Comparison of Preemptive Analgesic Effects of a Single Dose of Nonopioid Analgesics for Pain Management After Ambulatory Surgery: A Prospective, Randomized, Single-Blind Study in Turkish Patients

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ABSTRACT

Background: Preemptive analgesia used for postsurgical pain management has been shown to reduce the requirements of postoperative analgesics.

Objective: The aim of this study was to compare the preemptive analgesic effects of diflunisal, naproxen sodium, meloxicam, acetaminophen, and rofecoxib (no longer available in some markets) in patients undergoing ambulatory dental surgery and the need for postoperative pain management in these patients.

Methods: This prospective, randomized, single-blind study was conducted at the Departments of Anesthesiology and Reanimation and Oral and Maxillofacial Surgery, Baskent University, Adana Teaching and Medical Research Center, Adana, Turkey. Turkish outpatients aged ≥16 years with American Society of Anesthesiologists physical status 1 (i.e., healthy) and scheduled to undergo surgical extraction of an impacted third molar were enrolled. Patients were randomly assigned to receive diflunisal 500 mg, naproxen sodium 550 mg, meloxicam 7.5 mg, acetaminophen 500 mg, or rofecoxib 12.5 mg. All medications were administered orally 1 hour before surgery as preemptive analgesia and after surgery if needed, up to the maximum recommended dose. Surgery was performed with the patient under local anesthesia (articaine hydrochloride). Pain intensity was assessed using a 100-mm visual analog scale (VAS) (0 = none to 100 = worst possible pain) at 2, 4, 6, and 12 hours after ambulatory surgery. The use of additional analgesics was recorded for 24 hours using patient diaries. Postoperative adverse events were recorded using the diaries.

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Results: One hundred fifty patients (108 women, 42 men; mean [SE] age, 26.8 [0.6] years; 30 patients per group) had data available for analysis. Demographic data were similar between the 5 groups. No significant differences in mean VAS scores were found between the 5 groups at any time point. All mean VAS scores indicated minor pain. The rate of additional postoperative analgesics required was significantly lower in the diflunisal group compared with groups receiving naproxen sodium, meloxicam, acetaminophen, and rofecoxib (3 [10%] patients vs 11 [37%], 15 [50%], 15 [50%], and 14 [47%] patients, respectively; all, $P < 0.05$). Bleeding at the surgical site was reported in 2 patients each in the diflunisal, naproxen sodium, meloxicam, and acetaminophen groups, and in 1 patient in the rofecoxib group; the between-group differences were not significant. No significant differences in the prevalences of other adverse effects (eg, nausea, vomiting, allergy, gastrointestinal symptoms) were found between the 5 treatment groups.

Conclusions: In the present study in patients undergoing third molar extraction, adequate preemptive analgesia, based on VAS scores, was found with all of the nonopioid analgesic agents used. Fewer patients required rescue medication with diflunisal. All 5 study drugs were similarly well tolerated. (Curr Ther Res Clin Exp. 2005;66:541–551) Copyright © 2005 Excerpta Medica, Inc.

Key words: preemptive analgesia, ambulatory surgery, NSAIDs.

INTRODUCTION

An increasing number of studies have focused on the use of preemptive analgesia for postoperative pain relief.1 It has been found that pain scores immediately after surgery are significantly improved with the use of preemptive analgesia.2 NSAIDs and other nonopioid analgesics are commonly used for postoperative pain relief in ambulatory surgery.3,4 Studies have found that the analgesic effect of rofecoxib administered postoperatively was significantly greater than that achieved with celecoxib, acetaminophen plus codeine, ibuprofen, or diclofenac sodium.5–8 However, rofecoxib was withdrawn from some markets due to concerns regarding cardiovascular adverse effects. Also, these studies are controversial because the maximum recommended daily dose of rofecoxib was prescribed, whereas in other studies,7,8 it was not. Among NSAIDs, diflunisal, naproxen sodium, ibuprofen, acetaminophen, and rofecoxib have been used for preemptive analgesia, and have been found to be effective in alleviating various degrees of postoperative pain.4,9–12

Surgical extraction of impacted third molars constitutes an accepted model to clinically assess the need for analgesic medications.5,7 The aim of the present study was to compare the preemptive analgesic effects of medications (diflunisal, naproxen sodium, meloxicam, acetaminophen, and rofecoxib) currently used in Turkey for postoperative pain management in ambulatory surgery.
PATIENTS AND METHODS
This prospective, randomized, single-blind study was conducted at the Departments of Anesthesiology and Reanimation and Oral and Maxillofacial Surgery, Baskent University, Adana Teaching and Medical Research Center, Adana, Turkey, between February and July 2004. Approval of the protocol was obtained from the local ethics committee. Consecutive Turkish outpatients aged ≥16 years with American Society of Anesthesiologists physical status I (ie, healthy) and scheduled to undergo surgical extraction of an impacted third molar were enrolled. Written informed consent was obtained from patients or their parents/legal guardians for those under 18 years of age. Patients were excluded if they had allergy to any analgesic, asthma, peptic ulcer disease, a bleeding disorder, intolerance to NSAIDs, and/or a history of renal and/or hepatic insufficiency. Patients who were pregnant also were excluded.

Study Medications
On the morning of surgery, eligible patients were randomly assigned, in a 1:1 ratio using a computer-generated list of random numbers, to receive oral treatment with diflunisal, naproxen sodium, meloxicam, acetaminophen, or rofecoxib. The dose selected for each drug was that most commonly prescribed based on information in the literature (MEDLINE search; key terms: nonopioid analgesics, efficacy, and tolerability; years: 1980–2005),13–16 and were as follows: diflunisal, 500 mg; naproxen sodium, 550 mg; meloxicam, 7.5 mg; acetaminophen, 500 mg; and rofecoxib, 12.5 mg. The first dose was administered 1 hour before surgery. The second dose was administered not before 2 hours after surgery as rescue medication on patient request. The third dose was also administered on patient request and was not allowed before the stated dosing interval for each drug (12 hours after the second dose for diflunisal, naproxen sodium, meloxicam, and rofecoxib; 6 hours for acetaminophen). The use of a second dose before the recommended dosing interval was considered additional analgesic use. The maximum total amount allowed per 24-hour period was determined based on the recommended dosing interval of each drug, as follows: diflunisal, 1500 mg17; naproxen sodium, 1650 mg18; meloxicam, 22.5 mg19; acetaminophen, 4000 mg15; and rofecoxib, 50 mg.3,13

Blinding of the study investigators, surgeons, and other health care staff was maintained using identical packaging of the study drugs. Patients were unblinded to treatment and they had full knowledge of the analgesic agent used; they received prescriptions for the medications before surgery and could use them if needed in the postoperative period.

The same surgeon performed all of the surgeries in a standardized manner, with each patient receiving local anesthesia (inferior alveolar, lingual, and buccal nerve blocks maintained using 2 mL of articaine hydrochloride 40 mg/mL with epinephrine hydrochloride 0.006 mg/mL). At 1 hour after surgery, patients were discharged with study medication and a diary and advised to rest at home for 12 hours.
Assessments

Pain intensity was assessed using a written 100-mm visual analog scale (VAS) (0 = none to 100 = worst possible pain) at 2, 4, 6, and 12 hours after surgery. Patients used a diary to record the need for additional analgesic for 24 hours. Postoperative adverse effects, including nausea, vomiting, allergy, and bleeding from the surgical site, also were recorded in the diary over 24 hours.

Statistical Analysis

Statistical analyses were performed using SPSS version 11.0 (SPSS Inc., Chicago, Illinois). A sample size of 30 for each group was determined for a power of 80% at an α level of 0.05. The χ² test was used to analyze group differences in the distribution of categoric data; 1-way analysis of variance for repeated measurements was used to compare the 5 groups; and the Kruskal-Wallis and Mann-Whitney U tests were used to compare nonparametric data between the groups. Data are presented as mean (SE). P < 0.05 was considered statistically significant.

RESULTS

Study Population

Two hundred eight patients were enrolled in the study; 153 completed it. Forty patients were excluded because of a lack of consent; 15, because of exclusion criteria. Three of the 153 patients who completed the study did not return for follow-up and were excluded from the analysis. Thus, 150 patients returned for follow-up and returned the questionnaire and patient diary and were included in the analysis (108 women, 42 men; mean [SE] age, 26.8 [0.6] years; 30 patients per group) (Table I). The mean operative time was 12.34 (0.77) minutes. No significant between-group differences in the baseline criteria were found.

Efficacy

No statistically significant between-group differences were found in mean VAS scores at 2, 4, 6, or 12 hours after surgery (Table II).

The rate of additional postoperative analgesics required was significantly lower in the diflunisal group compared with groups receiving naproxen sodium, meloxicam, acetaminophen, and rofecoxib (3 [10%] patients vs 11 [37%], 15 [50%], 15 [50%], and 14 [47%] patients, respectively; all, P < 0.05) (Figure).

Tolerability

Bleeding at the surgical site was reported in 2 patients each in the diflunisal, naproxen sodium, meloxicam, and acetaminophen groups, and in 1 patient in the rofecoxib group; the between-group differences were not significant. No significant differences in the prevalences of other adverse effects (eg, nausea, vomiting, allergy, gastrointestinal [GI] symptoms) were found between groups. The most common drug-related adverse events were nausea and vomiting.
Table 1. Demographic and baseline clinical characteristics of the study patients.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Diflunisal (n = 30)</th>
<th>Naproxen Sodium (n = 30)</th>
<th>Meloxicam (n = 30)</th>
<th>Acetaminophen (n = 30)</th>
<th>Rofecoxib (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SE), y</td>
<td>26.23 (1.27)</td>
<td>26.77 (1.31)</td>
<td>27.63 (1.58)</td>
<td>24.93 (0.98)</td>
<td>28.7 (1.49)</td>
</tr>
<tr>
<td>Sex, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>21 (70.0)</td>
<td>24 (80.0)</td>
<td>18 (60.0)</td>
<td>24 (80.0)</td>
<td>21 (70.0)</td>
</tr>
<tr>
<td>Male</td>
<td>9 (30.0)</td>
<td>6 (20.0)</td>
<td>12 (40.0)</td>
<td>6 (20.0)</td>
<td>9 (30.0)</td>
</tr>
<tr>
<td>Weight, mean (SE), kg</td>
<td>59.0 (10.3)</td>
<td>60.1 (11.5)</td>
<td>58.0 (9.2)</td>
<td>61.0 (10.5)</td>
<td>59.6 (12.4)</td>
</tr>
<tr>
<td>Duration of surgery, mean (SE), min</td>
<td>13.0 (2.1)</td>
<td>13.0 (1.7)</td>
<td>12.2 (1.5)</td>
<td>11.2 (1.7)</td>
<td>12.1 (1.5)</td>
</tr>
</tbody>
</table>

*No significant between-group differences were found.
Table II. Postoperative visual analog scale scores.* Values are mean (SE).

<table>
<thead>
<tr>
<th>Study Group</th>
<th>2 Hours</th>
<th>4 Hours</th>
<th>6 Hours</th>
<th>12 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diflunisal (n = 30)</td>
<td>22.67 (4.1)</td>
<td>22.93 (4.0)</td>
<td>22.33 (3.6)</td>
<td>19.93 (3.3)</td>
</tr>
<tr>
<td>Naproxen sodium (n = 30)</td>
<td>16.93 (4.4)</td>
<td>26.10 (4.8)</td>
<td>25.36 (4.6)</td>
<td>21.56 (4.5)</td>
</tr>
<tr>
<td>Meloxicam (n = 30)</td>
<td>16.60 (4.4)</td>
<td>19.23 (3.8)</td>
<td>18.76 (4.3)</td>
<td>17.96 (4.6)</td>
</tr>
<tr>
<td>Acetaminophen (n = 30)</td>
<td>16.56 (3.8)</td>
<td>27.23 (4.4)</td>
<td>27.16 (4.8)</td>
<td>20.90 (5.2)</td>
</tr>
<tr>
<td>Rofecoxib (n = 30)</td>
<td>13.10 (3.5)</td>
<td>24.10 (4.9)</td>
<td>24.10 (4.9)</td>
<td>18.20 (3.4)</td>
</tr>
<tr>
<td>( p )</td>
<td>0.591</td>
<td>0.743</td>
<td>0.737</td>
<td>0.968</td>
</tr>
</tbody>
</table>

*Scale: 0 = no pain to 100 = worst possible pain.

Figure. Postoperative additional analgesic requirements by study group. *\( p < 0.05 \) diflunisal versus all other groups.
(22.7% and 4% of patients, respectively). Severe bleeding, persistent nausea and vomiting, or NSAID-related acute erosive gastritis was not reported.

**DISCUSSION**

Effective analgesia after ambulatory surgery is important in maintaining patient comfort. Preemptive use of oral NSAIDs has been shown to provide effective postoperative analgesia after ambulatory surgery. Surgical extraction of an impacted third molar is an accepted model for assessing analgesic efficacy. Thus, the present study was designed to compare the preemptive analgesic effects of nonopioids (diflunisal, naproxen sodium, meloxicam, acetaminophen, rofecoxib) commonly used in ambulatory dental surgery.

**Effectiveness**

Studies have found that preemptive administration of diflunisal 1000 mg, naproxen sodium 550 to 1000 mg, and rofecoxib 25 to 50 mg provided sufficient analgesia after ambulatory dental surgery. In the present study, because all of the mean VAS scores were <30 mm at 2, 4, 6, and 12 hours postoperatively in each group, it could be stated that postoperative analgesia was adequate with all 5 agents.

Because a significantly lower proportion of patients who preemptively received diflunisal required additional postoperative analgesia compared with patients in the other groups, we consider that the preemptive analgesic effect of diflunisal was greater than that of the other analgesics studied.

**Dosing Considerations**

According to the study protocol, the first dose of the analgesic agent, which would otherwise be prescribed postoperatively, was administered 1 hour before surgery. Doses of analgesics given did not exceed recommended maximum daily doses. Although the doses selected for the analgesics were derived from the literature, with the assumption that these doses represented the optimal analgesic doses of these drugs, we recognize that the doses of the study drugs might not have been equipotent.

In the authors' opinion, whether the total daily dose of prescribed analgesic should be administered once preemptively or the first divided dose of the daily regimen should be received preemptively is debatable. Postoperative administration of a prescribed daily dose of a selected analgesic on an outpatient basis as an additional analgesic at the patient's request, with the first dose having already been given preemptively, could be a more accurate and feasible approach. The analgesic regimen could then be continued postoperatively for 24 to 48 hours.

Inadequate pain relief after the preemptive administration of rofecoxib 50 mg (maximum daily dose) might result in maintenance of the same analgesic agent postoperatively; hence, there is a risk for exceeding the maximum recommended daily dose or the need to prescribe another analgesic. Administration
of rofecoxib 50 mg preemptively is disadvantageous because of the high incidence of severe adverse effects associated with the use of maximum doses when postoperative analgesic use is required. However, White\textsuperscript{3} recommended a dose of 25 to 50 mg of rofecoxib for preemptive analgesia, and administration of rofecoxib 12.5 mg BID is a common practice in acute pain management after oral surgery.\textsuperscript{29} The review of the literature did not find other studies using preemptive administration of rofecoxib 12.5 mg; hence, this dose of rofecoxib as used in our study could be considered low. However, recent studies indicate that doses of rofecoxib >25 mg are associated with an increased risk for sudden cardiac death and acute myocardial infarction.\textsuperscript{30,31} Considering this, we do not suggest a preemptive dose of rofecoxib >12.5 mg. If patients in the present study experienced pain after surgery, they received the preemptively administered drugs again postoperatively based on the recommended daily doses.

**Tolerability**

NSAIDs have been associated with GI bleeding and dyspepsia\textsuperscript{9,32–35} The incidence of GI adverse effects, including dyspepsia and bleeding, with the administration of cyclooxygenase-2 (COX-2) inhibitors has been reported as being lower compared with that found with nonselective NSAIDs. This finding could be considered an advantage of COX-2 inhibitors.\textsuperscript{35–38} However, Laporte et al\textsuperscript{33} failed to confirm that greater selectivity for COX-2 inhibitors was associated with less risk for upper GI bleeding compared with other NSAIDs. Instead, they found that the risk for GI complications was dependent on the particular drug and its dose. As mentioned previously, Layton et al\textsuperscript{32} did not find any significant differences in the prevalences of adverse effects in patients receiving rofecoxib or meloxicam. Use of rofecoxib for pain management after third molar extraction has not been associated with prolonged bleeding from the surgical site.\textsuperscript{38} The present study did not find any significant between-group differences in the prevalences of bleeding or other complications. It should be noted that some COX-2 inhibitors have been removed from the US market.

**Study Limitations**

Limitations of this study include a relatively small sample size per group and the lack of blinding of the patients. In addition, the results cannot be extrapolated to patients undergoing third molar extraction who do not meet the inclusion criteria of this study. Last, as mentioned, the doses used might not have been equipotent. Future studies should be performed on equipotent doses of analgesics because their comparisons are more accurate.

**CONCLUSIONS**

In the present study in patients undergoing third molar extraction, adequate preemptive analgesia, based on VAS scores, was found with all of the nonopioid
analgesic agents used. Fewer patients required rescue medication with diflunisal. All 5 study drugs were similarly well tolerated.

REFERENCES


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