ABSTRACT

Objective: To compare ketoprofen and diclofenac sodium as a preemptive analgesic in impacted third molar surgery in terms of mean pain score and mean time of first analgesic postoperatively.

Study Design: Double blinded, parallel arm Randomized Controlled Trial (RCT).

Place and Duration of Study: The study was conducted from 15th April, 2016 to 5th November, 2016 at Oral and Maxillofacial Surgery Department of Islamic International Dental Hospital, Riphah International University.

Materials and Methods: Eighty patients requiring surgical extraction of impacted mandibular third molar were selected by using randomized sampling technique. These patients were randomly assigned two groups using lottery method, resulting in sample size of 40 in each group. Preoperatively diclofenac sodium was administered intramuscularly in group A and ketoprofen in group B using double blinded technique. Pain score was measured 3 hours after surgery using visual analogue scale (VAS) and the time of first analgesic consumption post-operatively was recorded in hours. Statistical Package for Social sciences (SPSS version 16) was used for data analysis and Independent sample T test was applied to compare mean pain score and time of first rescue analgesics between two groups with 0.05 as a level of significance.

Results: Results showed that mean pain score was less in Ketoprofen group (3.42±1.08) than diclofenac sodium group (4.02±1.20) with significant p-value of 0.02. Time interval for first analgesic post-operatively was also measured in hours. Results were highly significant revealing prolonged analgesic effect in Ketoprofen group with p-value of 0.007.

Conclusion: Preemptive Ketoprofen provides better and prolonged pain control as compared to Diclofenac Sodium in impacted third molar surgery.

Key Words: Diclofenac Sodium, Ketoprofen, Preemptive Analgesia, Pain Score.

Introduction
Successful pain management is one of the main factors that have allowed surgery to progress to the current status. It relies solely on the surgeon to attempt every possible approach to eliminate postoperative pain and discomfort in patients. Surgical removal of impacted mandibular third molar is a common procedure carried out in routine dental practice which requires reflection of extensive mucoperiosteal flap and bone guttering which leads to the severe post-operative discomfort and pain.

Numerous studies have reported that postoperative pain reaches to its peak at 6-8 hours after surgery and require strong analgesics. Trauma to periosteum and bone during surgery results in the initiation of nociceptive stimulus by generation of prostaglandins and leukotrienes leading to peripheral sensitization and acute pain. Certain active mediators results in transmission of nerve impulses to brain leading to central sensitization and hyper excitability of neurons in central nervous system.

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to relieve pain of mild to moderate intensity and have analgesic, anti-inflammatory and anti-pyretic effects. NSAIDs are non-selective cyclooxygenase (COX) enzyme inhibitors.

Ketoprofen and diclofenac sodium both belong to NSAIDs and are commonly prescribed for pain control after third molar surgery. Biological half-life...
of ketoprofen is 2-2.5 hours and is readily distributed into the central nervous system and crosses the blood brain barrier within 15 minutes, due to its high level of liposolubility. Diclofenac has a biological half-life of 1.2-2 hour.

Preemptive analgesia is administration of analgesics preoperatively before the initiation of nociceptive stimulus and provides better pain relief. It blocks the nociceptive stimulus thus preventing or reducing the peripheral and central sensitization. Idea of preemptive analgesia gained attention in 1980’s. Preemptive analgesia emphasizes on both the prevention and treatment of postoperative pain.

Several studies have compared and documented the effectiveness of two different drugs as a preemptive analgesic in the literature. Velásquez et al compared ketoprofen and diclofenac sodium as a preemptive analgesic in third molar surgery, stating that ketoprofen is better than diclofenac sodium in terms of prolonging the time interval needed for the first analgesic postoperatively. They also reported that ketoprofen is better than diclofenac sodium in terms of postoperative pain control. Mario et al demonstrated that preoperative oral ketorolac plus submucosal tramadol results in reduced consumption of analgesics after third molar surgery than oral ketorolac alone with p-value of 0.04.

There is little or no published research comparing diclofenac sodium and ketoprofen as a preemptive analgesic in third molar surgery in Pakistan. The evidence to suggest which of the two NSAIDS work better for preemptive analgesia is inconclusive. Further research in this area is warranted. This study aims to fill this research gap by comparing the analgesic effect of ketoprofen and diclofenac sodium in providing preemptive analgesia in third molar surgery in a tertiary care dental setup in Islamabad, Pakistan. This study will not only provide an evidence-based practice to minimize the pain intensity after surgical removal of third molar and to reduce the need of taking a large number of analgesics after surgery, but will also serve as a published literature in comparing ketoprofen and diclofenac sodium, so as to serve as a baseline for further research in Pakistan. This study is also expected to improve the patient’s perception towards dental treatment which is mostly considered as a painful experience by patients by providing an evidence-based standard for treating pain and discomfort.

**Materials and Methods**

This was a quantitative research employing double blinded randomized control trial methodology to compare ketoprofen and diclofenac sodium as preemptive analgesics in impacted mandibular third molar surgery. This study was conducted from 15th April, 2016 to 5th November, 2016 at Oral and Maxillofacial Surgery Department of Islamic International Dental Hospital, Riphah International University. We used simple randomized sampling technique and total sample size was 80 patients with impacted mandibular third molar. All patients were between age group 18-35 years. These patients were randomly assigned to group A and B using lottery method. Double blinded technique was used while administering the drugs where neither operator nor patient knew about the medicine being received pre-operatively and all procedures were carried out by the same operator to control bias.

Ethical approval of the study was obtained from the ethical committee of IIDH (Ref. No. IIDC/IRC/2015/03/003). This was a minimal to no risk study as special care was taken to exclude all the patients who have contraindications for NSAIDs. A written informed consent was taken from all the patients before intervention. All the participants of the study were fully explained about the procedure, aim of research and all possible side effects. No participant was forced or pressurized to participate. The participants were ensured that the data will not be used for any other study without their consent. The criteria of inclusion were any patient reporting in the study setting with mesioangular class II class B mandibular impaction during the study period. The criteria of exclusion were any patient with pericoronitis, pain on the day of surgery, medical conditions in which NSAIDs are contraindicated and other oral surgical indications.

Intramuscular (IM) injection of ketoprofen 100mg was given to one group and diclofenac sodium 75 mg to other group 30 minutes prior to the surgical procedure. Then inferior alveolar nerve was blocked with 2% lignocaine and 1:80,000 epinephrine before the procedure was performed. Paracetamol 500 mg was prescribed as postoperative analgesic. Patients were advised to record the pain scores 3 hours
Mean age in group A was 28.98±4.00 SD and that for group B was 29.00±4.42 SD with an insignificant statistical difference \( p=0.97 \) among both groups as shown in table II.

<table>
<thead>
<tr>
<th>Age</th>
<th>Group</th>
<th>N</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>40</td>
<td>28.98</td>
<td>4.00</td>
<td>4.42</td>
<td>0.97</td>
</tr>
<tr>
<td>Group B</td>
<td>40</td>
<td>29.00</td>
<td>4.00</td>
<td>4.40</td>
<td></td>
</tr>
</tbody>
</table>

The results for independent sample T test revealed a significant difference between the mean pain scores at 3 hours among two groups that is; mean pain score at 3 hours was 4.02±1.20 in diclofenac sodium group (A) and 3.42±1.08 in ketoprofen group (B) with \( p \)-value 0.02 at 95% Confidence Interval as shown in table III.

<table>
<thead>
<tr>
<th>Description</th>
<th>Group</th>
<th>N</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain score at 3 hours post-operatively</td>
<td>Group A</td>
<td>40</td>
<td>4.02</td>
<td>1.20</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Group B</td>
<td>40</td>
<td>3.42</td>
<td>1.08</td>
<td></td>
</tr>
</tbody>
</table>

Result clearly showed that ketoprofen provided better pain control than diclofenac sodium as a preemptive analgesic.

Results of independent sample t test for the comparison of time interval in two groups at which first analgesic was taken postoperatively revealed that mean time interval for first rescue analgesic was 2.90±1.24 hours in diclofenac group (A), and was 3.61±1.02 hours in ketoprofen group (B), with \( p \)-value of 0.007 at 95% confidence interval, so there was significant difference between both groups as shown in table IV.

<table>
<thead>
<tr>
<th>Time interval for 1st rescue analgesic (hours)</th>
<th>Group</th>
<th>N</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A</td>
<td>40</td>
<td>2.90</td>
<td>1.24</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>Group B</td>
<td>40</td>
<td>3.61</td>
<td>1.02</td>
<td></td>
</tr>
</tbody>
</table>
pain scores at 3 hours among two groups that is; mean pain score at 3 hours was $4.02 \pm 1.20$ in diclofenac sodium group and $3.42 \pm 1.08$ in ketoprofen group. This demonstrates that patients administered with ketoprofen pre-operatively reported significantly less pain at 3 hours post-operatively as compared to the patients administered with diclofenac. We also report the comparison of time interval in two groups at which first analgesic was taken post operatively. The results of our study revealed that mean time interval for first rescue analgesic post-operatively was significantly less in diclofenac group ($2.90 \pm 1.24$ hours) as compared to the ketoprofen group ($3.61 \pm 1.02$ hours) demonstrating that pre-operatively administered ketoprofen provided longer post-operative pain control than diclofenac sodium.

The results of our study are consistent with a similar double blinded randomized control trial carried out by Velásquez et al. They also compared analgesic effect of ketoprofen and diclofenac and report a significantly prolonged pain control with ketoprofen ($p$ value $0.006$) supporting our results. Velásquez et al, however suggest that the mean pain score at 3 hours post operatively was insignificant between two groups. Tai et al also support result of our study who compared ketoprofen 200 mg and diclofenac 100 mg in multiple doses for 4 days after third molar surgery demonstrating that ketoprofen provides significantly better pain control with the $p$-value of $0.086$. Tai et al, however do not evaluate surgical difficulty level of impaction. Our study includes only mesioangular Class II and Class B impactions and excludes all the cases with surgical time above 60 mins. The results of our study are also consistent with the results of Shah et al, which state that ketoprofen induced a longer duration of analgesic effect.

On the other hand, Niemi et al compared analgesic effect of intravenous (IV) diclofenac 1 mg/kg and ketoprofen 1.35 mg/kg 30 minutes before and 4 hours after surgery, and also prescribed $0.03$mg/kg IV oxycodone as the rescue medication in first 24 hours. The results demonstrate a lower requirement of oxycodone in the diclofenac group in comparison with the ketoprofen with $p$-value of $<0.01$. The difference of the results of this study from our results

<table>
<thead>
<tr>
<th>Serial #</th>
<th>Authors (Reference #)</th>
<th>Drugs compared</th>
<th>Conclusion</th>
</tr>
</thead>
</table>
| 1       | Velásquez et al$^2$    | i)Ketoprofen  
ii)Diclofenac | Prolonged pain control with ketoprofen |
| 2       | Tai et al$^1$, $^3$    | i)Ketoprofen 
ii)Diclofenac | Ketoprofen provided better pain control |
| 3       | Shah et al$^4$        | i)Ketoprofen 
ii)Diclofenac | Ketoprofen provided analgesic effects for longer duration |
| 4       | Niemi et al$^5$       | i)Ketoprofen 
ii)Diclofenac | Lower consumption of analgesics in diclofenac group |
| 5       | Kaczmazik et al$^6$   | i)Ketoprofen preoperatively  
ii)Ketoprofen postoperatively | Postoperative administration of ketoprofen was more effective than pretreatment administration |
| 6       | Manani et al$^1$, $^6$| i)Ketoprofen 
ii)Naproxen | Ketoprofen provided better pain control |
| 7       | Lopez et al$^1$, $^7$ | i)Diclofenac sodium  
ii)Methylprednisolone | Less inflammation with methylprednisolone |
| 8       | Nazar et al$^8$       | i)Diclofenac sodium 
ii)Tenoxicam | Diclofenac sodium provided better pain relief |

It showed that ketoprofen provided pain control for longer duration than diclofenac sodium.

**Discussion**

The practice of treating pain after surgical trauma is now being replaced by preventive approaches that aim to block transmission of the painful nerve impulses before and during surgery$^2$. Pre-operative administration of NSAIDs provides better and prolonged pain relief by blocking the release of prostaglandins and leukotrienes, thus blocking peripheral and central sensitization leading to reduced number of analgesics taken post-operatively and better patient compliance$^3,6$.

This study compares the preemptive effect of IM ketoprofen with IM diclofenac sodium and reports that ketoprofen provides better and prolonged pain control in comparison to diclofenac. The results for independent sample t test in our study clearly revealed a significant difference between the mean pain scores at 3 hours among two groups that is; mean pain score at 3 hours was $4.02 \pm 1.20$ in diclofenac sodium group and $3.42 \pm 1.08$ in ketoprofen group. This demonstrates that patients administered with ketoprofen pre-operatively reported significantly less pain at 3 hours post-operatively as compared to the patients administered with diclofenac.
can be explained on the basis of not considering the level of difficulty of the surgery.
In another study Kaczmarzyk T et al, compared analgesic effect of orally administered ketoprofen 100mg, 60 min preoperatively and 60 min post-operatively and reported that the mean pain score in pre-operative group was 45.7±10.53 and in post-operative group was 33.10±7.91 with p value of 0.031. The study also compared mean time interval in minutes for first rescue analgesic in both groups and reported that the mean time interval for first rescue analgesic is less in pre-operative group (336.75±10.43 minutes) as compared to that in post-operative group (409.93±12.69 minutes) with p-value of 0.0013. Their results showed better and prolonged pain control with post-operative ketoprofen. Our study however does not evaluate the analgesic effect of post-operative administration of NSAIDs.

There is an extensive literature that compares diclofenac and ketoprofen with other medicines in terms of pain control. Manani et al, showed that ketoprofen is more effective in pain control compared with naproxen and have higher analgesic properties.

In another study Lopez et al compared anti-inflammatory properties of diclofenac sodium with methylprednisolone in a third molar surgery and suggests that despite of less inflammation observed in methylprednisolone group, there is no significant difference in the reduction of trismus. Nazar et al compared intramuscular (IM) diclofenac sodium with tenoxicam for the pain relief. It stated that IM diclofenac sodium produced significant pain relief compared to tenoxicam. All studies discussed here are summarized in table V.

The extensive literature supports the results of our study and suggests that pre-operative administration of ketoprofen not only reduces the severity of post-operative pain but also prolongs the onset time of post-operative pain in comparison to pre-operatively administered diclofenac.

There are few limitations in the present study. Age and gender were not matched at the baseline. This may have biased the results since pain threshold may vary across gender and age variations. Another shortcoming is the selection of only mesioangular impaction with class B and type II. Therefore, the results of this study may not be used to ascertain effectiveness of both drugs for other types of mandibular 3rd molar impaction. This study includes sample from just one dental hospital in Islamabad, thus it can affect the generalizability of the results.

There is a need of further and extensive research to compare effects of different types of analgesics in Pakistan, so as to provide an evidence-based approach towards pain free experience for patients in this era of surgical advancement.

**Conclusions**

Based on this study we conclude that preemptive analgesia is a better option in minor oral surgical procedures. Preemptive analgesics works best in the cases of inflammation, reduces the post-operative morbidity and pain by blocking the release of prostaglandins and peripheral and central sensitization of pain. NSAIDs are more commonly used as preemptive analgesics and according to this study ketoprofen 100mg provides better analgesic effects than diclofenac sodium 75mg in terms of reducing pain intensity and pain control for longer duration.

**REFERENCES**