

## ORIGINAL RESEARCH

# Preemptive Analgesic Efficacy of Diclofenac Sodium for Surgical Removal of Impacted Third Molars

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## ABSTRACT

**Introduction:** Preemptive analgesia is an evolving concept where therapeutic intervention be made prior to the onset of pain. This study was done to evaluate the effectiveness of diclofenac sodium 100 mg as preemptive analgesic administered 1 hour before removal of impacted third molars using split mouth study model.

**Materials and methods:** A randomized placebo control study was done on 30 patients requiring bilateral impacted tooth removal. Patients were administered 100 mg of diclofenac sodium and placebo 1 hour prior to surgery at different appointments. Patients were assessed for intraoperative pain and postoperative pain with visual analog scale on 1st, 2nd, and 3rd postoperative days.

**Results:** Statistical difference was found in pain experience during 1st postoperative day ( $p = 0.0153$ ). Patients after receiving diclofenac sodium 100 mg experienced less pain compared to placebo side. There was no difference found in pain experience between the study and control groups on subsequent postoperative days and overall pain experience.

**Conclusion:** Better management of pain improves quality of life after procedure. Thus, preemptive analgesia may be beneficial in reducing pain intensity. Larger sample blinded studies may prove efficiency of preemptive analgesia.

**Keywords:** Diclofenac sodium, Postoperative pain, Preemptive analgesia.

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## INTRODUCTION

Preemptive analgesia is an evolving concept in pain control and involves administration of analgesic before noxious stimulus sets in. Preemptive analgesia is claimed to prevent central sensitization and therefore reduces

postoperative pain significantly. This prevents “memory” of pain stimulus which would amplify pain and inflammatory response.<sup>1</sup> The concept of preemptive analgesia was first proposed by Crile.<sup>1</sup> Later his proponents gave the term “preemptive analgesia.”<sup>2,3</sup>

Various methods of achieving preemptive analgesia have been employed. These include infiltration with long-acting local anesthetics,<sup>4,5</sup> nerve block,<sup>6</sup> epidural block,<sup>7,8</sup> intravenous analgesics,<sup>9</sup> and anti-inflammatory drugs.<sup>10,11</sup>

Good postoperative analgesia will improve patient comfort and quality of life. Preemptive analgesia may be effective in minor oral surgical procedures as onset of noxious stimulus is known. By decreasing prostaglandin production, nonsteroidal anti-inflammatory drugs (NSAIDs) attenuate the response of the peripheral and central components of the nervous system to noxious stimuli. This property makes NSAIDs ideal drugs to use in preemptive fashion in multimodal postoperative pain management. Diclofenac sodium is the most commonly prescribed NSAID prescribed worldwide, as it has a fast onset and long duration of action.<sup>12</sup>

The aim of this randomized placebo controlled study is to evaluate the effectiveness of diclofenac sodium 100 mg as preemptive analgesic administered 1 hour before removal of impacted third molars using split mouth study model.

## MATERIALS AND METHODS

The study was done on randomly selected 30 patients requiring bilateral impacted tooth removal. Data was collected from three maxillofacial surgery clinics with prior consent. Patients between ages of 18 and 30 years with bilateral impacted tooth were included in the study. Patients with known systemic illness, pregnant patients, and patients with history of recent antibiotic and analgesic therapy, allergy to NSAIDs, history of peptic ulcer were excluded from the study.

Patients were administered 100 mg of diclofenac sodium 1 hour prior to surgery on one side and on the other side placebo was administered at different appointment. Surgical removal of impacted tooth was done under local anesthesia (lignocaine 2% with 1:100,000 adrenaline). All surgeries were performed by single operator and all the procedures were completed within 1 hour. Patients were prescribed diclofenac sodium 50 mg thrice a day for both groups for next 3 days. Patients were assessed for intraoperative pain using pain

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questionnaires immediately after surgery, postoperative pain with visual analog scale (VAS) on 1st, 2nd, and 3rd postoperative day. Tramadol 50 mg was prescribed as rescue analgesic and patients were instructed to inform any additional analgesics taken. Swelling, trismus, and any other complications were noted.

Swelling was assigned the scores as follows:

- No swelling – 0
- Mild swelling – 1
- Moderate swelling – 2
- Severe swelling – 3

Data collected was tabulated and statistically analyzed.

**STATISTICAL METHOD**

The results were presented in number and percentage for discrete data and mean and standard deviation (SD) for continuous data. The mean values were compared using Student’s t test. The mixed model of repeated measure (MMRM) was fitted with subject as a random effect, and visit, sequence, and study group fitted as fixed effect. Unstructured covariance structure was used. The data

was analyzed using Statistical Package for the Social Sciences (SPSS) software (version 18.0). The p-value <0.05 was considered as statistically significant.

**RESULTS**

The study group included 30 patients between age group of 18 and 30 (mean 22.5 Table 1) of which 19 were males and 11 were females, who underwent removal of bilateral impacted third molar (Table 2).

The pain experience evaluated by VAS did not show any statistical difference in intraoperative period between control group (placebo) and study group (diclofenac) (Table 3).

Statistical difference was found in pain experience during 1st postoperative day (p = 0.0153). Patients after receiving diclofenac sodium 100 mg experienced less pain compared to placebo side (Table 3). There was no difference found in pain experience between the study and control group on subsequent postoperative days, as shown in Graph 1.

There was no difference in overall pain intensity experienced at different time intervals (Graph 2). No obvious

**Table 1:** Age distribution

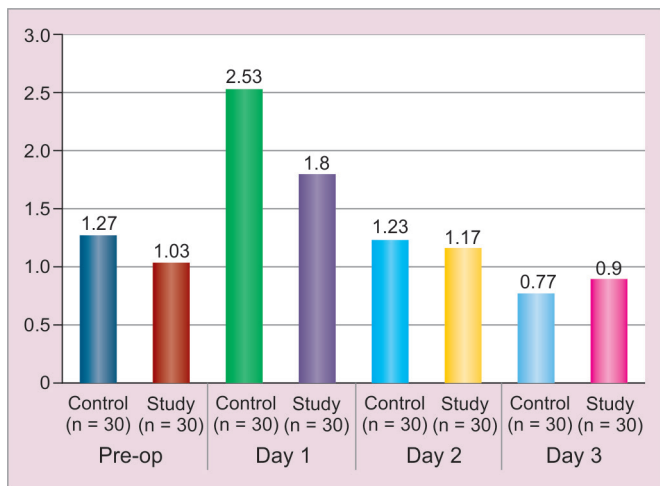
n	Mean	Std. dev.	Median	Minimum	Maximum
30	22.53	2.97	22.50	18.00	28.00

**Table 2:** Gender distribution

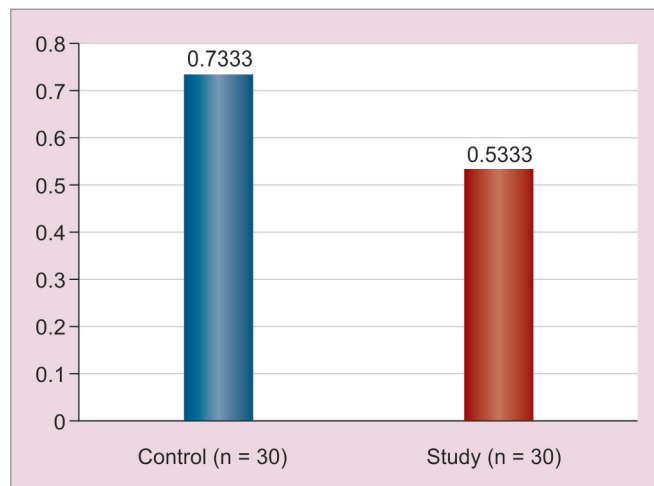
Sex	Frequency	Percent
Male	19	63.33
Female	11	36.67

**Table 3:** Pain experience on VAS

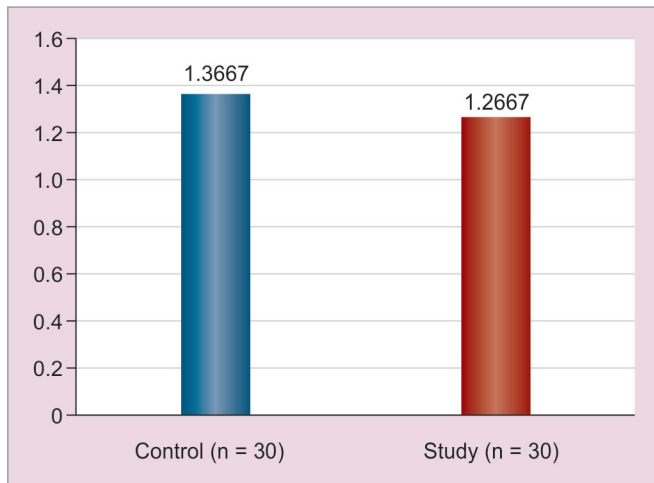
Visit	Group	n	Mean	Std. dev.	Median	Min.	Max.	Diff	SE of diff	t-value	p-value
Intraoperative	Control	30	1.27	1.23	1.00	0.00	4.00	-0.2447	0.3064	-0.80	0.4277
	Study	30	1.03	1.13	1.00	0.00	3.00				
Day 1	Control	30	2.53	1.11	3.00	0.00	5.00	-0.7447	0.2980	-2.50	0.0153
	Study	30	1.80	1.19	2.00	0.00	4.00				
Day 2	Control	30	1.23	0.86	1.00	0.00	3.00	-0.07807	0.2407	-0.32	0.7468
	Study	30	1.17	0.99	1.00	0.00	3.00				
Day 3	Control	30	0.77	0.94	0.50	0.00	3.00	0.1219	0.3136	0.39	0.6988
	Study	30	0.90	1.42	0.50	0.00	7.00				



**Graph 1:** Pain intensity at different time intervals



**Graph 2:** Swelling in two groups



**Graph 3:** Overall pain ratings

difference noted in amount of swelling between two sides (Graph 3).

Comparative analysis was made on surgeries performed first with diclofenac sodium and placebo second time and surgery performed first with placebo and second time diclofenac sodium; order of the drug was not a significant factor.

## DISCUSSION

Preemptive analgesia concept was extensively studied by Woolf and Chong.<sup>13</sup> The use of preemptive analgesia is controversial in clinical settings because human studies have not shown clear evidence of its benefits.<sup>2</sup> Kelly has described the important conditions for effective preemptive analgesia are the establishment of an effective level of antinociception before injury and the continuation of this effective analgesic level well into the postinjury period to prevent central sensitization during the inflammatory phase.<sup>3</sup> The initial response to a noxious stimulus is brief and correlates with the sharp, well-localized initial pain. The second phase of the response is more prolonged and correlates with the dull, diffuse pain experienced after the initial injury. Preventing the initial neural cascade could lead to long-term benefits by eliminating the hypersensitivity produced by noxious stimuli.<sup>14</sup>

Various NSAIDs have been used as preemptive analgesics. Aznar-Arasa et al<sup>11</sup> have administered ibuprofen 600 mg 1 hour prior to surgery. Ong and Tan<sup>15</sup> compared ketorolac and tramadol for third molar extractions. Shah et al<sup>16</sup> have administered 50 mg of diclofenac sodium in their study. Kaczmarzyk et al<sup>10</sup> used ketoprofen 100 mg 1 hour before surgery, and Sisk and Grover<sup>17</sup> have done similar cross-over study on 30 patients with naproxen sodium 550 mg, and administered 30 minutes prior to procedure.

Due to its ease of availability, minimal complications, and effectiveness in pain control after surgical removal of third molars,<sup>18</sup> diclofenac sodium 100 mg has been used in the present study. The name "diclofenac" derives from its chemical name: Dichloranilino phenylacetic acid. Diclofenac was first synthesized by Alfred Sallmann and Rudolf P Fister and introduced as Voltaren by Ciba-Geigy (now Novartis) in 1973.<sup>19</sup>

Diclofenac is efficiently absorbed from the gastrointestinal tract; peak plasma concentrations occur 1 to 2 hours after ingestion in fasting subjects. Even though diclofenac has a relatively short elimination half-life in plasma (1.5 hours), it persists in synovial fluid. The drug is metabolized in the liver and is eliminated by urinary and biliary excretion.<sup>20</sup> Administration of drug 1 hour before procedure to achieve plasma concentration is valid as preemptive analgesia.

Mean time taken for the procedure in study group (24.4 minutes) and control group (26.6 minutes) was similar as duration of procedure can influence the inflammation and therefore pain.

Pain measurement is difficult to establish, because its perception and intensity are multifactorial, encompassing sensorial and affective factors. Although VAS may show deficiencies regarding understanding and perception, it provides a validated and meaningful measure.

The results of our study suggest that there is difference in pain experience, which is less in study group compared to placebo on 1st postoperative day. Shah et al<sup>16</sup> have done similar study with use of 50 mg of diclofenac sodium and have found significant difference in tenderness at 3rd and 5th postoperative day between experimental and control groups ( $p$ -value <0.05). Trismus and swelling, at any stage, did not see any difference between experimental and control groups, which is comparable to our study.

We did not observe any difference in pain intensity on 2nd and 3rd postoperative day, in contrast to studies done by Shah and Sisk. Velásquez et al<sup>21</sup> in their study suggest that ketoprofen is more effective than diclofenac after oral surgery when used as a preemptive analgesic. The methodology followed in their study is comparable to our study. Liporaci Junior<sup>22</sup> showed no significant difference in his results using ketoprofen as the drug for preemptive analgesia. Zacharias et al<sup>23</sup> evaluated preemptive analgesia by separating the patients into three groups: Placebo, diclofenac 100 mg, and methadone 10 mg administered orally 60 to 90 minutes before surgery, and found no significant difference between groups, which is comparable to our study.

Local anesthetic administered will also affect the pain perception. Depth and effectiveness of local anesthesia could be one of the confounding factors in the study.

Three patients reported better pain control with placebo which can be explained by above reason. One of the patients in the study reported with severe pain on 3rd postoperative day, which was diagnosed as dry socket and was considered as an outlier.

Within the study group, the drug was given first in 17 patients and in second surgery in 13 patients. Placebo was given following first surgery in 13 patients and second in 17 patients. Pain scores when drug was given first and second were compared statistically, which showed no difference in pain intensity with change in order of drug. Costa et al<sup>24</sup> have done meta-analysis of NSAID as preemptive analgesic in third molar surgery and have found only two cross-over studies in the literature. They suggested that more homogeneous and well-delineated clinical studies are necessary to determine efficacy of preemptive analgesia.

## CONCLUSION

Extraction of third molar is the most common oral surgical procedure performed, which produces moderate to severe pain postoperatively. Better management of pain improves quality of life after procedure. Thus preemptive analgesia may be beneficial in reducing pain intensity. The underlying principle is that the therapeutic intervention be made prior to the onset of pain, rather than as a reaction to it. Larger sample blinded studies may prove the effectiveness of diclofenac sodium as preemptive analgesia.

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