Pre-Emptive Intravenous Paracetamol and Lornoxicam in Third Molar Surgery

By Esra Cagiran, Can Eyigor, Bahar Sezer & Meltem Uyar

Ege University Faculty of Medicine Anestesiology Dept., Turkey

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Materials and Methods: This was a prospective, double-blind, randomized, placebo-controlled study where 50 patients had both of their identical impacted mandibular third molars impacted. Before the removal of the impacted third molar tooth on one side either of the two drug regimens (1g paracetamol or 8 mg lornoxicam) administered preemptively and 15 days later second surgical approach was performed but this time for comparison the other drug regimen (which was not chosen initially) was carried out as the preemptive agent; and all of the operations were performed by the same surgeon. Diclofenac sodium up to 75 mg daily was provided as rescue medication. The postoperative rescue analgesic consumption was recorded and pain scores were evaluated with a Verbal Rating Scale (VRS) at 15,30 min and 1,2, 4, 6, 12, 24 h postoperatively.

Results: There was a significant difference in mean second hour VRS scores between paracetamol and lornoxicam group in favor of the lornoxicam (p<0.05). But, conversely, there was no statistically significant difference in the need of use and the consumption of rescue analgesic medication between two drug groups.

Conclusion: Pre-emptive IV paracetamol and lornoxicam effectively decreased the pain scores as compared to placebo in third molar surgery.

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I. Introduction

Third molar surgery is frequently performed by maxillo-facial and dental surgeons. In the postoperative period mild to moderate pain is the most common complaint observed. Postoperative pain induces long-term changes in both central and peripheral nervous systems. Induction of cyclooxygenase and consequent prostaglandin release results in localized long term hyperalgesia, due to sensitization of peripheral nociceptors. Preemptive analgesia, first defined by Woolf in 1983, was shown to decrease the duration and intensity of postoperative pain. It has been shown that analgesic agents applied before the injury remarkably decrease postoperative pain in comparison to the analgesics given afterwards, related to the desensitization of central nervous system.

Non-steroid anti-inflammatory drugs (NSAIDs) used before the operation avert the progression of pain by inhibiting early inflammatory mediator synthesis and desensitization of the nervous system. Lornoxicam is a NSAID which decreases prostaglandin synthesis by inhibiting cyclooxygenase. It has analgesic, antipyretic and anti-inflammatory effects. The short plasma half-life of lornoxicam (approximately 4 hours) may provide advantages over other NSAIDs, which were convicted previously for having a higher incidence of adverse effects because of their long plasma half-lives.

Hein and colleagues showed that use of prophylactic lornoxicam markedly abates the pain in and after the minor surgical approaches. Pektas et al. found that 16 mg preemptive oral use of lornoxicam, seems to be effective in postoperative management of pain after third molar surgery.

On the other hand, as an antipyretic non-opioid analgesic, paracetamol is drastic in mild to moderate pain. Even though the exact mechanism of action is still unknown being speculated that its primary effect is carried out by the inhibition of early prostaglandin synthesis in central nervous system. According to the evidence-based medical literature, paracetamol is one of the most important analgesic agent in pain management for patients having jaw surgery. However, it is out of its particular value when NSAIDs are contraindicated, perhaps by a known hypersensitivity or a history of gastrointestinal ulceration or bleeding.

The onset of analgesic action is an significant factor, in terms of the clinical efficacy for a drug especially in the management of postoperative pain. Patients having surgery crave for an effective and fast-acting pain relief. The oral application is not effective and sometimes not possible if rapid analgesia is needed, which is often frequent after such a surgery. Therefore, intravenous (IV) administration is the route of choice, with recent introduction of IV forms of lornoxicam and paracetamol, effective consequences have been obtained in postoperative pain management. Accordingly, our study aimed to compare the effects of preemptively used IV forms of lornoxicam and paracetamol, on postoperative pain in patients (cases-da kullanılabılır) undergoing bilateral lower third molar surgery.
II. Material and Methods

The study were designed as a randomized, placebo-controlled and prospective process and performed in Department of Oral and Maxillofacial Surgery of the Faculty of Dentistry of Ege University following the approval of the Ethics Committee of Ege University Faculty of Medicine. Written informed consent was obtained from 50 ASA physical status I outpatients (aged 18–35 years), undergoing the surgical removal of bilateral impacted third molars.

The sequence of drug administration was determined randomly by computer.

As the basic selection criteria, patients having bilaterally impacted lower third molars with the same anticipated degree of extraction difficulty were included; and the cases whom voluntarily signed up their written informed consents were enrolled to this study.

Impacted third molars were confirmed with panoramic radiograms, and according to their radiologic examination cases seems to be in Class II Position-B under Pell-Gregory classification (Table1) were included.

Exclusion criteria included known allergy or sensitivity to any NSAID and local anesthetics.

History of asthma or chronic obstructive pulmonary disease, blood dyscrasia or coagulation disorders, cardiac insufficiency or gastrointestinal disease, renal and hepatic insufficiency, and pregnancy. Patients were not allowed to receive any analgesic within 24 hours prior to operation.

Those were also excluded from the study; who developed alveolitis, postoperative infection, numbness and trismus in 15 days between two extractions in order not to effect the evaluation of postoperative pain.

a) Study Design

As the initial surgical approach, one of the bilateral impacted lower third molar teeth was removed with using either of two drugs being assessed preemptively and then with an interval of 15 days the tooth on the contralateral side was removed at the second appointment with the preemptive administration of alternative analgesic agent (split-mouth design). Each patient received a single IV pre-emptive dose of either 1000 mg of paracetamol or 8 mg oflornoxicam, 15 minutes prior to surgery. Although the surgeon and study staff remained blinded to the treatment group by pre-packaging of the drugs had been studied, the patients had full knowledge of the analgesic agent which had been used, as they were prescribed the medications before operation. On the other hand, patients in control group were exposed to operation for one of lower third molar each.

All drugs dissolved in 100 ml of 0.9% NaCl and then administered via IV infusion in 15 minutes. After the drug infusion, all operations were performed by the same surgeon in a standardized manner under local anesthesia (inferior alveolar, lingual and buccal nerve blocks maintained by 2 ml of articaine hydrochloride 40 mg/ml with epinephrine HCl; 0.006 mg/ml for each case). The surgical procedure was standarized and involved creation of triangular mucoperiosteal flap followed by bone removal using a drill cooled with water. After extraction, the wound was rinsed with a sterile saline solution and achieving local haemostasis, the wound was sutured.

Diclofenac sodium up to 75 mg (oral dose of 25 mg 3 times daily) was supplied as rescue medication for patients who did not achieve adequate analgesia (VRS ≥2) with preemptive administration. In addition the use of rescue analgesic was not permitted within 2 hours following the operation.

All patients were discharged at 1 h after the surgery and asked to complete a questionnaire. The questionnaire had comprised VRS and a survey concerning the effects of postoperative pain on patients' physical and social activities, including the consumption of solid food, speech, sleeping, maintenance of work or school, maintenance of daily work and maintenance of social life and favourable activity during the first postoperative 24 h. Additionally side effects including nausea, vomiting, allergy, and gastrointestinal adverse effects were recorded. Postoperative bleeding from the surgical site was evaluated by the surgeon for 1 h until the patients were discharged from the postoperative care unit. The degree of difficulty of extraction, mean duration of surgery, amount of local anaesthetic used and preoperative or intraoperative additional anaesthetic use were also recorded. The classification of surgical difficulty for removal of impacted mandibular third molars was determined using the difficulty index described by Pell Gregory. Patients were informed on about the Verbal Rating Scale (VRS) (0 = no pain, 5 = worst possible pain) in the preoperative proces.

Postoperative pain scores were evaluated with the VRS at 15, 30 min and 1, 2, 4, 6, 12, 24 h postoperatively (the time of incision was considered the baseline). Moreover, the duration of the operation (from application of local anaesthetic agents until the end of saturation), the time of first analgesic use, patient and doctor satisfaction and side effects (nausea, vomiting, hemorrhage, vertigo and dispepsi) were also recorded.

Patients who used rescue medication recorded the exact date and time by themselves. The questionnaires were returned and then checked at a control visit one week after the second operation.

b) Statistics

Statistical analyses were performed by using SPSS for Windows (version 11.0; SPSS, Inc., Chicago, IL, USA). A sample size of 25 individuals for each group was determined for a power of 90% at a level of 0.05.

Changes in VRS pain scores were assessed by Wilcoxon signed-rank test and the global assessments.
tested by Chi-square statistic. A value of $p<0.05$ was considered to be significant.

III. Results

The present study was carried out by a total of 75 observations in 50 patients. There were no statistically significant differences in patient age and the duration of the operation between three groups (Table 2).

No significant differences among three groups were found in the degree of difficulty of extraction, mean duration of surgery, amount of local anesthetic used and preoperative or intraoperative additional anesthetic use. Again, the difference among three groups was non-significant for the effects of postoperative pain on patients’ physical and social activities during first postoperative 24 h and side effects. Postoperative bleeding from the surgical site was reported in none of the patients in the three group. None of the patients in either group recorded postoperative bleeding allergy, nausea, vomiting or other gastrointestinal adverse effects associated with study medications.

Both paracetamol and lornoxicam provided adequate postoperative analgesia than placebo: patients who had pre-emptively taken either of two drugs experienced effective pain relief at all of the timelines being measured (Fig. 1).

There was only a significant difference in mean second hour VRS scores between the paracetamol and lornoxicam group in favor of lornoxicam ($p<0.05$). The overall analgesic effect of paracetamol was similar to that of lornoxicam: no statistically significant differences were found between two groups for pain intensity in the mean VRS scores at 15, 30 min and 1, 4, 6, 12, 24 h after the surgery.

Somewhere we had detected a slight difference between the paracetamol and lornoxicam groups (3.54±1.61 and 3.78±1.14 hours respectively) regarding to the time of first rescue analgesic was taken, but it was not statistically significant ($p>0.05$). On the other hand, the same time interval was measured as 1.3±1.1 hours in placebo group and which was significantly shorter ($p<0.05$) than that in the other two drug groups (Figure 2).

There were also differences among the three groups with respect to the patients satisfaction and doctor satisfaction. Statistically analysis revealed that patient satisfaction showed no significant difference between three group ($p>0.05$), furthermore the doctor satisfaction was significantly lower in the placebo group ($p<0.05$) (Table 3).

IV. Discussion

As the epidemiologic and pathophysiologic knowledge of postoperative pain improves, a new analgesic concept has been developed and applied for the prevention of pain whereby. Analgesic treatment is started prior to trauma and surgical intervention. Within this concept, referred to as pre-emptive analgesia, it is believed that through application of an analgesic medicine or technique, pain could be either subside or be prevented before the painful stimulus. This effect is achieved by suppressing central or peripheral sensitization either together or separately. Pre-emptive analgesia gives rise to a subsiding pain pattern, a decrease in analgesic requirements, a decline in morbidity and promoting wellness to minimize length of hospital stays.14

The surgical extraction of impacted third molar teeth induces acute pain and thus has been used as an excellent clinical trial model for pain studies.6,15 Studies which uses different drugs upon two extractions in the same patient (split-mouth design) for postoperative analgesia enable him or her to decrease impact of individual factors on pain severity to attain more reliable results. This study was also planned as split-mouth design, meaning to diminish individual factors likely to effect pain severity. A variety of agents have been used in preemptive analgesia for postoperative pain following third molar tooth operation.8,16,17

As it is reviewed from the past medical literature that there was not any study for investigating the analgesic effects of preemptively used IV paracetamol and lornoxicam in third molar surgery.

According to the study where the postoperative analgesic effects of intravenous metamizol, paracetamol and lornoxicam had been searched and compared in postoperative pain management following lumbar disc surgery, Korkmaz et al. found that pain was reduced in the metamizol and paracetamol groups, but not in the lornoxicam and control groups during a postoperative 24 h follow up period.18

Ong et al.16 compared the efficacy of preemptive and postoperative administration of IV 30 mg ketorolac after bilateral third molar surgery and mentioned that analgesic effect of preemptive application was significantly higher compared to placebo.

Due to the acute tissue damage, prostaglandin concentration reaches a maximum level within 3-4 hours where as the postoperative pain becomes most severe.19 Similarly in this study, the most severe pain was experienced after 4 hours, indicated by VRS=3.6±3.3 in paracetamol group and VRS=3.9±3.4 in the lornoxicam group. Pektas et al.9 also showed that the most severe pain in the diflunisal group was at the postoperative 4th hour while the most severe pain in the lornoxicam group was not experienced at the postoperative 4th but at 12th hour. Sener and coworkers16 compared the preemptive analgesic efficacies of 4 different NSAIDs given orally, and discovered that after the usage of acetaminophen one hour prior to third molar surgery, the most severe pain started in postoperative 4th hour. Moreover, they did not detect a
could be used safely for postoperative pain management. Juhl and colleagues, respectively. Therefore, the differences between two groups were not statistically significant (p>0.05). On the other hand, Juhl and colleagues, specified that the median duration of analgesia, as measured by the time elapsing to a request for rescue medication was significantly longer after IV paracetamol (p < 0.0001) longer after IV paracetamol 2 mg (5.03 h) in comparison to IV paracetamol 1 g (3.23 h), with two significantly different active treatments (p < 0.0001) from placebo (1.03 h).

A study with oral rofecoxib and paracetamol used after third molar surgery showed that the durations of first analgesic use were 2.8±0.5 and 3.1±0.9 hours respectively. Therefore, the differences between two groups and placebo were found out as not statistically significant (p>0.05). The durations of first analgesic use, when ketorolac IV was used preemptively and postoperatively after third molar tooth surgery, were 8.9 and 6.9 hours respectively which was statistically significant. 

During the course of this study, side effects were not observed in any of these three groups and both agents specified and considered as confident and could be used safely for postoperative pain management. Juhl and colleagues, compared postoperative 1 and 2 g of paracetamol with placebo and found a significant analgesic effect without any other adverse effects after third molar surgery. On the other hand, Haglund and von Bülzingslöwen, reported side effects in 18.7 % of their patients. They observed side effects in 30% of their patients in the paracetamol group, including fatigue, dizziness and stomach pain in 3, 2 and 1 patients respectively.

Pektas et al. detected bleeding at the site of third molar surgery in one patient (2.5%) after the preemptive usage of 16 mg oral lornoxicam, but there was not any additional side effect that required any further treatment. Correspondingly, in the present research no side effects were observed in all of the three study groups.

In conclusion, this study suggests that preemptive IV paracetamol and lornoxicam are a safe and efficacious analgesic for postoperative third molar surgery compared to placebo.

Availability of injectable formulations of paracetamol and lornoxicam may be considered as an advantage for patients who cannot tolerate oral drug administration.

**References Références Referencias**


9. Amin MM, Laskin DM. Prophylactic use of indomethacin for prevention of postsurgical

Table 1: The Pell–Gregory classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>The occlusal plane of the impacted tooth is at the same level as the occlusal plane of the second molar.</td>
</tr>
<tr>
<td>B</td>
<td>The occlusal plane of the impacted tooth is between the occlusal plane and the cervical line of the second molar.</td>
</tr>
<tr>
<td>C</td>
<td>The impacted tooth is below the cervical line of the second molar.</td>
</tr>
<tr>
<td>I</td>
<td>There is sufficient space between the ramus and the distal part of the second molar for the accommodation of the mesiodistal diameter of the third molar.</td>
</tr>
<tr>
<td>II</td>
<td>The space between the second molar and the ramus of the mandible is less than the mesiodistal diameter of the third molar.</td>
</tr>
<tr>
<td>III</td>
<td>All or most of the third molar is in the ramus of the mandible</td>
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</table>

Table 2: Demographic properties and operation duration (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Paracetamol (n=25)</th>
<th>Lornoxicam (n=25)</th>
<th>Placebo (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>24±3.8</td>
<td>24±3.8</td>
<td>22.4±3.6</td>
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<tr>
<td>Operation duration(min)</td>
<td>10.3±0.9</td>
<td>11.7±0.9</td>
<td>12±4.2</td>
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</tbody>
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Table 3: Doctor and patient satisfaction

<table>
<thead>
<tr>
<th></th>
<th>Dentist Satisfaction (n, %)</th>
<th>Patient Satisfaction (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Paracetamol (n=25)</td>
<td>Placebo (n=25)</td>
</tr>
<tr>
<td>Moderate</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Good</td>
<td>21 (84%)</td>
<td>19 (76%)</td>
</tr>
<tr>
<td>Perfect</td>
<td>4 (16%)</td>
<td>6 (24%)</td>
</tr>
</tbody>
</table>

*p < 0.05: Placebo versus Paracetamol and Lornoxicam

Figure 1: VRS score during the first 24 hours period after surgery paracetamol (Group A), lornoxicam (Group B) and placebo (Group C) groups. Values are means ± SD

$ p < 0.05: $ Group A versus Group B
*p < 0.05: $ Group A versus Group C
# p < 0.05: $ Group B versus Group C
Figure 2: The time of first analgesic use during the first 24 hours period after surgery paracetamol (Group A), lornoxicam (Group B), and placebo (Group C) groups. Values are means±SD.

*p<0.05 : Group C versus Group A and Group B