Comparison of the Effects of Lornoxicam Versus Diclofenac in Pain Management After Cardiac Surgery: A Single-Blind, Randomized, Active-Controlled Study

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ABSTRACT

Background: Inadequate pain management after cardiac surgery may result in increased morbidity and length of hospital stay. Although opioids are the mainstay of postoperative analgesia, nonsteroidal anti-inflammatory drugs (NSAIDs) may be used instead to avoid the adverse effects (AEs) associated with opioids. Lornoxicam is a newly developed NSAID, the use of which is increasing. However, lornoxicam has not been studied for use in pain management after cardiac surgery.

Objective: The objective of this study was to compare the efficacy and tolerability of lornoxicam and diclofenac sodium, an NSAID well established for use in pain management after major surgery, in pain management after coronary artery bypass grafting (CABG).

Methods: This single-blind, randomized, active-controlled study was conducted at the Gaziantep University Hospital, Gaziantep, Turkey. Adult patients scheduled to undergo valve or CABG surgery for the first time were included. Patients were premedicated with diazepam 10 mg PO at 10 PM on the evening before surgery. General anesthesia was induced using fentanyl, midazolam, and propofol, and maintained using fentanyl and isoflurane in pure oxygen. After extubation and when they stated that they felt pain, patients were randomly assigned to 1 of 2 treatment groups: lornoxicam 8 mg IM q8h or diclofenac 75 mg IM q12h, for 48 hours. Meperidine 1 mg/kg IM was given for additional analgesia when needed (rescue medication). Pain relief was assessed using an 11-point visual analog scale (0 = no pain to 10 = worst pain imaginable) immediately before the first injection (baseline), and at 15 and 30 minutes and 1, 2, 3, 4, 6, 12, 18, 24, and 48 hours after the first injection. Sedation was assessed using a 5-point scale (0 = awake and alert to 4 = deep sedation) at the same time points. Tolerability was assessed by monitoring of AEs using patient interview and laboratory analyses.

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Results: Forty patients were enrolled in the study (30 men, 10 women; mean [SD] age, 54.4 [11.1] years; 20 patients per treatment group). The demographic and clinical characteristics and mean baseline pain relief scores were statistically similar between the 2 treatment groups. The mean pain relief scores at 15 and 30 minutes were statistically similar to baseline values in the 2 treatment groups. However, the mean pain relief scores at ≥1 hour after the first injection were significantly lower compared with baseline values (both groups, \( P < 0.05 \) at time points ≥1 hour). No significant between-group differences in mean pain relief scores were found at any time point. The overall mean pain relief scores were statistically similar between the 2 treatment groups. The mean sedation scores were significantly higher at 30 minutes, 1 hour, and 2 hours after the first injection in the diclofenac group compared with the lornoxicam group (all, \( P < 0.05 \)). No AEs were observed. The need for rescue medication was statistically similar between the 2 treatment groups (lornoxicam, 2 patients; diclofenac, 3 patients).

Conclusions: In this study of adult patients who underwent CABG, the efficacy of lornoxicam and diclofenac were similar in postoperative pain management. Both study drugs were well tolerated. (Curr Ther Res Clin Exp. 2005;66:107-116) Copyright © 2005 Excerpta Medica, Inc.

Key words: postoperative analgesia, cardiac surgery, diclofenac, lornoxicam.

INTRODUCTION

Inadequate pain management after cardiac surgery may result in increased morbidity and length of hospital stay.\(^1\)-\(^3\) Postoperative analgesia may facilitate the resumption of activities of daily living, including ambulation, deep breathing, and effective coughing.\(^4\) Opioids are the mainstay of pain management after major surgical procedures. However, their use may lead to adverse effects (AEs) (eg, respiratory depression, sedation, nausea, and constipation).\(^5\),\(^6\) Nonsteroidal anti-inflammatory drugs (NSAIDs) may be used for postoperative pain management to avoid the AEs associated with opioids.\(^7\)

Lornoxicam is an NSAID developed ~7 years ago.\(^8\) It has pharmacokinetic and pharmacodynamic properties similar to those of the often-used drug piroxicam. It has been shown to be as effective as morphine, pethidine (meperidine), and tramadol in managing pain after several types of major surgery (eg, lumbar disk surgery, dental surgery, hysterectomy).\(^8\)-\(^11\) However, based on a MEDLINE search (key terms: lornoxicam, cardiac surgery, and postoperative pain control; years: 1960-2004), lornoxicam has not been studied for use in pain management after cardiac surgery. Thus, the aim of the present study was to compare the efficacy and tolerability of lornoxicam and diclofenac sodium (an NSAID with a good safety profile well established for use in pain management after major surgery\(^7\),\(^12\),\(^13\)) in pain management after valve or coronary artery bypass grafting (CABG) surgery.
PATIENTS AND METHODS
This single-blind, randomized, active-controlled study was conducted at the Gaziantep University Hospital, Gaziantep, Turkey. Approval of the study protocol was obtained from the ethics committee at the hospital. Written informed consent was obtained from each eligible patient before the study.

Inclusion and Exclusion Criteria
Patients aged 18 to 65 years scheduled to undergo valve or CABG surgery for the first time using a pump oxygenator were eligible for the study.

Patients were excluded if they had hepatic or renal disease, diabetes mellitus, cancer, and/or were receiving oral contraceptives.

Surgical Procedures
Patients were admitted to the hospital on the night before surgery and were premedicated with diazepam 10 mg PO at 10 PM on the evening before surgery. Patients were monitored using electrocardiography, pulse oximetry, and arterial and central venous catheterization. Anesthesia was induced using IV administration of fentanyl 2 µg/kg, midazolam 0.02 to 0.05 mg/kg, and propofol 1 to 2 mg/kg, and maintained using fentanyl 0.1 µg/kg·min IV and inhalational isoflurane 0.6% to 1.0% in pure oxygen. Neuromuscular blockade was achieved using vecuronium bromide 0.1 mg/kg IV and maintained using IV infusions of vecuronium bromide bolus 0.03 mg/kg at 30-minute intervals. All surgical procedures were performed through a full median sternotomy by the same surgical team in each patient.

After surgery, while in the intensive care unit (ICU), patients underwent mechanical ventilation and were switched to synchronized intermittent mandatory ventilation plus pressure support. Patients were extubated when they were hemodynamically stable, cooperative, without excessive chest tube drainage, and fulfilled the extubation criteria (negative inspiratory force, >−20 cm H2O; arterial carbon dioxide tension, <45 mm Hg; fraction of inspired oxygen, <0.5%; pH >7.30). The extubation time was recorded in each patient.

Administration of Study Medication
After extubation and when they stated that they felt pain, patients were randomly assigned, using a computer-generated table of random numbers, to 1 of 2 treatment groups: lornoxicam 8 mg IM q8h or diclofenac 75 mg IM q12h, for 48 hours. The study investigators were blinded to the administration schedules of the 2 study drugs. Meperidine 1 mg/kg IM was given for additional analgesia in cases of inadequate pain relief (rescue medication).

Efficacy Assessment
Pain relief and sedation were assessed by the physician responsible for postoperative care of the patients, immediately before the first injection of study medication (baseline; time 0) and at 15 and 30 minutes and 1, 2, 3, 4, 6, 12, 18, 24, and
48 hours after the first injection. Pain relief was assessed using an 11-point visual analog scale (VAS) (0 = no pain to 10 = worst pain imaginable). Sedation was assessed using a 5-point scale (0 = awake and alert to 4 = deep sedation).

**Tolerability Assessment**

ADs (eg, gastric discomfort, nausea, vomiting, hypotension, bradycardia, renal impairment) were monitored throughout the study using patient interview and laboratory analyses. Nausea was to be treated using metoclopramide 10 mg IV. Bleeding at the operative site was assessed using visualization through a chest tube each hour for 72 hours after surgery.

**Statistical Analysis**

Statistical analyses were performed using SPSS version 10.0 (SPSS Inc., Chicago, Illinois). Results are presented as mean (SD). The chi-square test and the Fisher exact test were used to compare occurrences between the 2 treatment groups. The unpaired Student t test was used to compare measured data (VAS or sedation score) between the 2 groups. A P value <0.05 was considered statistically significant.

**RESULTS**

Forty patients were enrolled in the study (30 men, 10 women; mean [SD] age, 54.4 [11.1] years; 20 patients per treatment group). The demographic and clinical characteristics of the study patients were statistically similar between the 2 treatment groups (Table I).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lornoxicam (n = 20)</th>
<th>Diclofenac (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53.3 (12.2)</td>
<td>55.7 (10.3)</td>
</tr>
<tr>
<td>Sex, no. of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Type of surgery, no. of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Valve</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Duration of surgery, h</td>
<td>4.46 (0.32)</td>
<td>4.23 (0.28)</td>
</tr>
<tr>
<td>CPB time, min</td>
<td>95 (25)</td>
<td>110 (34)</td>
</tr>
<tr>
<td>Extubation time, min</td>
<td>224 (34)</td>
<td>216 (24)</td>
</tr>
<tr>
<td>Chest tube drainage, mL/24 h</td>
<td>420 (50)</td>
<td>460 (70)</td>
</tr>
</tbody>
</table>

CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass.

*No significant between-group differences were found.*
Efficacy

The baseline mean pain relief scores were statistically similar between the 2 groups (Figure). The mean (SD) extubation times were 224 (34) and 216 (24) minutes in the lornoxicam and diclofenac groups, respectively. The lornoxicam group received the first dose of study medication at 108 (26) minutes (mean [SD]) after extubation, and the diclofenac group, at 96 (12) minutes (mean [SD]) after extubation. The mean pain relief scores at 15 and 30 minutes after the first injection of study medication were statistically similar to baseline values in the 2 treatment groups (Table II). At ≥1 hour after the first injection in the 2 treatment groups, the mean pain relief scores were significantly lower compared with baseline values (nearly zero at 48 hours) (both groups, P < 0.05 at time points ≥1 hour). The pain relief scores were statistically similar between the 2 groups at all time points (Table II).

In the diclofenac group, the mean sedation scores were significantly higher at 30 minutes, 1 hour, and 2 hours after the first injection compared with those in the lornoxicam group (Table II) (all, P < 0.05).

Tolerability

None of the patients receiving either study drug experienced gastric discomfort, nausea, vomiting, hypotension, bradycardia, or renal damage (Table III). Two patients in the lornoxicam group and 3 patients in the diclofenac group required rescue medication. The mean (SD) additional analgesia times were

![Figure. Mean (SD) pain relief scores in the study population (N = 40). Pain relief was assessed using an 11-point visual analog scale (0 = no pain to 10 = worst pain imaginable). *P < 0.05 versus preinjection (0 min).]
Table II. Mean (SD) pain relief* and sedation† scores in the study population (N = 40).

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Pain Relief Score</th>
<th>Sedation Score</th>
<th>Pain Relief Score</th>
<th>Sedation Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lornoxicam (n = 20)</td>
<td></td>
<td>Diclofenac (n = 20)</td>
<td></td>
</tr>
<tr>
<td>Before injection (baseline)</td>
<td>5.35 (0.98)</td>
<td>3.78 (2.10)</td>
<td>5.15 (2.85)</td>
<td>4.75 (3.00)</td>
</tr>
<tr>
<td>After injection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 min</td>
<td>6.25 (1.68)</td>
<td>2.00 (0.67)</td>
<td>6.12 (2.41)</td>
<td>2.00 (0.64)</td>
</tr>
<tr>
<td>30 min</td>
<td>5.25 (1.99)</td>
<td>0.41 (0.09)</td>
<td>5.10 (2.42)</td>
<td>1.90 (0.71)†</td>
</tr>
<tr>
<td>1 h</td>
<td>3.70 (2.25)§</td>
<td>0.60 (0.13)</td>
<td>3.72 (2.30)§</td>
<td>1.25 (0.78)§</td>
</tr>
<tr>
<td>2 h</td>
<td>2.55 (2.37)§</td>
<td>0.51 (0.11)</td>
<td>3.47 (2.35)§</td>
<td>1.10 (0.91)§</td>
</tr>
<tr>
<td>3 h</td>
<td>0.25 (0.78)§</td>
<td>0.41 (0.09)</td>
<td>3.45 (3.15)§</td>
<td>0.75 (0.55)</td>
</tr>
<tr>
<td>4 h</td>
<td>0.10 (0.44)§</td>
<td>0.44 (0.10)</td>
<td>2.55 (2.43)§</td>
<td>0.70 (0.57)</td>
</tr>
<tr>
<td>6 h</td>
<td>1.10 (0.65)§</td>
<td>0.52 (0.11)</td>
<td>2.60 (1.75)§</td>
<td>0.25 (0.44)</td>
</tr>
<tr>
<td>12 h</td>
<td>2.65 (2.10)§</td>
<td>0.58 (0.13)</td>
<td>3.25 (2.90)§</td>
<td>0.90 (1.97)</td>
</tr>
<tr>
<td>18 h</td>
<td>0.65 (1.72)§</td>
<td>0.22 (0.05)</td>
<td>1.95 (0.90)§</td>
<td>0.20 (0.41)</td>
</tr>
<tr>
<td>24 h</td>
<td>1.67 (1.43)§</td>
<td>0.00 (0.00)</td>
<td>1.25 (0.86)§</td>
<td>0.05 (0.22)</td>
</tr>
<tr>
<td>48 h</td>
<td>1.23 (0.33)§</td>
<td>0.00 (0.00)</td>
<td>1.10 (0.30)§</td>
<td>0.00 (0.00)</td>
</tr>
</tbody>
</table>

*Pain relief was assessed using an 11-point visual analog scale (0 = no pain to 10 = worst pain imaginable).
†Sedation was assessed using a 5-point scale (0 = awake and alert to 4 = deep sedation).
§P < 0.05 versus lornoxicam group.
*P < 0.05 versus baseline.

Table III. Hemodynamic properties of the study population (N = 40).* Data are mean (SD).

<table>
<thead>
<tr>
<th>Property</th>
<th>Lornoxicam Before Surgery (n = 20)</th>
<th>Lornoxicam 24 h After Surgery (n = 20)</th>
<th>Diclofenac Before Surgery (n = 20)</th>
<th>Diclofenac 24 h After Surgery (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb, mmol/L</td>
<td>10.5 (0.9)</td>
<td>7.5 (1.1)</td>
<td>11.2 (2.9)</td>
<td>7.1 (0.7)</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>36.2 (1.6)</td>
<td>31.7 (2.6)</td>
<td>35.8 (2.4)</td>
<td>30.7 (2.6)</td>
</tr>
<tr>
<td>SCC, μmol/L</td>
<td>1.1 (0.1)</td>
<td>1.2 (0.9)</td>
<td>0.8 (0.2)</td>
<td>1.4 (0.7)</td>
</tr>
<tr>
<td>Platelet count, cells × 10⁹/L</td>
<td>222 (59)</td>
<td>164 (36)</td>
<td>234 (65)</td>
<td>158 (42)</td>
</tr>
<tr>
<td>INR</td>
<td>1.2 (0.1)</td>
<td>1.6 (0.3)</td>
<td>1.1 (0.2)</td>
<td>1.4 (0.4)</td>
</tr>
</tbody>
</table>

Hb = hemoglobin concentration; SCC = serum creatinine concentration; INR = international normalized ratio.
*No significant between-group differences were found.
5.9 (0.4) hours in the lornoxicam group and 5.2 (0.3) hours in the diclofenac group. No significant between-group differences were found in the prevalence of bleeding at the operative site (Table I), and none of the patients required repeat surgery during the study period.

DISCUSSION
Opioids are frequently used for pain management after cardiac surgery, with morphine being most commonly prescribed. In 1 study, lornoxicam was found to be as effective as morphine in total pain relief after microsurgical lumbar disk surgery. Our study compared lornoxicam with diclofenac, and the results suggest that the 2 drugs have similar analgesic efficacy.

The analgesic efficacy and tolerability of lornoxicam, at differing doses and routes of administration, have been compared with other analgesics in previous studies. Hein et al compared the analgesic effects of lornoxicam 8 mg PO with those of paracetamol 1 g PO after gynecologic surgery and found similar, satisfactory analgesia with both study drugs. Thienthong et al studied lornoxicam 16 mg IV in patients undergoing spinal surgery and found adequate pain relief 2 hours postoperatively. In another study, Trampitsch et al reported that lornoxicam 8 mg IV was associated with improved quality of analgesia after gynecologic surgery compared with controls. Based on our literature search, no studies have compared the doses and effects of lornoxicam and diclofenac. However, studies comparing the effects of diclofenac with those of other analgesics in patients undergoing surgeries other than cardiac surgery have shown diclofenac 75 to 100 mg administered 2 to 4 times daily to be effective. Although lornoxicam and diclofenac are not equipotent, the doses used in the present study have been found to be effective for postoperative analgesia in various types of surgery.

Opioids have been associated with AEs (eg, respiratory depression, sedation, nausea, and constipation). For example, the sedation frequently seen with the use of opioids may cause delayed extubation, delayed and/or restricted ambulation, and increased length of stay in the ICU. For this reason, some investigators have suggested substituting opioids with other drug classes, such as NSAIDs, in postoperative pain control. However, NSAIDs also have been associated with serious AEs (eg, hypotension, bradycardia, gastric discomfort, renal damage, nausea and vomiting, bleeding disorders). In fact, Griffin concluded that NSAIDs should not be used routinely in cardiac surgery because of these AEs. For example, NSAIDs inhibit prostaglandin synthesis, which may result in impaired platelet function and, hence, bleeding at the surgical site. However, because NSAIDs inhibit cyclooxygenase action to differing extents, their antiplatelet action differs. Based on the literature search, the present study is the first to compare the effects of lornoxicam and diclofenac in cardiac surgery. Thus, the effects of these 2 drugs on operative-site bleeding in cardiac surgery have not been reported. However, the effects of various NSAIDs have been compared in various surgeries other than cardiac surgery (eg, tonsillectomy), and
the need for repeat surgery due to bleeding at the operative site has been found to be greater with NSAIDs compared with controls. In the study by Hein et al., lornoxicam was associated with better pain relief compared with paracetamol in gynecologic surgery, and no significant between-group difference was found in the prevalence of operative-site bleeding. Niemi et al. reported reversible platelet dysfunction with long-term diclofenac use in healthy volunteers. In the present study, no serious postoperative bleeding was found with either NSAID.

Although the mean sedation score was higher in the diclofenac group compared with the lornoxicam group at 30 minutes, 1 hour, and 2 hours after the first injection of study medication (all, \( P < 0.05 \)), all sedation scores in both groups were <3 (easy to wake up when slightly shaken).

Study Limitations
The number of patients in the present study was fairly small. Furthermore, this study had a single-blind design. Future studies with larger sample sizes and using additional comparator drugs and a double-blind design are necessary to investigate the effectiveness of these drugs in relieving pain after cardiac surgery.

CONCLUSIONS
This comparison of the effects of lornoxicam and diclofenac in adults undergoing CABG suggests that pain after cardiac surgery may be controlled with either drug. Both study drugs were well tolerated.

REFERENCES


