Evaluation of NSAIDs in Acute Odontogenic Pain: A Quadriblind Study

Karthik R Mohan, Mohan Narayanan, Pethagounder Thangavel Ravikumar, Saramma M Fenn, Sabitha Gokulraj, Amirthaleka

ABSTRACT
Odontogenic pain refers to pain arising from the teeth or their supporting structures, the oral mucous membrane, the maxilla or mandible, or periodontal ligament membrane. Management of odontogenic pain becomes challenging in the modern era to the clinician due to its diversified etiologies.

Aim: The primary aim is to evaluate the efficacy of NSAIDs in treating acute odontogenic pain due to acute pulpitis, acute periapical abscess, and acute pain after root canal therapy.

Materials and methods: Patients visiting the outpatient department, Vinayaka Missions Sankarachariyar Dental College, Vinayaka Missions Research Foundation, with odontogenic pain due to acute pulpitis and acute periapical abscess were randomly selected. A total of 80 patients were considered and divided into 4 groups (n = 20 were prescribed paracetamol, n = 20 were prescribed ibuprofen, n = 20 were prescribed aceclofenac, n = 20 were prescribed ketorolac). The patients in each group were not aware of the analgesic drug prescribed. (quadriblind drug trial). Pain was analyzed by the visual analog score (VAS) graded from 0 to 10, and the VAS scores were recorded at initial, 30-minutes, 1-hour, and 2-hours intervals.

Result: Ketorolac is better in relieving the odontogenic pain when compared to paracetamol, ibuprofen, and aceclofenac.

Conclusion: Ketorolac is an effective NSAID in relieving the odontogenic pain.

Clinical significance: This study helps to evaluate the effectiveness of nonsteroidal anti-inflammatory drugs for odontogenic pain and helps in identifying the more potent NSAID for odontogenic pain without the use of inferior alveolar nerve block.

Keywords: Analgesics, Irreversible pulpitis, Odontogenic pain.


INTRODUCTION
Pain is an unpleasant noxious stimuli associated with actual or potential tissue damage or associated in terms of such damage. Odontogenic pain refers to pain initiating from the teeth or their supporting structures—the oral mucous membrane, gingiva, maxilla, mandible, and periodontal ligament.1 Insult of the tooth due to dental caries causes the bacterial products to infiltrate the underlying pulp via the dentinal tubules. Or trauma resulting in exposed pulp or dental restoration such as polyacrylic acid that leaches from a glass ionomer restoration or acid etching with 37% phosphoric acid prior to application of composite restoration that are closer to the dental pulp results in pulpal inflammation (pulpitis). If such tooth affected by pulpitis are neglected from root canal treatment procedure, that leads to chronic irreversible pulpitis; if further neglected, such tooth becomes infected with periapical abscess due to the spread of microorganisms through the apical foramen of the affected root into the underlying supportive structure, maxilla and mandible or can cause inflammation of the apical periodontal ligament fibers (apical periodontitis). Dental pain is the most common reason for a patient to seek dentist for treatment. A variety of NSAIDs are used in dentistry today. The primary aim and objective is to evaluate the efficacy of NSAIDs paracetamol, ibuprofen, aceclofenac, ketorolac in acute odontogenic pain due to acute pulpitis, acute periapical abscess, and pain after endodontic treatment.

MATERIALS AND METHODS
Patients visiting the outpatient department, Vinayaka Missions Sankarachariyar Dental College, Vinayaka Missions Research Foundation, with odontogenic pain due to acute pulpitis, acute exacerbation of chronic irreversible pulpitis, if further neglected, such tooth becomes infected with periapical abscess due to the spread of microorganisms through the apical periodontal ligament fibers (apical periodontitis). Dental pain is the most common reason for a patient to seek dentist for treatment. A variety of NSAIDs are used in dentistry today. The primary aim and objective is to evaluate the efficacy of NSAIDs paracetamol, ibuprofen, aceclofenac, ketorolac in acute odontogenic pain due to acute pulpitis, acute periapical abscess, and pain after endodontic treatment.

Inclusion Criteria
Patients aged >15 but less than 40 years with acute odontogenic pain due to acute pulpitis, acute exacerbation of chronic irreversible pulpitis; if further neglected, such tooth becomes infected with periapical abscess due to the spread of microorganisms through the apical periodontal ligament fibers (apical periodontitis). Dental pain is the most common reason for a patient to seek dentist for treatment. A variety of NSAIDs are used in dentistry today. The primary aim and objective is to evaluate the efficacy of NSAIDs paracetamol, ibuprofen, aceclofenac, ketorolac in acute odontogenic pain due to acute pulpitis, acute periapical abscess, and pain after endodontic treatment.

Conflict of interest: None


Source of support: Nil

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pulpitis and acute periapical abscess, and patients revisiting outpatient department for odontogenic pain after root canal therapy.

**Exclusion Criteria**

Patients aged >40 years and less than 15 years, patients with known history of drug allergy to NSAIDS, patients who were not willing to participate or give an informed consent for the study, patients with known history of renal or hepatic disorders, patients who were pregnant, patients who were diabetic, patients who were bedridden or terminally ill, and patients with oral cancers.

**RESULTS**

Among the total \( N = 80 \) population, study groups were divided into 4 groups comprising 20 per group \( (n = 20 \) for paracetamol, \( n = 20 \) for ibuprofen, \( n = 20 \) for aceclofenac, \( n = 20 \) for ketorolac). The mean age group of the population was 30 years. Among the total 80 study population, 57% were males and 43% were females (Fig. 1).

About 33.8% of the population were diagnosed with acute pulpitis, 13.8% were diagnosed with acute exacerbation of chronic irreversible pulpitis, 21.3% were diagnosed with acute periapical abscess, and 31.3% were diagnosed with pain after root canal treatment procedures (Fig. 2).

The comparison of the various NSAIDs drug group with VAS scores is depicted in Figure 3.

The overall effectiveness of the NSAIDs in each conditions of odontogenic pain is depicted in Figure 4.

The logistic regression curve clearly depicts that all the NSAIDS included in the study population reduced the VAS score and hence useful in relieving the odontogenic pain (Fig. 5).

The various research studies of NSAIDS in odontogenic pain was summarized in Table 1.

To find the significant difference in the multivariate analysis, the Kruskal–Wallis test was used and for repeated measures in VAS (visual analog scores), the Friedman test was used, and the probability value 0.0005 is considered as statistically significant level between the study groups.

The Kruskal–Wallis test showed a statistically significant \( p \) value of 0.0005 for ibuprofen, aceclofenac, and ketorolac group except for paracetamol group with a \( p \) value of 0.119, which is not statistically significant (Table 2).

The Friedman test showed a statistically significant \( p \) value of 0.0005 and the Chi-square values for paracetamol, ibuprofen, aceclofenac, and ketorolac group (Table 3).

Ibuprofen (600 mg) is more effective in treating postoperative odontogenic pain after root canal therapy. In endodontic pain.

![Fig. 1: Distribution of gender among the study groups](image1.png)

![Fig. 2: Distribution of diagnosis made among the study population with odontogenic pain](image2.png)

![Fig. 3: Comparison of NSAIDs based on VAS scores](image3.png)

![Fig. 4: Distribution of VAS scores among various NSAIDs](image4.png)
Evaluation of NSAIDs in Acute Odontogenic Pain

Paracetamol has poor ability to inhibit COX in the presence of high
and is the active metabolite of phenacetin and acetanilide.

The analgesic and antipyretic action started from the use of willow
bark (Salix alba), salicylic acid obtained by hydrolysis of the bitter
glycoside obtained from this plant. Sodium salicylate was used for
fever and pain in 1875. The nonsteroidal anti-inflammatory drugs act
synthesis that is released from diseased pulp tissue, but some also

patients, a single dose of ibuprofen sodium dihydrate provides
faster onset of pain relief and a greater reduction in spontaneous
evoked pain compared with ibuprofen acid. The Friedman test
result for ibuprofen, aceclofenac, and ketorolac group showed a
statistically significant value of 0.005. This shows that ibuprofen,
aceclofenac, and ketorolac has a better efficacy in odontogenic
pain due to acute pulpitis, acute exacerbation of chronic irreversible
pulpitis, acute periapical abscess, and pain after root canal therapy
than paracetamol, which is mainly concerned for its antipyretic
action than analgesic action.

**Discussion**

**Brief History of NSAIDs**

The analgesic and antipyretic action started from the use of willow
bark (Salix alba), salicylic acid obtained by hydrolysis of the bitter
glycoside obtained from this plant. Sodium salicylate was used for
fever and pain in 1875. The nonsteroidal anti-inflammatory drugs act
by peripheral pain mechanisms by the inhibition of prostaglandin
synthesis that is released from diseased pulp tissue, but some also
act in central nervous system (CNS) to raise pain threshold.4

Joseph von Mering was the first person who used paracetamol
(acetaminophen) in Humans in 1893. Paracetamol is used for mild-
to-moderate dental pain. Paracetamol belongs to aniline analgesics
and is the active metabolite of phenacetin and acetanilide.
Paracetamol has poor ability to inhibit COX in the presence of high
concentrations of peroxides, as are found at sites of inflammation.
The pharmacological properties have been reviewed by Brune.5
Oral paracetamol has excellent bioavailability. Peak plasma
concentration of paracetamol taken orally occurs within 30–60
minutes and its half-life is about 2 hours. A small proportion
of paracetamol undergoes CYP-mediated N-hydroxylation to
form N-acetyl-p-benzoquinoneimine (NAPQI), a highly reactive
intermediate. This metabolite normally reacts with sulphydryl
groups in glutathione (GSH) and is thereby rendered harmless.
The antipyretic effect of paracetamol is reviewed by Ouellet and
Percival, and Boutaud et al.6,7

Paracetamol is particularly useful when NSAIDS are
contraindicated due to hypersensitivity or history of gastrointestinal
ulceration or bleeding. Paracetamol is hepatotoxic and nephrotoxic
in high doses.

Aceclofenac, a highly selective cox-2 inhibitor, was approved for
medical use in 1992, NSAID of phenyl acetic acid group. It belongs
to class II biopharmaceutical classification system (BCS) based on
its solubility and permeability. Aceclofenac is insoluble in water but
gets conjugated in the human hepatocytes and gets metabolized
to a major metabolite 4-hydroxy aceclofenac. The mean plasma
half-life of aceclofenac is 4–4.3 hours. Aceclofenac acts as a potent
anti-inflammatory drug by decreasing the expression or synthesis
of mediators of inflammation including interleukin (IL-1β), tumor
necrosis factor (TNF), cell adhesion molecules from neutrophils,
selectively inhibits cox-2 enzyme, and prevents the formation of PGE2. Aceclofenac acts by inhibition of cyclooxygenase that is
involved in prostaglandins production that results in pain.
Aceclofenac does not inhibit gastro-duodenal blood flow; hence,
the ulcerogenic potential of gastric mucosal lining of stomach by
aceclofenac is considerably lesser than ibuprofen, hence preferred
by clinicians in the treatment of odontogenic pain when compared
to ibuprofen. The oral dose of aceclofenac for the treatment of
odontogenic pain is 100 mg twice daily. Aceclofenac must not be
prescribed for treating odontogenic pain in pregnant patients as
it may cause patent ductus arteriosus in neonates.

Aceclofenac has better gastric tolerance than other NSAIDS.
Aceclofenac is a novel NSAID that exerts chondroprotective
action by stimulating glycosaminoglycans, the main extracellular
cartilage matrix macromolecule. Aceclofenac significantly
diminished the e-selectin-dependent neutrophil adhesion to
endothelial cells.8

Ibuprofen was discovered by Dr Stewart Adams and his
colleagues in the United Kingdom in the 1950s. Ibuprofen belongs
to propionic acid derivative discovered by British Boots company
during 1960s. Ibuprofen is absorbed rapidly, bound avidly to
protein, and undergoes hepatic metabolism (90% is metabolized
to hydroxylate or carboxylate derivatives. The half-life of ibuprofen
is around 2 hours.9

Ketorolac was developed in 1989 by Syntex Corp. Ketorolac
is a potent analgesic but only a moderately effective anti-
inflammatory drug. Ketorolac has a greater systemic analgesic
than anti-inflammatory activity. It inhibits platelet aggregation
and promotes gastric ulceration. The pharmacology of ketorolac
has been reviewed by Buckley and Brogden.10

Ketorolac has a rapid onset of action, extensive protein
binding, and a short duration of action oral bioavailability is 80%.
Urinary excretion accounts for 90% of eliminated drug, with about
10% excreted unchanged and the remainder as a glucuroninated
conjugate. Ketorolac (administered orally (10 mg twice daily) as
a tromethamine salt used as a short-term alternative to opioids
for about 5 days for the treatment of moderate to severe pain.
Unlike opioids tolerance, withdrawal and respiratory depression do
not occur. The common side effects of ketorolac include nausea,
dizziness, headache, gastrointestinal pain, and somnolence.

Studies by Aggarwal et al., Jena et al., and Yadav et al. have
shown the efficacy of oral premedication with ketorolac in
anesthetic efficacy of inferior alveolar nerve block in patients with
chronic irreversible pulpitis whereas our study shown the analgesic
efficacy of ketorolac in patients with chronic irreversible pulpitis
without inferior alveolar nerve block.

Studies conducted by Pulikkotil and Nagendrababu et al.
have shown the efficacy of ibuprofen in improving the anesthetic
efficacy of inferior alveolar nerve block in patients with chronic
irreversible pulpitis.
Our study correlated with the findings of Curtis et al., who stated that ketorolac effectively reduces severe odontogenic pain within 40 minutes after administration in human subjects, with minimal side effects.² Our study correlated with the study by Praveen et al. who stated that ketorolac showed effective reduction in pain scales when compared with other NSAIDS.³
Sivaramakrishnan et al. concluded in their study that oral ketorolac can be successfully administered as a premedication before conventional inferior alveolar nerve block for endodontic treatment for irreversible pulpitis.19

Our study also correlated with Vieyra et al. who concluded that oral ketorolac was as safe and effective for postoperative pain relief in patients with symptomatic apical periodontitis.20

Our study is contradictory to the study by de Geus et al. who concluded that ibuprofen premedication is beneficial for the success of inferior alveolar nerve block in patients with irreversible pulpitis.22

**Limitations**

The limitation in our study is that our study does not evaluate the efficacy of NSAIDs in other causes of odontogenic pain such as acute pericoronitis, acute pericoronal abscess, and oral cancer. Our study also does not evaluate the analgesic efficacy in medically compromised patients such as uncontrolled diabetes, patients with known renal or hepatic disorders and in pregnant patients.

**Conclusion**

Among the NSAIDs, ketorolac has more potent analgesic efficacy in the treatment of odontogenic pain when compared to other NSAIDs.

**References**

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**Authors Contributions**

Karthik R Mohan contributed in drafting. Mohan Narayanan participated in idea. Ravikumar PT participated in material collection. Saramma M Fenn participated in statistical analysis.


