	54%	1.85
Group D (Diclofenac)	0/50 (0%)	54%	1.85

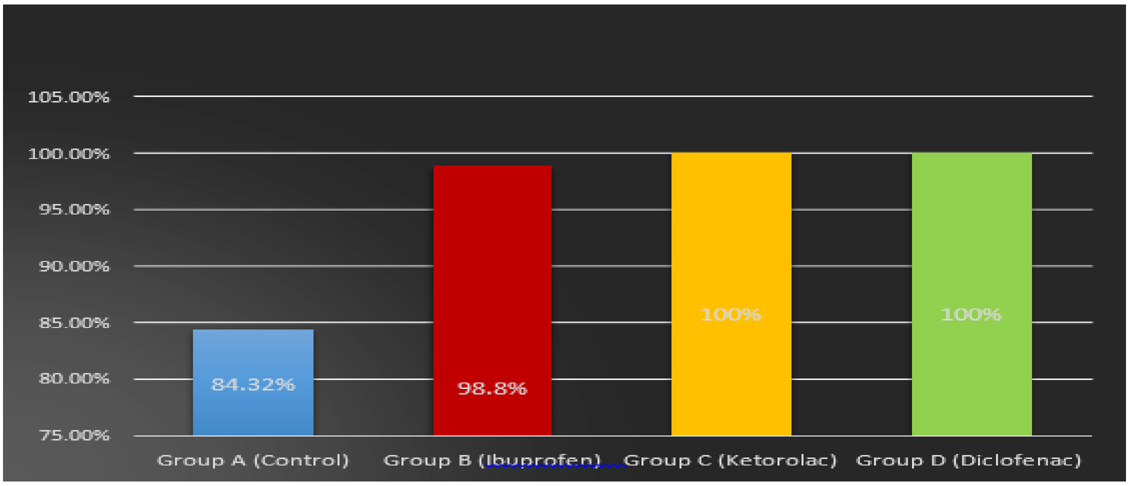

Figure 1: Comparison of NNT among different study groups

The escape drug was used by 19 subjects in the control group, seven subjects in the Ibuprofen group, three subjects in the Ketorolac group, and one subject in the Diclofenac group.

At baseline, the Kruskal-Wallis test revealed no statistically significant differences (p>0.05) among the four study groups, confirming the effectiveness of randomization and ensuring equal distribution across groups (Table 2, Figure 2).

Table 2: Effectiveness of randomization and equal distribution across groups

	Baseline Mean(SD)	6 hrs Mean (SD)	12hrsMean (SD)	24hrsMean (SD)	48hrsMean (SD)	72hrsMean (SD)	% Reduction in pain score
Group A (Control)	6.38 (1.63)	4 (1.23)	3.28 (1.47)	2.44 (1.31)	1.8 (1.27)	1 (1.04)	84.32%
Group B (Ibuprofen)	6.48 (1.31)	3.23 (1.44)	1.4 (1.47)	0.52 (0.9)	0.2 (0.40)	0.08 (0.27)	98.8%
Group C (Ketorolac)	8.32 (1.36)	3.26 (2.05)	0.7 (1.17)	0.08 (0.3)	0 (0%)	0 (0%)	100%
Group D (Diclofenac)	6.64 (1.52)	1.52 (1.97)	0.76 (1.57)	0.1 (0)	0 (0)	0 (0)	100%
p value Kruska WallisHtest	p= 0.387	p=0.017*	p <0.001**	p<0.001**	p<0.001**	p<0.001**	

At 6 hours, pain intensity was highest in Group A (Control), followed by Group C (Ketorolac), Group B (Ibuprofen), and lowest in Group D (Diclofenac). A statistically significant difference (p<0.05) was observed among the groups.

At 12 hours, pain was highest in Group A (Control), followed by Group B (Ibuprofen), Group D (Diclofenac), and lowest in Group C (Ketorolac), with a statistically significant difference (p<0.05) observed among the groups.

At 24 hours, pain intensity remained highest in Group A (Control), followed by Group B (Ibuprofen), Group C

(Ketorolac), and lowest in Group D (Diclofenac), with a statistically significant difference ($p < 0.001$) observed between the groups.
At 48 hours, pain was highest in Group A (Control), followed by Group B (Ibuprofen), with no pain reported in Groups C (Ketorolac) and D (Diclofenac). A statistically significant difference ($p < 0.001$) was observed across the groups.
At 72 hours, pain was again highest in Group A (Control), followed by Group B (Ibuprofen), with no pain in Groups C (Ketorolac) and D (Diclofenac). A higher statistical significance ($p < 0.001$) was observed among the groups.
The highest percentage of pain reduction was observed in Groups C and D (100%), followed by Group B (98.8%), and the lowest pain reduction was observed in the control group (Group A) at 84.32% by the end of 72 hours.

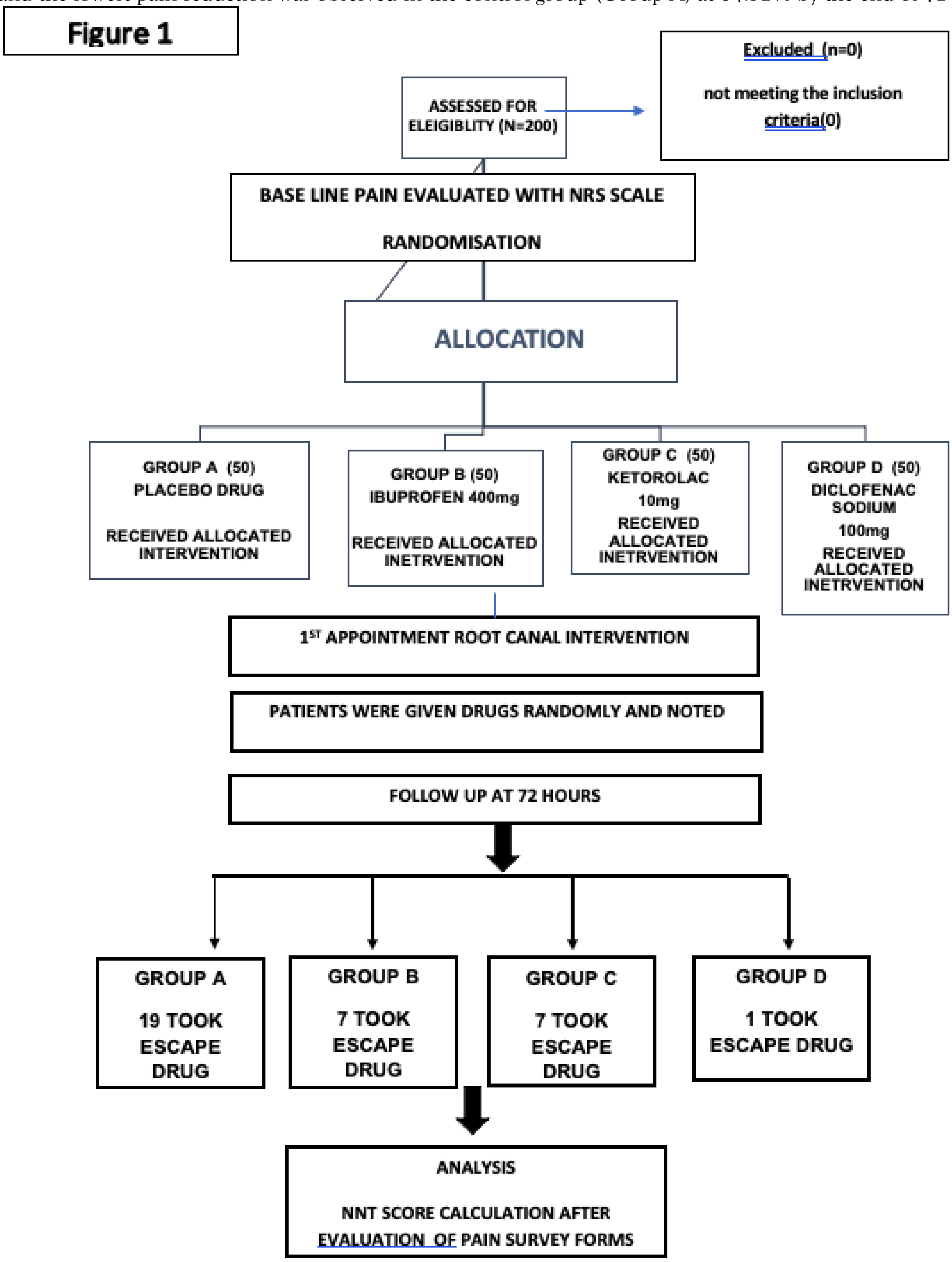

Figure 2: Flowchart of consort

DISCUSSION

Prophylactic NSAID medication has been shown to reduce postoperative pain in both oral surgery (Dionne R A et al) [15] and endodontic models (R K Flath et al) [16]. Sutherland and Matthews [17] conducted a meta-analysis on the efficacy of therapies employed in the emergency management of AAP, which revealed that pre-emptive NSAIDs, in combination with root canal therapy, provided a considerable benefit. The gold standard in clinical research is to quantify a drug's efficacy as the incremental benefit over that of the placebo group, expressed as the NNT.In the present study, a single dose of Ibuprofen 400 mg had a NNT of 2.17 for at least 50% pain relief compared with placebo. In contrast, Ketorolac 10 mg and diclofenac sodium 100 mg had a NNT of 1.85. This is because 8 % subjects in Group B (Ibuprofen) had pain at the end of 72 hrs. None of the subjects in Group C (Ketorolac) and Group D (Diclofenac sodium) had pain at the end of 72 hours.

Ibuprofen blocks both the COX-1 and COX-2 enzymes, providing highly effective analgesic and anti-inflammatory action for post-endodontic pain. In this study, Ibuprofen demonstrated significantly lower pain ratings at 6 hours compared with Group A (Control) and Group C (Ketorolac). However, the pain ratings at 12, 24, 48, and 72 hours for ibuprofen were significantly higher than their rating at 6 hours. This could be attributed to the drug's metabolic half-life, which is between 4 and 6 hours. The finding of this study is in concurrence with the survey in which Rofecoxib was compared with Ibuprofen on post endodontic pain (Gopikrishna V, and A Parameswaran) [18].Attar S et al [19] also found similar results. In a study by Menhinicket al. [20], a combination of ibuprofen with acetaminophen was found to be more effective than ibuprofen alone for managing postoperative endodontic pain. However, a systematic review by Collins SL et al. [21] found no statistically significant difference between the single-dose efficacy of ibuprofen and diclofenac. Some authors have found that 600 mg of ibuprofen significantly reduces post-endodontic pain [22]. Additionally, doses of 50 to 800 mg of ibuprofen were used to relieve pain. Derry et al [23] suggested that 200 mg and 400 mg of ibuprofen had better efficacy in dental studies. In our study, prophylactic 400 mg ibuprofen was found to be more effective in reducing postoperative pain at 6 hours compared with the other drugs. In future studies, researchers should compare different doses of ibuprofen to determine the optimum dose of prophylactic ibuprofen.

The results of this study indicated no statistically significant difference between the analgesic effect of Group C (Ketorolac) and Group D (Diclofenac sodium). This finding may be because the data from the patients who dropped out because of severe or unbearable postoperative pain, and had taken Tramadol 100 mg for relief, were excluded from statistical analysis.Ketorolac tromethamine is a NSAID. It is a member of the pyrrolo-pyrrole group of NSAIDs and exerts its effect by inhibiting the cyclo-oxygenase enzyme system that metabolizes arachidonic acid to PGs. The highest percentage of pain reduction was observed in Group C (Ketorolac), with a 100% reduction at the end of 72 hours. This finding correlates with the results of studies by Sadeghein et al. [24], Forbes et al. [25], and Vangen et al.[26]Group D (Diclofenac sodium) also showed the highest percentage of pain reduction, i.e., 100% at the end of 72 hours, which could be attributed to its ability to block the additional pathways of inflammation, the lipoxygenase pathways, thereby reducing the formation of leukotrienes.It may also inhibit phospholipase A2. Metri et al [27] exhibited postoperative pain at 6, 12, and 24 hours following preoperative diclofenac sodium treatment using a visual numeric scale in 2017.It was found that the efficacy of preoperative administration of diclofenac sodium in reducing post-endodontic pain may aid patients with a low pain threshold in controlling their pain. A similar result was found in a study by Nadia et al.[28]

The findings of this study is in concurrence with the oxford league table of analgesic efficacy where Ibuprofen 400 mg has NNT of 2.5, Ketorolac 10 mg has NNT of 2.6 which is slightly inconsistent with the current study and Diclofenac Sodium 100 mg has the lowest NNT of 1.8 and the highest analgesic efficacy than the other two which is in concurrence with the present study.

CONCLUSION

Within the limitations of the study, it was concluded that Ibuprofen 400 mg had an NNT of 2, which was slightly higher than the NNT of 1.85 observed in both Ketorolac 10 mg and Diclofenac Sodium 100 mg, indicating that the latter two groups were more effective than Ibuprofen in reducing postoperative pain. The highest percentage of pain reduction was observed in the Ketorolac and Diclofenac Sodium groups, both of which showed a 100% reduction in pain at the end of 72 hours. These results suggest that premedication with Diclofenac Sodium and Ketorolac may be beneficial for patients with symptomatic AAP. However, further studies are necessary to confirm the efficacy of other available analgesic options for this patient group.

Conflicts of Interest: Nil
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