ORIGINAL ARTICLE

Comparison of analgesic efficacy of acetaminophen monotherapy versus acetaminophen combinations with either pethidine or parecoxib in patients undergoing laparoscopic cholecystectomy: a randomized prospective study

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ABSTRACT

Aim To investigate analgesic effect of three different regimens of combination of analgesics administered to patients undergoing laparoscopic cholecystectomy.

Methods Patients undergoing laparoscopic cholecystectomy were randomly allocated to one of three groups on admission, depending of a prescribed post-operative analgesic regimen. Patients allocated to the group A received a combination of intravenous (IV) acetaminophen and intramuscular (IM) pethidine, patients in the group B received a combination of IV acetaminophen and IV parecoxib, and the patients of the group C received IV acetaminophen monotherapy. Analgesic therapy was administered at regular intervals. Pain was evaluated utilizing the numeric rating scale (NRS) at 5 time points: the first assessment was done at 45 minutes, the second, third, fourth and fifth at 2, 6, 12, and 24 hours post-administration, respectively. Postoperative pain intensity was measured by NRS within the groups and between the groups at each time they analysed using one-way repeat measured ANOVA and Post Hoc Test-Bonferroni Correlation.

Results A total of 316 patients were enrolled. The analgesic regimens of groups A and B (combination regimens consisting of IV acetaminophen and intramuscular pethidine and IV acetaminophen and IV parecoxib, respectively) were found to be of equivalent efficacy (p=1.000). In contrast, patients in group C (acetaminophen monotherapy) had higher NRS scores, compared to both patients in groups A (p<0.01) and B (p<0.01).

Conclusion This study confirms the notion of a significant opioid-sparing effect of parecoxib in postoperative pain management after laparoscopic cholecystectomy.

Key words: analgesia, numerical rating scale, post-operative pain

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INTRODUCTION

One of the most common minimally invasive surgical procedures is laparoscopic cholecystectomy. This technique has almost replaced the open technique for routine cholecystectomies since early 1990s (1). Currently, this procedure is indicated for the treatment of both acute and chronic cholecystitis, symptomatic cholelithiasis, biliary dyskinesia, acalculous cholecystitis, gallstone pancreatitis, and gallbladder tumours or polyps (2). Although, the greatest advantages of laparoscopy is the reduction of postoperative pain, when compared to open surgery, this still remains a considerable factor affecting perioperative course of the patients (3).

Pain leads to increased morbidity and is the primary reason for prolonged hospitalization after laparoscopic cholecystectomy (4,5). Patients' most common complains are back and shoulder pain and discomfort at port-site incisions (6). Shoulder and sub-diaphragmatic pain occur in about 12- 60% of patients (7). Peak intensity of pain occurs during the first few postoperative hours and usually declines after 2 or 3 days (8).

Several methods of pain control have been harnessed in this setting, such as the administration of intravenous (IV) non-steroidal anti-inflammatory drugs (NSAIDs), intramuscular opioids or intraperitoneal local anaesthetics, with questionable outcomes regarding the optimum approach to pain management (9). The NSAIDs inhibit the enzymes cyclooxygenase (COX) -1 and -2. Only the inhibition of COX-2 is thought to be involved in analgesic, anti-inflammatory, and antipyretic effects of NSAIDs (10).

Albeit, mechanism of action of acetaminophen remains unclear. In contrast to opioids, acetaminophen has no known endogenous binding sites and, unlike NSAIDs, causes only weak inhibition of peripheral cyclooxygenase activity, with apparent selectivity for COX-2. There is increasing evidence of an additional central antinociceptive effect (11). Although the mechanism of analgesic efficacy of paracetamol remains intangible, it may also involve direct and indirect inhibition of central cyclooxygenases. Furthermore, the activation of the endocannabinoid system and spinal serotonergic pathways also seems to be essential in its analgesic action (12)

There are two non-opioid analgesics, parecoxib and acetaminophen, with proven effectiveness after different surgical procedures (13). Wide use of non-opioid analgesics can reduce opioid-induced side-effects (14,15).

The aim of this prospective interventional cohort study was to compare the analgesic efficacy of three analgesic regimens in the setting of laparoscopic cholecystectomy: acetaminophen monotherapy versus acetaminophen combinations with either pethidine or parecoxib. Although there are many studies in the literature about post-operative management after laparoscopic cholecystectomy. studies investigating and contrasting analgesic effect of combined pethidine/acetaminophen and parecoxib/acetaminophen have not been published so far.

PATIENTS AND METHODS

Patients and study design

This prospective, randomized trial was conducted at the University Hospital of Patras in Greece between February 2017 and May 2019, and included 316 patients undergoing elective laparoscopic cholecystectomy.

All patients provided a written informed consent. Ethical approval was obtained from the Ethics Committee of the General University Hospital of Patras. (No 838-10/3/2017).

Inclusion criteria were age between 35 and 65 years, American Society of Anesthesiologists physical status classification I or II (16), and diagnosis of cholelithiasis that was scheduled to be treated by elective laparoscopic cholecystectomy. Preoperative evaluation for general anaesthesia was performed. Exclusion criteria were heart failure, liver failure, renal dysfunction, diabetes, severe bronchial asthma, neurological or psychiatric disease, history of chronic pain or opioid intake, difficulties in communication due to language barriers or intellectual disability, and history of adverse events after NSAIDs (acetaminophen, parecoxib) or pethidine administration. The day before surgery, the patients gave informed written consents to the study. The day prior to surgery patients were introduced to the numerical rating scale (NRS) for pain documentation (17).

All participants were randomly assigned to each of the three groups before surgery using a com-

puter-generated random number generator and sequentially numbered opaque sealed envelopes. The patients in group A were randomized to receive IV acetaminophen 1000 mg every 8 hours and intramuscular pethidine 50 mg every 12 hours, the patients in group B were randomized to receive a combination of IV acetaminophen 1000 mg every 8 hours and IV parecoxib 40mg every 12 hours, and the patients in group C were randomized to receive IV acetaminophen 1000 mg every 8 hours only. The patients who asked for more postoperative analgesics were excluded from this trial.

All operations were conducted by the same group of surgeons and anaesthesiologists. General anaesthesia consisted of IV fentanyl 0.5-1.5 μg/kg and propofol. All patients received IV acetaminophen 1000 mg, IV parecoxib 40 mg and intramuscular pethidine 50 mg during the procedure.

Methods

After patient's extubating in the operating room, surgical information was recorded such as surgery time, intra-operative complications, and analgesics used. Following surgery, patients were transferred to the surgical ward. Patients were evaluated at the bedside at 45 minutes, 2 hours, 6 hours, 12 hours and 24 hours after receiving the first analgesic dose from their allocated regimen. Patients' NRS pain ratings were recorded on postoperative monitoring charts. The scale ranged from 0-10: 0 means no pain and 10 corresponds to the maximum possible pain.

Statistical analysis

Data were collected and expressed as mean ± standard deviation. The analysis of pain scores was expressed as mean and 95% confidence interval. The postoperative pain intensities measured by NRS within the groups and between the groups at each time interval were analysed using one-way repeat measured ANOVA and Post Hoc Test-Bonferroni Correlation. The $p<0.05$ was considered significant. Normality of the data was tested using Shapiro-Wilk test for normality.

RESULTS

A total of 316 patients, including 152 males and 164 females, were enrolled in the study. The youngest patient was 36, the oldest one was 63 years old. A total of 106 patients received IV paracetamol and IM pethidine as an analgesic therapy, 113 received IV paracetamol and IV parecoxib postoperatively, whereas 107 patients received IV paracetamol (monotherapy). Thirty patients from group C asked for more postoperative analgesics and were excluded from this trial (Table 1, Figure 1).

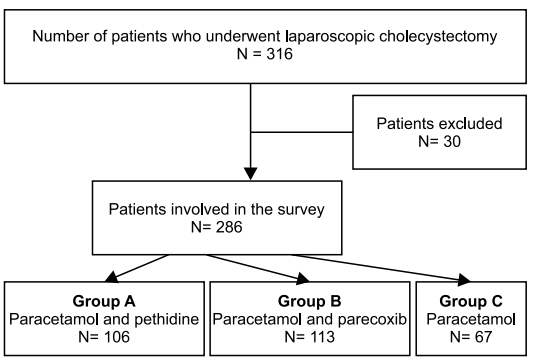

Figure 1. Flowchart of 316 patients who underwent laparoscopic cholecystectomy

All patients were discharged following one day of postoperative hospitalization. No intra-operative complications were recorded.

The mean NRS for patients that were treated with IV paracetamol and IM pethidine (Group A) was 5.18 at 45 minutes (0.75 hours), 3.73 at 2 hours, 2.55 at 6 hours, 1.82 at 12 hours and 0.98 at 24 hours (Figure 2). The mean NRS for patients that were treated with IV paracetamol and IV parecoxib (Group B) was 5.02 at 45 minutes (0.75 hours), 3.87 at 2 hours, 2.61 at 6 hours,1.89 at 12

Table 1. Number of patients, gender, mean age, hospitalization and duration of surgery according to the patient's group

Variable	Group A Paracetamol and pethidine	Group B Paracetamol and parecoxib	Group C Paracetamol (monotherapy)
Number of patients (n=286)	106	113	67
Males/Females (137/149)	52/54	54/59	31/36
Mean age (No) (years)	48 (38-60)	51 (41-63)	47 (36-59)
Hospitalization (± SD) (days)	1	1	1
Intraoperative complications (No)	0	0	0
Mean operative (± SD) time (minutes)	36.8±9.1	39.4±7.4	38±6.3
Dosage	Paracetamol 1gr/8h Pethidine 50mg/6h	Paracetamol 1gr/8h Parecoxib 40mg/12h	Paracetamol 1gr/8h

hours and 1.01 at 24 hours, while the mean NRS for patients that were treated with only IV paracetamol (Group C) was 5.81 at 45 minutes (0.75 hours), 4.89 at 2 hours, 3.63 at 6 hours, 2.90 at 12 hours and 1.84 at 24 hours (Figure 2).

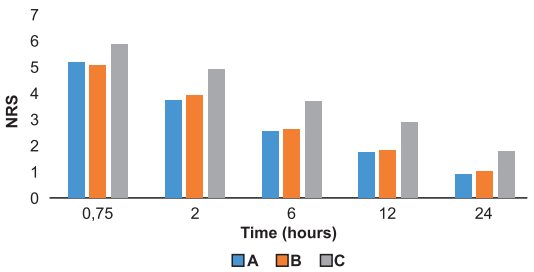

Figure 2. Mean numerical rating scale (NRS) between the patients of group A (paracetamol and pethidine) group B (paracetamol and parecoxib) and group C (paracetamol -monotherapy) based on time

The NRS scores of the group C (paracetamol monotherapy) were significantly higher than those of the groups A (pethidine + paracetamol, $p<0.01$) and B (paracetamol + parecoxib, $p<0.01$), while there was no significant difference between the patients of group A and group B ($p=1.00$) (Table 2).

Table 2. Mean numerical rating scale (NRS) between the three groups of patients based on time of administration

Time of administration (hours)	Mean NRS according in the group		
	Group A Paracetamol and pethidine	Group B Paracetamol and parecoxib	Group C Paracetamol (monotherapy)
at 0.75	5.18	5.02	5.81
at 2	3.73	3.87	4.89
at 6	2.55	2.61	3.63
at 12	1.82	1.89	2.9
at 24	0.98	1.01	1.84

DISCUSSION

According to the results of our study, the combinations of pethidine/paracetamol and parecoxib/paracetamol showed a comparable analgesic effectiveness and they were better than paracetamol monotherapy for the management of postoperative pain after laparoscopic cholecystectomy. One of the most important interference in minimizing sedation, impaired pulmonary function and constipation among operated patients is the reduction in doses of opioids by using postoperative non-opioid analgesics (13). In our study, we have rummaged the effect of paracetamol and its combination with parecoxib and pethidine on postoperative pain in a randomized, controlled trial. All patients who were included in this study were treated with laparoscopic cholecystectomy under general anaesthesia using standardized surgical and anaesthetic techniques. Pain was evaluated utilizing the numeric rating scale (NRS). This scale was chosen because comparing to other pain intensity scales it is more preferable by patients, as well as in comparison to other pain scales (such as the Visual Analogue Scale, VAS) (18), it is more sensitive in calculating the pain intensity changes that occur (18, 19).

The outcomes of this randomized, prospective study suggest that there was no statistically significant difference in postoperative analgesic treatment among acetaminophen/parecoxib and acetaminophen /pethidine. It is noteworthy to mention that both aforementioned combinations were found to be superior when compared to acetaminophen monotherapy in achieving pain control, in patients with laparoscopic cholecystectomy and should therefore be preferred in this setting. Based on the fact that these two pharmacologic regimens of analgesics appear to be equivalent in efficacy, the combination of acetaminophen and parecoxib might be preferable over acetaminophen and pethidine in order to reduce opioid consumption and associated adverse events (20,21).

Parecoxib is the first parenteral COX-2 inhibitor available for clinical use in pain management (22,23). It is well known from previous clinical trials that its peak serum concentrations occur about 30 minutes after intravenous (IV) administration and 1 hour after intramuscular (IM) injection. Its first perceptible analgesic effect occurs within 7-13 minutes, with clinically meaningful analgesia demonstrated within 23-39 minutes and a peak effect within 2 hours following administration of single doses of 40 mg by IV or IM injection (23). The analgesic efficacy of parecoxib sodium 20 and 40 mg, IV or IM, has been found to be similar to that of ketorolac 15-30 mg IV and 30-60 mg IM, and IV morphine 12 mg (23-25). The advantages of this analgesic include its morphine-sparing effects as shown in multiple studies (23, 26, 27). Several randomized controlled trials indicated a reduction in postoperative opioid consumption after parecoxib in different operations such as total hip or knee arthroplasty, hysterectomy and laparoscopic cholecystectomy (13). However, studies investigating and contrasting the analgesic effect of combined pethidine/acetaminophen and parecoxib/acetaminophen have not been published so far.

One limitation of this study that should be considered is that we did not record data during mobilization, as pain scores were recorded only at rest. The pain rating at rest alone is not very helpful as it is the functional outcome that is of clinical interest. Evaluation of pain during movement might be the initiative for a further study to be conducted (28).

In conclusion, the combination of postoperative analgesic treatment with IV paracetamol and IV parecoxib IV seems to be equivalent to the combination of IV paracetamol and intramuscular pethidine in patients undergoing laparoscopic cholecystectomy. Both combinations of postoperative analgesics outweigh the paracetamol monotherapy and should be therefore preferred in laparoscopic cholecystectomy. Furthermore, our study confirms the notion of a significant opioid-sparing effect of parecoxib in postoperative pain management after laparoscopic cholecystectomy.

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TRANSPARENCY DECLARATION

Conflict of interests: None to declare.

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