Postoperative Analgesia in Impacted Third Molar Surgery: The Role of Preoperative Diclofenac Sodium, Paracetamol and Lornoxicam

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Key Words

Preemptive analgesia • Diclofenac sodium • Intravenous paracetamol • Lornoxicam • Third molar surgery

Abstract

Objective: The aim of this study was to compare the postoperative analgesic effects of preoperative intravenous (i.v.) paracetamol, diclofenac sodium and lornoxicam (nonsteroidal anti-inflammatory drugs). **Subjects and Methods:** Sixty patients with impacted third molar who underwent surgical removal were randomly allocated into three groups: group P (n = 20), group D (n = 20) and group L (n = 20). Group P received preoperatively 1 g paracetamol i.v., group D 75 mg diclofenac sodium i.m. and group L 8 mg lornoxicam i.v. Postoperative pain intensity, additional consumption of analgesics postoperatively and postoperative complications were compared among groups. **Results:** The groups were comparable for pain scores ($p > 0.05$). Maximum pain scores were recorded in postoperative 4th h in all groups (group L 22, 14–44 mm; group P 24, 13–43 mm; group D 14, 10–24 mm, $p = 0.117$). Patients experienced high satisfaction scores which were comparable among groups (group L 85, 75–100 mm; group P 87, 70–95 mm; group D 84, 77–98 mm, $p = 0.457$). **Conclusion:** Preoperative intramuscular diclofenac,

intravenous paracetamol and lornoxicam effectively decreased the pain scores. The patients were satisfied with the three postoperative pain management regimens.

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Introduction

Impacted third molar surgery is one of the most frequently performed interventions in the field of oral and maxillofacial surgery and postoperative pain management is a vital issue. Particularly, demonstration of the negative effects of insufficient administration of analgesia in cases of acute pain on cardiovascular, pulmonary and emotional systems aroused interest and highlighted the clinical importance of this subject [1, 2].

During surgery, tissue damage, inflammation and other noxious stimuli trigger a range of changes in the peripheral nervous system. It has been well documented that nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in relieving postoperative pain. The NSAIDs affect the site of injury by acting peripherally and preoperative administration of NSAIDs reduces this tissue damage. The NSAIDs inhibit the production of arachidonic acid metabolites such as prostaglandins and throm-

boxanes, which mediate the inflammatory process. These metabolites are produced locally at the site of cell injury and as such do not migrate to distant sites. In addition, NSAIDs alter peripheral nociceptors by reducing the local concentration of these allogeic chemicals, which are activated by peripheral tissue injury [3–5]. Preoperative analgesia that can prevent postoperative pain is of great interest.

The effectiveness of preoperative administration of NSAIDs is well documented in the literature [6–10]. Parenteral administration of paracetamol has recently been established in medicine. Preoperative use of this analgesic agent in third molar surgery has not been researched yet.

There have been several studies on preoperative analgesia for surgical procedures and in particular on surgical procedures of the head and neck region. These studies have aimed to decrease the surgical and extraction pain for patients undergoing tooth removal and periodontal surgeries [11–13].

Local signs of inflammation, including pain, are usually examined after the removal of impacted third molars. This procedure has been widely used as a model for evaluation of analgesic efficacy of various drugs [14–16]. Postoperative pain after the surgical removal of third molar teeth is a highly sensitive model to evaluate analgesic efficacy of NSAIDs, since the pain is confined to the surgical area with apparent inflammation [17]. The analgesic effects of NSAIDs such as naproxen, meloxicam, rofecoxib, acetaminophen, diflunisal, ibuprofen, ketorolac have been reported using this pain model [18–20]. In this study third molar surgery was also chosen to examine the postoperative analgesic effects of preoperative diclofenac sodium (i.m.), lornoxicam (i.v.) and paracetamol (i.v.); effects are compared using postoperative pain scores, analgesic demand and postoperative early and late side effects.

Subjects and Methods

This randomized, double-blind study was performed on patients undergoing third molar surgery in the Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Ankara University. Sixty patients were enrolled in the study after obtaining the Institutional Ethics Committee approval. Patients were selected among 15-year-old cooperative volunteers. The inclusion criterion was class B third molar surgery requiring bone removal according to the Pell and Gregory [21] classification. Patients who had a previous history of paracetamol or NSAID allergy, who were uncooperative, who had a current or previous history of renal or hepatic disease, who had a bleeding diathesis, and subjects with peptic ulcer were excluded. Patients were randomly allocated to

three groups via sealed envelope technique. Sixty sealed envelopes containing the names of the groups (20 for each) were prepared before the initiation of the study. A nurse picked one of the envelopes and delivered the proper medication to the patient.

Patients were informed about the Visual Analogue Scale (VAS, 0–100 mm), Verbal Pain Scale (VPS, no pain: 0, mild pain: 1, moderate pain: 2, severe pain: 3, and very severe unbearable pain: 4) in the preoperative period.

Patients in group L (n = 20), group P (n = 20) and group D (n = 20) received 8 mg of the NSAID lornoxicam (i.v.), 1 g paracetamol (i.v.) and 75 mg of the NSAID diclofenac sodium (i.m.), respectively, 30 min before the administration of local anesthesia. In order to double-blind i.m. and i.v. drugs, a nurse administered a premixed 100-ml i.v. solution containing 8 mg lornoxicam, 1 g paracetamol or placebo. The same nurse performed i.m. injections of 75 mg diclofenac or placebo according to the group assignment of patients. The researchers who assessed postoperative pain intensity were unaware of the patient's medications. There was no placebo group in this study, because there was a group of patients receiving diclofenac sodium, which served as a reference drug. Diclofenac sodium is accepted as a gold standard protocol of preemptive analgesic efficacy for the postoperative pain after surgical removal of third molar teeth [22–24]. The surgery was performed in the outpatient clinic by the same surgical team (A.M.T.O., assisted by D.Y. and supervised by A.O.) under local anesthesia using 3 ml of articaine hydrochloride (40 mg/ml, epinephrine HCl 0.006 mg/ml) for inferior alveolar nerve block and buccal infiltration anesthesia. The classic envelope flap with a sulcal incision from the first to the second molar and a distal relieving incision to the mandibular ramus was used [22]. Anesthesia and surgical times were recorded. Hemodynamic variables such as systolic blood pressure and heart rate were recorded preoperatively, at intraoperative 5th minute and at the end of the surgery. The severity of postoperative pain was evaluated postoperatively at 15 and 30 min, 1, 2, 3, 4, 8, 12, 20, 24 and 48 h via Visual Analog Scale Rest (VASR, 0–100 mm), Visual Analog Scale Cough (VASc), Visual Analog Scale Swallowing (VASS), Verbal Pain Scale Rest (VPSR, 0–4), Verbal Pain Scale Cough (VPSC) and Verbal Pain Scale Swallowing (VPSS). Postoperative side effects at 48 h such as excessive perspiration, itching, rash, erythema, skeletal pain, myalgia, fatigue, vertigo, headache, paresthesia, anorexia, migraine, leg cramp, nausea, vomiting, abdominalgia, xerostomia, dehydration, palpitation, urinary retention, micturition problems, fever, dorsal pain, malacia, rigor, chest pain, diplopia, hemorrhage at the surgical site and petechiae were recorded as positive or negative.

All the patients received oral 875 mg amoxicillin hydrate and 125 mg clavulanic acid (Augmentin b.i.d. 1,000 mg, GlaxoSmith-Kline) twice a day for 5 days for antibiotic prophylaxis of postoperative wound infection. Also benzydamine hydrochloride mouth rinse twice a day was recommended.

Total postoperative flurbiprofen (p.o.) consumption, the time to the first onset of pain and the first rescue analgesia taken, the number and the times of analgesia demanded and taken were recorded.

Statistical Analyses

A power analysis was performed before the initiation of the study to establish the number of patients for each group based on a previous study [25]; a difference of 30% in VAS scores in

Table 1. Patient characteristics and duration of operation

	Group L (n = 20)	Group P (n = 20)	Group D (n = 20)	p
Age, years	23.55 ± 3.70	26.05 ± 6.81	25.65 ± 5.67	0.600
Gender, male/female	0.3571 ± 0.49	0.2857 ± 0.46	0.5 ± 0.51	0.502
Weight, kg	64.50 ± 10.81	60.80 ± 10.80	67.65 ± 13.60	0.222
Height, cm	168.80 ± 9.81	168.75 ± 8.60	168.75 ± 8.60	0.952
Anesthesia time, min	228.90 ± 57.47	211.05 ± 56.41	211.05 ± 56.41	0.377
Duration of surgery, min	27.15 ± 6.25	25.05 ± 5.78	25.05 ± 5.78	0.579
Previous surgery	0.571 ± 0.51	0.00 ± 0.00	0.50 ± 0.51	0.003

Data are shown as mean ± SD (n = number of patients). Group L: lornoxicam 8 mg (i.v.); group P: paracetamol 1 g (i.v.); group D: diclofenac sodium 75 mg (i.m.).

patients who underwent third molar surgery was considered as clinically significant. Twelve patients per group were needed to ensure a type 1 error of 0.05 and type 2 error of 0.20. All of the statistical analyses were performed using a statistical package program, Statistical Program for Social Sciences, Chicago, Ill., USA, SPSS version 16.0, with an IBM-compatible personal computer. Age, weight and operative time were analyzed with Kruskal-Wallis one-way ANOVA with Mann-Whitney U test as a post hoc analysis. Analysis of variance for repeated measures was used for the hemodynamic data. As the pain scores, total flurbiprofen consumption data did not fulfill the criteria for normal distribution, these data were analyzed using Kruskal-Wallis one-way ANOVA with Mann-Whitney U test as a post hoc analysis and the data were presented as median and quartiles [26]. The incidence of side effects was evaluated with the χ^2 test. The area under the pain variables versus time curves were calculated and further analyzed by one-way ANOVA with Bonferroni correction as a post hoc test. Data were presented as mean and standard deviation, median and quartiles, percentages and number of patients; p values <0.05 were considered as statistically significant.

Results

There was no difference between the groups regarding age, weight, height, gender, anesthesia time, surgical time and having a previous operation (table 1). The hemodynamic data regarding heart rate and systolic blood pressure were comparable among the groups. No periods of hypotension, hypertension, bradycardia or tachycardia were observed in patients enrolled in the study.

The VASR and VPSR are given in table 2. VASR and VPSR values at all measurement points were lower than baseline measurements within the groups. There was no significant difference in VPSR scores between the three groups ($p > 0.05$) whereas there was a significant differ-

ence in VASR scores at 12 h ($p < 0.05$). VASR scores for group L at 12 h were significantly lower than for the diclofenac and paracetamol groups ($p = 0.012$, $p = 0.024$ compared to group D and group P, respectively). The VASR scores of 45 patients from the three groups were lower than 40 mm. VASR scores were lower than 40 mm except at 4 and 8 h for all of the three drugs (table 2). Seventy-five percent of the VASR scores at 4 and 8 h were lower than 50 mm for all of the three groups.

The VASC and VPSC are given in table 3. VASC and VPSC values at all measurement points were lower than baseline measurements within the groups. VASC scores of the lornoxicam group at 12 h were statistically lower than those of the paracetamol group ($p = 0.013$). VPSC scores at 15 and 30 min, 1, 2, 8 and 12 h for the lornoxicam group were lower than those for the paracetamol and diclofenac groups ($p < 0.05$). VPSC scores of the paracetamol group at 4, 20 and 24 h were significantly higher than those of the lornoxicam group ($p < 0.05$).

The VASS and VPSS are given in table 4. There was no significant difference between the VASS scores among the three groups ($p > 0.05$). VPSS scores at 15 min, 1, 2, 12 and 24 h for the lornoxicam group were significantly lower than those for the paracetamol and diclofenac groups ($p < 0.05$).

Total postoperative flurbiprofene (p.o.) consumption, the times to the first onset of pain and the first rescue analgesia taken, the number and the times of analgesia demanded and taken are given in table 5. There was no significant difference between the three groups ($p > 0.05$). The three medication protocols presented comparable postoperative analgesic profiles with similar incidence of side effects. There were no significant differences between the groups regarding the frequency of postopera-

Table 2. VASR and VPSR for groups L, P and D

	15 min	30 min	1 h	2 h	4 h	8 h	12 h	20 h	24 h	48 h
Group L (n = 20)										
VASR	0 (0–0)	0 (0–0)	0 (0–0)	12 (0–20)	22 (14–44)	12 (3–28)	0 (0–5)	0 (0–6)	0 (0–8)	0 (0–5)
VPSR	2 (2–2)	2 (1–2)	2 (1–2)	2 (1–2)	1 (0–2)	1 (0–1)	1 (0–1)	0 (0–1)	0 (0–0)	0 (0–0)
Group P (n = 20)										
VASR	0 (0–0)	0 (0–0)	0 (0–18)	10 (0–17)	24 (13–43)	20 (15–42)	10 (0–25)	5 (0–26)	8 (0–18)	3 (0–17)
VPSR	2 (1–2)	2 (1–2)	1 (1–2)	1 (1–2)	1 (1–1)	0 (0–1)	1 (0–1)	0 (0–1)	0 (0–0)	0 (0–0)
Group D (n = 20)										
VASR	0 (0–0)	0 (0–0)	0 (0–0)	10 (0–19)	14 (10–24)	17 (10–33)	10 (0–20)	5 (0–11)	0 (0–8)	0 (0–2)
VPSR	0 (0–0)	0 (0–0)	0 (0–0)	1 (0–1)	1 (1–2)	1 (1–2)	1 (0–2)	1 (0–1)	0 (0–1)	0 (0–0)
p VASR	0.360	0.354	0.063	0.976	0.117	0.118	0.012 ^a 0.024 ^b	0.240	0.103	0.101
p VPSR	0.341	0.340	0.007 ^c	0.998	0.424	0.129	0.011 ^a	0.128	0.227	0.007 ^c

Group L: lornoxicam 8 mg (i.v.); group P: paracetamol 1 g (i.v.); group D: diclofenac sodium 75 mg (i.m.). Data are VASR in mm, VPSR in numbers and expressed as median and quartiles.

^a Group L compared to group D. ^b Group L compared to group P. ^c Group P compared to group D.

Table 3. VASC (0–100 mm) and VPSC values in groups L, P and D

	15 min	30 min	1 h	2 h	4 h	8 h	12 h	20 h	24 h	48 h
Group L (n = 20)										
VASC	0 (0–0)	0 (0–0)	0 (0–0)	2 (0–13)	3 (0–15)	0 (0–5)	0 (0–0)	0 (0–8)	0 (0–14)	0 (0–0)
VPSC	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–1)	0 (0–1)	1 (0–1)	0 (0–0)	0 (0–1)	0 (0–1)	0 (0–0)
Group P (n = 20)										
VASC	0 (0–0)	0 (0–0)	0 (0–9)	5 (0–15)	8 (0–34)	6 (0–22)	1 (0–24)	5 (0–14)	5 (0–14)	0 (0–14)
VPSC	0 (0–0)	0 (0–0)	0 (0–1)	1 (0–1)	1 (0–2)	0 (0–1)	1 (0–1)	0 (0–1)	1 (0–1)	0 (0–1)
Group D (n = 20)										
VASC	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–13)	7 (0–16)	3 (0–14)	0 (0–11)	0 (0–5)	0 (0–9)	0 (0–0)
VPSC	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–1)	1 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)
p VASC	0.999	0.801	0.093	0.846	0.833	0.172	0.013 ^b	0.130	0.558	0.011 ^b
p VPSC	0.001 ^a 0.005 ^b	0.001 ^a 0.002 ^b	0.001 ^a 0.001 ^b	0.032 ^a 0.048 ^b	0.049 ^a 0.047 ^b	0.001 ^a 0.002 ^b	0.016 ^a 0.019 ^b	0.023 ^a 0.046 ^b	0.001 ^a 0.000 ^b	0.007 ^a 0.001 ^b

VPSC values: 0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain, 4 = very severe unbearable pain; group L: lornoxicam 8 mg (i.v.); group P: paracetamol 1 g (i.v.); group D: diclofenac sodium 75 mg (i.m.). p VASC and p VPSC = exact p values between groups, VASC is statistically not significant except the scores at 12 and 48 h. Data for VASC in mm, VPSC in numbers and expressed as median and quartiles.

^a Group L compared to group D. ^b Group L compared to group P.

tive side effects at 48 h postoperatively. However, 2 of the patients in group L experienced postoperative side effects – itching in one, myalgia and fatigue in the other. None of the patients in group P presented postoperative side effects. One patient in group D reported nausea and fatigue together.

Discussion

Diclofenac sodium is a nonselective cyclooxygenase enzyme inhibitor and lornoxicam is a new intravenously administered NSAID belonging to the oxycam group with balanced cyclooxygenase inhibition and excellent

Table 4. VASS (0–100 mm) and VPSS values in groups L, P and D

	15 min	30 min	1 h	2 h	4 h	8 h	12 h	20 h	24 h	48 h
Group L (n = 20)										
VASS	0 (0–0)	0 (0–0)	0 (0–0)	5 (0–15)	17 (0–45)	10 (0–28)	0 (0–9)	2 (0–12)	0 (0–10)	0 (0–0)
VPSS	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–1)	0 (0–1)	1 (0–1)	0 (0–0)	0 (0–1)	0 (0–1)	0 (0–1)
Group P (n = 20)										
VASS	0 (0–0)	0 (0–0)	0 (0–2)	6 (0–19)	23 (0–43)	22 (9–47)	9 (0–39)	10 (0–26)	9 (0–24)	0 (0–14)
VPSS	0 (0–0)	0 (0–0)	0 (0–1)	1 (0–1)	1 (0–2)	1 (0–1)	1 (0–1)	0 (0–1)	1 (0–1)	0 (0–1)
Group D (n = 20)										
VASS	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–16)	10 (0–24)	8 (0–19)	5 (0–13)	0 (0–6)	0 (0–10)	0 (0–0)
VPSS	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–1)	1 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)
p VASS	0.343	0.814	0.396	0.778	0.329	0.092	0.235	0.087	0.220	0.035
p VPSS	0.001 ^a	0.001 ^a	0.001 ^a	0.032 ^a	0.049 ^a	0.001 ^a	0.016 ^a	0.023 ^a	0.001 ^a	0.007 ^a
	0.005 ^b	0.002 ^b	0.001 ^b	0.048 ^b	0.047 ^b	0.002 ^b	0.019 ^b	0.046 ^b	0.000 ^b	0.001 ^b

VPSS values: 0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain, 4 = very severe unbearable pain; group L: lornoxicam 8 mg (i.v.); group P: paracetamol 1 g (i.v.); group D: diclofenac sodium 75 mg (i.m.). VASS is statistically not significant at all measurement points for all of the groups, p VPSS = exact p values between groups. Data for VASS in mm, VPSS in numbers and expressed as median and quartiles.

^a Group L compared to group D. ^b Group L compared to group P.

Table 5. Total postoperative flurbiprofene (p.o.) consumption, time to the first pain onset and to the first rescue analgesic taken, the number of analgesics demanded and taken in the first 48 h

	Group L (n = 20)	Group P (n = 20)	Group D (n = 20)	p
Time to first pain onset, min	374.40 ± 594.93	239.35 ± 105.62	219.75 ± 59.81	0.471
Time to first rescue analgesic taken, min	258.36 ± 113.36	398.0 ± 350.06	274.72 ± 160.96	0.595
Analgesics taken	1.35 ± 0.875	1.60 ± 0.82	1.61 ± 0.84	0.376

tolerability. In addition to this, i.v. paracetamol is a new clinically approved reliable agent that has no effect on platelet functions and the oral form of paracetamol was studied for the side effect profile. Lornoxicam has been shown to be clinically effective in the treatment of postoperative pain [27]. However, there is little evidence regarding its use as a preoperative analgesic agent for postoperative pain management [28]. In our study, VASR, VPSC and VPSS scores of the lornoxicam group were found to be significantly lower than the scores of diclofenac sodium and paracetamol at 12 h. VASR scores of the lornoxicam group were statistically lower than those of the paracetamol group. This shows that lornoxicam provided more satisfactory pain relief at 12 h postoperatively. In a study comparing the efficacy of ibuprofen versus lornoxicam after third molar surgery, it was reported that effective pain relief was provided

and there was no significant difference between the groups [29].

The concentration of prostaglandins in acutely injured tissue reaches its maximum level at 3 or 4 h after injury with the result of a peak intensity of postoperative pain [29]. Seventy-five percent of the VASR scores at 4 and 8 h were lower than 50 mm for all of the three groups. This shows that the treatment protocol for all of the three drugs provided efficient postoperative pain management. In this study, although there was no significant difference between the groups regarding the VASR and VPSR values, the peak intensity of postoperative pain was at 8 h postoperatively for the diclofenac sodium group (VASR = 17), whereas it was at 4 h postoperatively for the lornoxicam (VASR = 22) and paracetamol groups (VASR = 24). Thus, when comparing the half-life periods and action times of these drugs, this study is consistent

with earlier research that found diclofenac sodium to be a long-acting agent with a half-life period of 8–12 h, whereas lornoxicam is a short-acting NSAID with a half-life period of 3–4 h [30]. Forbes et al. [17] reported diflunisal as an agent having a long duration of analgesic action compared with acetaminophen; their patients rated their pain relief 12 h after medication.

Preemptive analgesic treatment aims to prevent pain due to surgical trauma instead of administering analgesic therapy in response to postoperative pain. NSAIDs prescribed before the surgery have been reported to more effectively prevent peripheral and central sensitization after surgery [31]. There are reports that preemptive administration of NSAIDs is less effective than the postoperative administration of the same drugs [32]. However, in this study the preoperative administration of NSAIDs such as diclofenac sodium and lornoxicam was found to be effective for pain relief after impacted third molar surgery. There was no significant difference between the groups regarding the total postoperative rescue analgesic consumption. In a study comparing diflunisal and lornoxicam, no statistically significant differences were found between the groups with respect to rescue analgesic consumption [33].

Although there were no significant differences between the groups regarding the side effects, 2 of the patients in the lornoxicam group experienced side effects (itching in one, myalgia and fatigue in the other). The risks of short-term use of most NSAIDs are minimal. Most serious side effects occur only after long-term use [4]. In the study by Pektas et al. [34], none of the patients

in the lornoxicam and diflunisal groups recorded allergy, nausea and vomiting or other gastrointestinal side effects.

In this study, intravenous paracetamol was used as an analgesic alternative in addition to NSAIDs. Although the effects of diclofenac sodium and lornoxicam have been reported individually, this study had a special design in that the effects of these drugs were also compared with the intravenous preoperative injection of paracetamol. VAS and VPS scores did not reveal the superiority of any of the drugs, but all of the drugs had similar clinical features of postoperative pain relief after third molar surgery. The availability of injectable formulations of paracetamol and lornoxicam may be considered as an advantage for patients that cannot tolerate oral drug administration.

Conclusion

Preoperative intramuscular diclofenac sodium, intravenous paracetamol or lornoxicam decreased the postoperative pain intensity for patients undergoing surgical removal of impacted third molars. The patients were satisfied with the three postoperative pain management regimens. The three drugs can be administered reliably and interchangeably irrespective of side effects for the postoperative pain management after third molar surgery. Further investigations are needed to compare the efficacy of these drugs with other preemptive analgesic medications.

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