A randomized, double-blind, controlled trial on non-opioid analgesics and opioid consumption for postoperative pain relief after laparoscopic cholecystectomy

S. ABDULLA, R. ECKHARDT, U. NETTER and W. ABDULLA

Abstract: Background: Following laparoscopic cholecystectomy, an effective post-operative pain control is necessary, at least during the first 24 hours. We present a randomized, double-blind trial on the effect of the combined use of intravenous parecoxib, and metamizol or paracetamol on piritramide consumption using a patient-controlled analgesia (PCA) pump in patients recovering from laparoscopic cholecystectomy.

Methods: 120 patients were randomly allocated to four patient groups treated with normal saline or one of non-opioid analgesics (parecoxib 40mg twice daily, metamizol 1 g three times daily, paracetamol 1 g three times daily) in addition to piritramide using the PCA pump. Beginning in the post-anesthesia care unit (PACU), patients were asked every 2 h for 6 hours and afterwards once every 6 h to quantify their pain experience at rest while piritramide consumption was recorded.

Results: In all groups, piritramide consumption was high in PACU. Only metamizol significantly reduced piritramide consumption compared to the others upon discharge from PACU. Overall, cumulative piritramide consumption was slightly lower in the metamizol group and higher in the NaCl group; however, these findings were statistically not significant. VAS scores were highest upon arrival in PACU and dropped almost continuously after surgery. A significantly lower postoperative pain intensity was only found in the parecoxib group at 24 h after surgery compared to the metamizol group.

Conclusion: The efficacy of tested additive medications on piritramide consumption and pain relief is weak and there is no clear-cut difference between the non-opioid drugs used.

Key words: Non-opioid analgesics; postoperative pain management; piritramide; PCA-pump; laparoscopic cholecystectomy.

INTRODUCTION

Laparoscopic cholecystectomy belongs to those surgical procedures with the highest incidence of moderate to severe pain for 24 hr post-operatively (1). Intravenous opioids delivered by patient-controlled analgesia (PCA) devices provide efficient pain relief, but opioid therapy is associat-ed with dose-related adverse effects. Therefore, drug combinations with different mechanisms of action are widely used in the treatment of acute pain, and constitute the basis for multimodal or balanced analgesia (2, 3). Numerous studies were conducted with different opioids alone and in combination with many other drugs to augment the analgesic effect or reduce the adverse events; the results, however, remain controversial. While in most studies and systematic reviews morphine consumption was decreased when combined with paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) or COX-2-inhibitors (4, 5), there are also newer studies who do not report any opioid-sparing effect (6, 7, 8, 9, 10, 11).

The aim was therefore to perform a prospective, randomized, double-blind, placebo-controlled study in patients undergoing laparoscopic cholecystectomy. The primary objective was to compare postoperative piritramide consumption alone or in combination with parecoxib, metamizol (dipyrone) or propacetamol (paracetamol) for providing pain relief in adult patients during the first 24 hours of their recovering from a laparoscopic cholecystectomy. Secondary outcomes included pain intensity and patient satisfaction.

PATIENTS AND METHODS

The investigative protocol was approved by the Institutional Review Board of our teaching
hospital, and all patients provided written informed consent before enrollment. The study began in March 2004 and ended in August 2007. Patients in the age between 18 and 75 years and ASA physical status I to III were included. Patients with a history of significant cardiac, pulmonary, hepatic, or renal disease, morbid obesity, chronic pain and drug or alcohol abuse, and contraindications or previous adverse reaction to any of the drugs used in the study were excluded. Also not included were patients unable to cooperate.

Patients meeting the inclusion criteria and scheduled for laparoscopic cholecystectomy under general anesthesia were visited the night before surgery and the use of PCA for postoperative pain relief as well as scales for the determination of pain intensity and patient satisfaction were explained. After informed consent, one hundred and twenty patients were assigned to one of four groups, based on a computer-generated randomization table (http://www.randomization.com) (Fig. 1).

The four study groups were A) placebo, B) parecoxib 40 mg, C) metamizol 1 g, and D) paracetamol 1 g (Table 1). The drugs were dissolved in 100 ml normal saline and given via IV infusion over 15 min. Patients of the placebo group received only 100 ml of normal saline. In all groups 10 min before extubation 2 mg piritramide (Dipidolor®, Janssen-Cilag) was injected. During the postoperative period, piritramide was offered in the form of a patient-controlled analgesia by means of a PCA pump as an electronically steered syringe pump.

The study solutions were prepared by one of the researchers who were not involved in the intraoperative and postoperative treatment of these patients. Postoperative data were collected by anesthesiologists who were blinded as to the treatment used. Other caretakers were also unaware of the analgesic drug that would be used for each patient during the study. The group assignment code was retained until the conclusion of the study. The observation time extended during a period of 24 hours after surgery.

For premedication, midazolam 7.5 mg (Dormicum®, Roche Pharma AG Grenzach-Wyhlen, Germany) was administered orally 60 min before the surgical procedure. On arrival in the operating room, standard monitors were applied. ECG, non-invasive arterial pressure, heart rate, and...
Peripheral oxygen saturation (SpO2) were monitored (Cicero PM 8040; Dräger, Lübeck, Germany). A crystalloid infusion (Infusionslösung E153®, Serumwerk Bernburg AG, Bernburg, Germany) was started after placing an 18-gauge catheter in the non-dominant hand for fluid administration intraoperatively. A second 18-G catheter in the other hand was used for the administration of anesthetic drugs; this catheter was removed upon discharge from the recovery room (postanesthesia care unit, PACU).

After the administration of oxygen via an anesthetic breathing circuit and facemask for 3 minutes, 1 mg vecuronium bromide (Norcuron®, Organon Gmbh, München, Germany) was given as pre-block while anesthesia was induced with 2 mg/kg propofol (Propofol® 1%, Fresenius Kabi Deutschland GmbH Bad Homburg, Germany) intravenously, followed by 1-1.5 mg/kg BW suxamethoniumchlorid (Lysthenon® 2%, Nycomed Deutschland GmbH Konstanz, Germany) to facilitate endotracheal intubation. After intubation, mechanical pressure controlled ventilation was initiated at a flow rate of 1 L/min in a semiclosed system (Cicero; Dräger, Lübeck, Germany) and nitrous oxide in oxygen at a ratio 1:1 was administered throughout surgery. The inspired oxygen and end-tidal concentrations of carbon dioxide (CO₂) were measured continuously at the proximal end of the endotracheal tube using a calibrated infrared gas analyzer (Dräger PM 8050, Dräger, Lübeck, Germany). Ventilation was adjusted to maintain end-tidal CO₂ between 4.5-5.0 kPa (34-38 mmHg).

Muscle relaxation was obtained with vecuronium bromide 0.6 mg/kg and monitored by the train-of-four stimulation method using a peripheral nerve stimulator. Anesthesia was maintained with a supplemental 3-6 mg/kg/h infusion of propofol and 3-10.5 µg/kg/h of remifentanil (Ultiva®, GlaxoSmithKline GmbH & Co. KG München, Germany), as to achieve an adequate depth of anesthesia with mean arterial pressure and heart rate within 20% range of preoperative values. Surgery was performed via a laparoscope after making a small incision and blindly inserting a Veress needle into the peritoneal cavity. In all patients, there was no need for blood transfusion.

Fifteen minutes before the expected end of surgery, each patient was treated according to randomization list (Table 1). Thereafter, the infusion of propofol and remifentanil was ceased and residual muscle relaxation as confirmed by train-of-four monitoring was reversed using 0.5 mg atropine and 5 to 10 mg pyridostigmine when necessary. The pre-programmed PCA equipment (Master PCA, Fresenius Vial Infusion Technology, Brezins, France) was provided to all patients with a 50-ml disposable syringe containing 45 mg of piritramide in 45 ml of saline solution. The PCA administered boluses were of 2 ml (= 2 mg piritramide) with a lockout interval of 10 min and a maximal volume of 30 ml in 4 h. A bolus of 2 mg piritramide was first injected 10 min prior to the extubation in the operating room.

Thereafter, the patients were directly transferred to PACU, where further clinical observations were done by an independent, blinded observer. On arrival, postoperative pain was treated by self-administration of small doses of IV piritramide using the PCA pump and patients were asked every 2 hours for the first 6 hours, and afterwards once every 6 hours, to quantify their pain experience at rest on a visual analogue scale (VAS) ranging between 0 and 10, with 0 representing no pain and 10 the worst imaginable pain. Likewise, pain relief was assessed by the patient on a 0-3 verbal rating scale (VRS) (0 = none, 1 = mild, 2 = moderate, 3 = complete). Patient satisfaction with the effectiveness of pain therapy was inquired at 6 hour intervals by using a 4 point-scale which shows the verbal expressed satisfaction of assigned numerical values: 1 = worse, 2 = moderate, 3 = good, 4 = very good. Postoperative piritramide consumption was recorded at discharge from PACU and after 6, 12 and 24 hours on the display of the PCA pump.

Data were first entered into Excel 2000 and then imported into SPSS for Windows Version 15.0

### Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>15 min prior to extubation</th>
<th>8 h postop.</th>
<th>12 h postop.</th>
<th>16 h postop.</th>
<th>24 h postop.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Placebo</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>B</td>
<td>Parecoxib</td>
<td>40 mg</td>
<td>NS</td>
<td>40 mg</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>C</td>
<td>Metamizol</td>
<td>1 g</td>
<td>1 g</td>
<td>NS</td>
<td>1 g</td>
<td>NS</td>
</tr>
<tr>
<td>D</td>
<td>Paracetamol</td>
<td>1 g</td>
<td>1 g</td>
<td>NS</td>
<td>1 g</td>
<td>NS</td>
</tr>
</tbody>
</table>
The incremental piritramide consumption in the four groups over 24 hours was presented in Figure 2. The highest mean values were recorded in PACU: NaCl group 11.2 ± 5.7 mg, parecoxib group 9.8 ± 5.5 mg, paracetamol group 10.5 ± 5.7 mg and the lowest with 6.1 ± 3.6 mg in the metamizol group. In the metamizol group, the required amounts of piritramide were significantly lower than in the NaCl group (P < 0.001), parecoxib (P = 0.003) and paracetamol groups (P = 0.002). However, the cumulative piritramide consumptions after 6, 12 and 24 hours showed no significant difference between the four groups. Accordingly, the cumulative piritramide consumption in all 4 patient groups showed a significant difference only between metamizol and NaCl after 6 hours (P = 0.001) and was slightly lower in the metamizol group and higher in the NaCl group at all recording times (Fig. 3). However, these findings were statistically not significant.

In all groups, VAS scores were highest upon arrival in PACU. The highest mean value was found in the NaCl group with 5.0 ± 2.2 and the lowest in the metamizol group with 4.4 ± 1.9 (Table 3). Afterwards, the VAS scores dropped in all groups almost continuously. A significant decrease of postoperative pain intensity (P < 0.05) was only found in the parecoxib group at 24 h compared to the metamizol group (P = 0.005). In addition, there was a high inter-individual variability in the intensity of pain after laparoscopic cholecystectomy: in all 4 patient groups, VAS-scores in the PACU spread from the lowest scores of 0 or 1 to a score of 8 (6 patients in the NaCl group, 1 in the parecoxib group, 1 in the metamizol group, 3 in the paracetamol group) or to a score of 9 (1 patient in the metamizol group) or even a score of 10 (1 patient in the parecoxib group).

### Table 2

Demographic and patient-referred data of the investigated four groups [Values are mean (SD) or number of patients as appropriate].

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo (n = 30)</th>
<th>Parecoxib (n = 30)</th>
<th>Metamizol (n = 30)</th>
<th>Paracetamol (n = 30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>24</td>
<td>22</td>
<td>21</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6</td>
<td>8</td>
<td>9</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>47.1 ± 13.9</td>
<td>54.9 ± 13.0</td>
<td>52.4 ± 15.6</td>
<td>52.5 ± 15.8</td>
<td>0.215</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.68 ± 0.08</td>
<td>1.67 ± 0.09</td>
<td>1.67 ± 0.07</td>
<td>1.67 ± 0.10</td>
<td>0.990</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>85.9 ± 19.9</td>
<td>77.0 ± 19.3</td>
<td>77.0 ± 15.6</td>
<td>79.7 ± 13.3</td>
<td>0.157</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.4 ± 6.3</td>
<td>27.2 ± 5.3</td>
<td>27.4 ± 4.7</td>
<td>28.5 ± 4.7</td>
<td>0.083</td>
</tr>
<tr>
<td>ASA physical status</td>
<td>II / III</td>
<td>20/10</td>
<td>17/13</td>
<td>17/13</td>
<td>16/14</td>
</tr>
<tr>
<td>Total remifentanil consumption (mg)</td>
<td>1.09 ± 0.49</td>
<td>0.95 ± 0.42</td>
<td>1.08 ± 0.53</td>
<td>1.11 ± 0.89</td>
<td>0.576</td>
</tr>
<tr>
<td>Duration of anesthesia (min)</td>
<td>107 ± 25</td>
<td>107 ± 24</td>
<td>117 ± 41</td>
<td>108 ± 36</td>
<td>0.546</td>
</tr>
</tbody>
</table>
Regarding patient satisfaction, there was no significant difference observed between the four groups at any time during the investigation period. In PACU, satisfaction of patients assessed on the 4 point-scale was moderate and rose then continuously to good and very good in all groups. Likewise the pain relief score showed no significant differences between groups at any recording time. No drug reactions, such as dizziness and respiratory depression occurred in our study. However, mild postoperative nausea and vomiting (PONV) were observed infrequently in all groups during the PACU stay, which were treated with 20 mg metoclopramide as an antiemetic.

**DISCUSSION**

In the present study, postoperative pain following laparoscopic cholecystectomy was most intense immediately after recovering from a
remifentanil-based anesthesia and decreased to low levels in all groups thereafter. The early intense pain after laparoscopic cholecystectomy seems to be complex in nature and does not resemble pain after other laparoscopic procedures (12). It is a conglomerate of three different and clinically separate components: incisional pain (somatic pain), visceral pain (deep intra-abdominal pain), and shoulder pain (presumably referred visceral pain) (13). In addition, the intensity of pain we observed immediately after laparoscopic cholecystectomy is characterized by a high inter-individual variability. This may partly be explained by the lockout time of 10 min between two doses of piritramide, which is routinely used in Germany (6). Smaller bolus doses with a shorter lockout time reduce piritramide consumption by enabling the patient to titrate analgesic effect more efficiently. However, they obviously do not reduce opioid-related side effects (14). A background infusion was not provided to our patients because of a possible increased risk of respiratory depression (15). Furthermore, remifentanil-based anesthesia has been shown to be associated with postoperative peri-incisional hyperalgesia (16, 17, 18, 19), a fact which may have contributed to overall pain in our patients. However, there was no significant difference in remifentanil consumption between the 4 groups in our study.

Accordingly, the required piritramide consumption was high upon arrival in PACU. A significantly lower level of early pain, and hence of piritramide consumption, was only observed in the metamizol group as compared to the NaCl, parecoxib and paracetamol groups. After the immediate postoperative period in PACU, piritramide consumption in the metamizol group remained slightly lower during the first 24 hours after surgery as compared to the 3 other groups (parecoxib, paracetamol and placebo). However, this was not statistically significant. Our study did not evidence any significant opioid-sparing effect of non-opioid analgesics over the entire 24 hour observation period. In a similar study in patients undergoing abdominal hysterectomy, we also did not find any significant difference with regard to an opioid-sparing effect of additional non-opioid agents, while VAS scores were significantly lower in the paracetamol and parecoxib groups at 6 h after surgery (11). Any further benefits were marginal and statistically not significant. These data are in accordance with the data

Fig. 3. — Cumulative piritramide consumption in mg (mean and standard deviations) in four groups over 24 hours postoperatively after laparoscopic cholecystectomy (Mann-Whitney-Test *P = 0.000 metamizol versus placebo, P = 0.003 metamizol versus parecoxib and P = 0.002 metamizol versus paracetamol; ** P = 0.003 metamizol versus NaCl).
published earlier in 2011 (6). This recent study compared 1 g intravenous paracetamol every 6 h with other intravenous non-opioids, including metamizol (1 g every 6 h) and parecoxib (40 mg every 12 h) as part of a multimodal concept for perioperative pain therapy in minor-to-intermediate surgery. The study showed that the efficacies of non-opioid analgesics were similar, and that piripramide consumption was not reduced by non-opioid analgesics (6). The data of the present study also confirm the previously published results with parecoxib and fentanyl after laparoscopic cholecystectomy (9), and other surgical procedures (8, 10). In contrast, another recent study assessed the analgesic efficacy of 80 mg parecoxib and 5 g paracetamol in patients undergoing elective thyroid or parathyroid surgery over a 24 hour period after surgery, and showed significantly reduced piripramide requirements (20). These results were similar to other studies after laparoscopic cholecystectomy or other procedures using parecoxib vs. lornoxicam (21, 7, 22, 23).

Apart from the superiority of metamizol combined with piripramide in PACU in this study, a significant difference (P < 0.05) in the documented visual analog scales (VAS pain scores) was found only at 24 h after surgery between parecoxib group as compared to the metamizol group. However, this finding does not allow any meaningful conclusion in so far as, at 12 hours and thereafter, all VAS scores were below 3, and hence pain intensity was very low. An additional benefit with an analgesic is not easy to demonstrate when baseline pain is low in all groups. Regarding patient satisfaction, no significant between group difference was found during the investigation period. No drug reactions, apart from mild nausea with or without vomiting, which were treated with antiemetic medications, occurred in our study.

A limitation of this study is that we used drugs which are not available in all countries. We also did not use the maximal doses recommended from the manufacturers with metamizol and paracetamol. Pain intensity was evaluated only at rest, and movement-related pain relief was not considered. In addition, the results might have been different if non-opioid analgesics had been given prior to surgery, as pre-emptive analgesia. We did not evaluate the role of timing of analgesia and the use of opioid only on demand. Finally, a comparison of the combined use of different drug classes (anti-inflammatory medications and paracetamol) given simultaneously as part of a multimodal treatment might be worthwhile.

**Conclusions**

Despite some limitations in our study, the efficacy of tested additive medications on piripramide consumption and pain relief was weak. There is no clear-cut difference between the non-opioid drugs used. The high pain scores during the immediate PACU period would not be recorded if portal site local anesthetic infiltration had been used in all groups, including the control group. Other emerging evidence in the literature supports the use of non-opioid analgesic medications at the start as opposed to the end of surgery for improving postoperative analgesia after laparoscopic cholecystectomy. Therefore, further studies are warranted in these areas.

**References**


© Acta Anaesthesiologica Belgica, 2012, 63, n° 1