SCIENTIFIC PAPER

Intraperitoneal and Intravenous Routes for Pain Relief in Laparoscopic Cholecystectomy

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ABSTRACT

Background: Postoperative abdominal and shoulder pain are the most common complaints after elective laparoscopic cholecystectomy. Postoperative pain is multifactorial in origin, and therefore multimodal therapy may be needed to optimize pain relief.

Methods: We conducted a double-blind study where patients were randomly allocated to 1 of 5 groups of 20 patients each. Statistical significance was considered $P<0.05$. Group 1 received 40mL bupivacaine 0.25% intraperitoneal spray. Group 2 received 40 mL bupivacaine 0.25% intraperitoneal spray mixed with 200 mg ketoprofen. Group 3 received 40 mL bupivacaine 0.25% intraperitoneal spray and intravenous 200 mg ketoprofen. Group 4 received 200mg ketoprofen intravenously. Group 5 was the control group.

Results: Demographic data were similar in the 5 groups. As compared with the control group, group 1 had significantly lower abdominal pain scores at 6 hours; group 2 at 0, 1, 2, and 6 hours; group 3 at 0, 1, 2, 6, 12, and 24 hours; and group 4 at 2 hours. Group 1 had significantly lower shoulder pain scores at 1 and 6 hours; group 2 at 0 and 6 hours; and groups 3 and 4 at 0, 1, and 6 hours. The number of patients requiring postoperative rescue analgesics and the incidence of postoperative vomiting were significantly lower in group 3 only.

Conclusions: A multimodal approach to pain management following elective laparoscopic cholecystectomy is best achieved with a combination of 40 mL bupivacaine 0.25% intraperitoneal spray and 200 mg intravenous ketoprofen, achieving the least incidence of postoperative vomiting.

Key Words: Laparoscopic cholecystectomy, Postoperative pain, Intraperitoneal bupivacaine, Intravenous ketoprofen.

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INTRODUCTION

The laparoscopic approach to cholecystectomy has been proven to reduce postoperative pain significantly and shorten the recovery period, therefore, reducing discharge time from 1 day to 3 days to same day discharge with an earlier return to a normal life.[1,2] Nonetheless, studies have shown that the first 24 hours to 48 hours after surgery are associated with moderate abdominal and shoulder pain in 35% to 63% of patients. Early postoperative pain is the most common complaint after elective laparoscopic cholecystectomy; pain intensity peaks during the first postoperative hours and usually declines over the following 2 days to 3 days.[3,4]

Numerous clinical studies have investigated the use of regional local anesthetics, in combination with other modalities for pain relief following laparoscopic cholecystectomy to avoid the adverse effects of opioids, which may delay recovery and hospital discharge.[5] Thirteen controlled studies have investigated the analgesic effects of bupivacaine administered in the right subdiaphragmatic or gallbladder region; only 7 of the 13 trials found that the overall pain scores were significantly reduced as compared with those of the control patients.[6]

Although nonsteroidal anti-inflammatory drugs provide morphine-sparing effects, they do not appear to provide, on their own, sufficiently reliable postoperative analgesia for laparoscopic surgery.[5] Salman et al[7] failed to observe an improvement in analgesia after laparoscopic surgery with the use of tenoxicam 20 mg intravenously. However, Elhakim et al[8] reported that a combination of tenoxicam 20 mg and lidocaine 1%, administered intraperitoneally under the right diaphragm and on the gallbladder bed after laparoscopic cholecystectomy, provided superior analgesia for movement and a faster return of bowel function as compared with intraperitoneal lidocaine and intravenous tenoxicam or placebo.

In view of these conflicting results, we designed in pa-

tients undergoing elective laparoscopic cholecystectomy this double-blind, prospective, placebo-controlled study to compare the degree of postoperative pain relief, nausea, and vomiting following intraperitoneal spray of bupivacaine alone or intravenous ketoprofen alone, versus the multimodal combination of intraperitoneal bupivacaine with intraperitoneal or intravenous ketoprofen.

METHODS

After obtaining institutional approval for the protocol and informed consent, 100 patients, ASA I-II aged 20 years to 60 years, scheduled for elective laparoscopic cholecystectomy without intraoperative cholangiography, were enrolled in the study. The criteria for exclusion were chronic pain diseases other than gallstone disease, and use of opioids, tranquilizers, steroids, nonsteroidal anti-inflammatory drugs, or alcohol. Also, exclusion criteria included amide local anesthetic allergy and contraindications to nonsteroidal anti-inflammatory drugs (allergy, peptic ulcer disease, gastroesophageal reflux disease, renal insufficiency, coagulopathy). In addition, patients with acute cholecystitis, conversion to an open cholecystectomy, postoperative complications that increased postoperative pain, and those whose pain evaluation was judged unreliable because of neurologic disease were excluded. Finally, patients who demonstrated the intraoperative need for more than 2 μg/kg fentanyl, as evidenced by an increase of more than 20% of mean arterial blood pressure or heart rate that is not controlled by increasing sevoflurane concentration for 5 minutes, were also excluded.

All patients were premedicated 1 hour before surgery with diazepam 5 mg orally, glycopyrrolate 0.2 mg intramuscularly, and ranitidine 50 mg intravenously. Intraoperative monitoring included continuous electrocardiogram, heart rate, Spo_2, end-tidal CO_2, sevoflurane concentration, intermittent noninvasive blood pressure, and neuromuscular block. General anesthesia was induced intravenously with propofol 2.0 mg/kg, fentanyl 2 μg/kg, and rocuronium 0.6 mg/kg, to be followed by orotracheal intubation. Anesthesia was maintained with sevoflurane 1.5% to 2.5% in oxygen/air mixture (1/2). Increments of 10 mg of rocuronium were administered repetitively to maintain a train-of-4 ratio (T4/T1)$<$0.5. During laparoscopy, carbon dioxide was insufflated intraperitoneally to maintain an intraabdominal pressure between 10 mm Hg to 15 mm Hg. Minute ventilation volume was adjusted to keep end-tidal PCO_2 at 35 mm Hg to 40 mm Hg. At the end of surgery, the CO_2 was carefully evacuated by manual compression of the abdomen with open trocars. The residual neuromuscular blockade was reversed with a mixture of neostigmine 0.05 mg/kg^{-1} and glycopyrrolate 0.01 mg/kg^{-1}.

Patients were randomly allocated to 1 of 5 groups, each of which consisted of 20 patients. Group 1 received a 40 mL solution of bupivacaine 0.25% intraperitoneal spray alone and 40 mL of normal saline intravenously. Group 2 received a 40 mL solution of bupivacaine 0.25% intraperitoneal spray mixed with 200 mg ketoprofen and 40 mL of normal saline intravenously. Group 3 received a 40 mL solution of bupivacaine 0.25% intraperitoneal spray alone and intravenous ketoprofen 200 mg diluted in 40 mL of normal saline intravenously. Group 4 received normal saline 40 mL intraperitoneally and 200 mg intravenous ketoprofen diluted in 40 mL of normal saline. Group 5 (control) received normal saline 40 mL intraperitoneally and 40 mL of normal saline intravenously.

A surgical scrub nurse who had no further involvement in the study prepared the solutions administered intraperitoneally to the study patients. An anesthesiologist not participating in the study administered 40 mL of a blinded solution (ketoprofen or saline) intravenously 30 minutes before the end of the operation to all patients. At the end of surgery and before evacuating the pneumoperitoneum, the surgeon sprayed 40 mL of a blinded solution (bupivacaine $\pm$ ketoprofen or saline) intraperitoneally in a standardized manner to the subdiaphragmatic space and gallbladder area. The anesthesiologists and nurses in the postanesthesia care unit and in the ward were unaware of the treatment to which each patient had been randomized. Postoperative abdominal and shoulder pain were evaluated in terms of intensity and location upon arrival to the recovery room, and at 1, 2, 6, 12, and 24 hours postoperatively. Pain scoring was evaluated by the same anesthesiologist who was blinded to all groups by a visual analogue score (VAS) of 0 to 10 (0=no pain, 10=unendurable pain), which was explained to the patients during the preanesthesia visit. In case of a pain score $>$5, a ketoprofen 100mg suppository was given and repeated every 6 hours for the first 24 hours if needed. The number of patients requiring rescue analgesics was recorded. Postoperative nausea and vomiting (PONV) was rated by the same anesthesiologist on a 3-point scale (0=no PONV, 1=Mild nausea, 2=Severe nausea, 3=Vomiting) upon arrival to the recovery room, and at 1, 2, 6, 12, and 24 hours postoperatively. If PONV scale was 2 or more, ondansetron 4mg was given intravenously and repeated as needed every 6 hours for the first 24 hours. The incidence of postoperative vomiting (PONV scale 3) was recorded.

Statistical Analysis

All data are reported as mean ± SD, except for the percentage of patients who needed postoperative rescue analgesics, and the incidence of postoperative vomiting. Postoperative abdominal and shoulder pain scores were compared with the analysis of variance with the Bonferroni post hoc test. The percentage of patients who needed rescue analgesics and the incidence of postoperative vomiting were compared by using the chi-square test. Statistical significance was considered at $P<0.05$. A 50% reduction in the incidence of pain was used in computing the power analysis. Also, a type I error of 5% as well as a type II error of 20% were used in the power analysis. The result of the power analysis indicated that a minimum of 20 patients was needed in each group.

RESULTS

Demographic Data

The demographic data are shown in **Table 1**. No significant difference was found between the 5 groups in terms of sex distribution, mean patient body weight and age, or ASA status and duration of surgery.

Abdominal Pain

Postoperative abdominal pain scores (mean ± SD) are shown in **Figure 1**.

Group 1 had significantly lower pain scores than did the control group at 6 hours only. Group 2 had significantly lower pain scores than did the control group at 0, 1, 2, and 6 hours. Group 3 had significantly lower pain scores than did the control group at 0, 1, 2, 6, 12, and 24 hours. Group 4 had significantly lower pain scores than did the control group at 2 hours only.

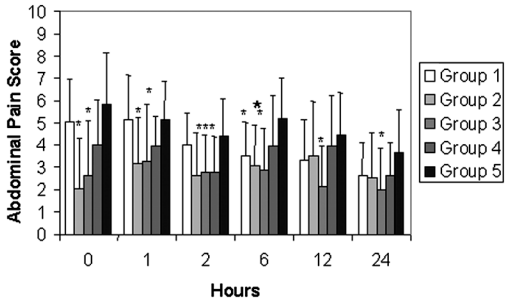

Figure 1. Mean and standard deviation of the abdominal pain scores in the different groups over time.

Shoulder Pain

Postoperative shoulder pain scores (mean ± SD) are shown in **Figure 2**.

Group 1 had significantly lower pain scores than did the control group at 1 and 6 hours. Group 2 had significantly lower pain scores than did the control group at 0 and 6 hours. Groups 3 and 4 had significantly lower pain scores than did the control group at 0, 1, and 6 hours.

Postoperative Rescue Analgesics

The percentage of patients requiring postoperative rescue analgesics was significantly less in group 3 only, as compared with analgesic needs in the control group **(Table 2)**.

Postoperative Vomiting

The incidence of postoperative vomiting was significantly less in group 3 only as compared with vomiting in the control group **(Table 3)**.

DISCUSSION

Postoperative pain and nausea are the most common complications of laparoscopic surgery, including chole-

Table 1.
Patient Characteristics and Surgical Data*

Variable	Group 1 n=20	Group 2 n=20	Group 3 n=20	Group 4 n=20	Group 5 n=20
Age (year)	48±15	47±20	46±18	46.6±12	47.2±17
Weight (Kg)	72±10	73±12	72.5±14	74±15	72±11
ASA I/II	10/10	9/11	10/10	11/9	9/11
Sex (male/female)	9/11	9/11	9/11	9/11	9/11
Duration of surgery (min)	100±19	98±22	101±16	103±18	99±20

*Data are expressed as mean±SD and numbers. No significant differences between groups.

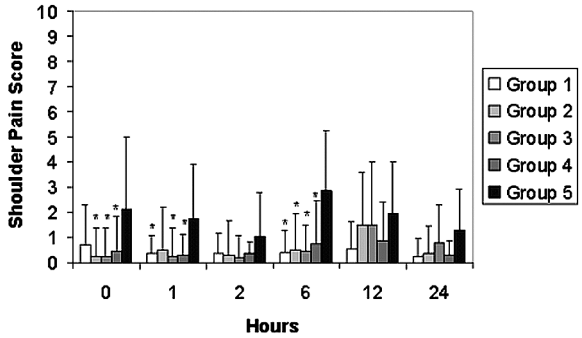

Figure 2. Mean and standard deviation of the shoulder pain scores in the different groups over time.

Table 2.
Number and Percentage of Patients Who Needed Postoperative Rescue Analgesics

Group 1	Group 2	Group 3	Group 4	Group 5
13/20	10/20	8/20*	12/20	17/20
65%	50%	40%*	60%	85%

*P<0.05 compared with group 5.

Table 3.
Number and Percentage of Patients Who Vomited

Group 1	Group 2	Group 3	Group 4	Group 5
5/20	8/20	3/20*	7/20	9/20
25%	40%	15%*	35%	45%

*P<0.05 compared to group 5.

cystectomy.[9] Both, particularly pain, prolong recovery and discharge times and contribute to unanticipated admission after ambulatory surgery. Pain also contributes to postoperative nausea and vomiting. Thus, the establishment of laparoscopic cholecystectomy as an outpatient procedure has accentuated the clinical importance of reducing early postoperative pain and nausea.[10] Improved postoperative pain management using opioid-sparing regimens may facilitate a high success rate of outpatient laparoscopic cholecystectomy.[11]

Early pain after laparoscopic cholecystectomy is multifactorial and complex. It includes different pain components due to different pain mechanisms: Abdominal wall penetration by trocars produces somatic pain; rapid distension of the peritoneum by CO_2 insufflation results in tearing of blood vessels, traction of nerves, and release of inflammatory mediators producing visceral pain; inflammation or local irritation around the gallbladder bed, liver, diaphragm or peritoneum, or both, secondary to gallbladder removal and abdominal muscle distension add to tissue injury and produce visceral pain. Shoulder pain results from peritoneal insufflation especially when an exaggerated Trendelenburg position is used.[12]

Because postoperative pain following laparoscopic cholecystectomy is multifactorial, multimodal therapy may be necessary to optimize pain relief. The present report shows that the best multimodal therapy that significantly decreases both abdominal and shoulder pain over the first 24 hours postoperatively, as compared with the control group, is a combination of 40 mL of bupivacaine 0.25% (100 mg) intraperitoneal spray and intravenous ketoprofen 200 mg. Furthermore, this combination has proven effective in decreasing the number of patients who needed rescue analgesics as well as the incidence of postoperative vomiting, as compared with that in the control group.

Bupivacaine is an amide-type local anesthetic that is capable of producing prolonged analgesia. The recommended dose for infiltration is a maximum of 2 mg/kg. Narchi et al[13] showed that intraperitoneal instillation of 100 mg of bupivacaine did not result in toxic plasma concentrations. The absence of toxicity was confirmed by Deans et al[14] who determined plasma concentrations after instillation of 1.5 mg/kg bupivacaine in the preperitoneal space during hernia repair.

In our study, intraperitoneal bupivacaine alone reduced postoperative shoulder pain significantly at 1 hour and 6 hours, and abdominal pain at 6 hours only. However, no significant difference occurred in the number of patients who needed rescue analgesics and in the incidence of postoperative vomiting as compared with that in the control group.

Because NSAIDs have analgesic properties comparable to properties of opioid compounds without opioid-related side-effects, these drugs are often administered as adjuvants during and after surgery.[15] A systematic review of published, randomized, controlled trials[16] found no significant differences in the analgesic effects between different NSAIDs, but found differences in toxicity with increasing doses. Because no documented evidence exists of the superiority of any particular NSAID for perioperative use, the choice of NSAID would depend on the toxicity, route of administration, duration of the analgesia, and cost. Therefore, we elected to use ketoprofen due to its availability and its routine use at our institution. Concerns have been raised regarding the potential side effects

of NSAIDs, such as gastric irritation, gastrointestinal bleeding, impaired coagulation, and renal dysfunction. However, the short-term use (48 hr to72 hr) of appropriate dosages of NSAIDs appears to be safe and well tolerated in patients undergoing ambulatory surgery.

Previous studies[7] have shown that the intravenous administration of the nonsteroidal anti-inflammatory drug tenoxicam failed to produce adequate analgesia following laparoscopic surgery. In our study, intravenous ketoprofen was effective in significantly reducing shoulder pain at 0, 1, and 6 hours postoperatively; however, it was effective in decreasing postoperative abdominal pain at 2 hours only. Also, no significant difference occurred in the number of patients who needed rescue analgesics or in the incidence of postoperative vomiting as compared with that in the control group.

The multimodal approach for pain management following laparoscopic cholecystectomy has been previously shown to be advantageous. Elhakim et al[6] showed that a combination of intraperitoneal lidocaine and tenoxicam was more effective in reducing pain scores and opioid consumption than either placebo or intraperitoneal lidocaine and intravenous tenoxicam, with no difference in the incidence of nausea between the groups. In our study, a combination of intraperitoneal bupivacaine and ketoprofen was effective in relieving postoperative abdominal pain at 0, 1, 2, and 6 hours. It was also effective against shoulder pain at 0 and 6 hours postoperatively. However, it did not relieve abdominal pain at 12 hours and 24 hours. Also, it did not provide a significant decrease in the number of patients who needed postoperative rescue analgesics, and it did not decrease the incidence of postoperative vomiting as compared with vomiting in the control group.

The present report shows that the best technique for pain relief following laparoscopic cholecystectomy is the multimodal approach using a combination of intraperitoneal bupivacaine and intravenous ketoprofen. This combination does not merely create an additive response but rather a synergistic one through its action at 2 different sites by 2 different mechanisms. While intraperitoneal bupivacaine alone results in abdominal pain relief at 6 hours only, and intravenous ketoprofen alone results in abdominal pain relief at 2 hours only, a combination of intraperitoneal bupivacaine and intravenous ketoprofen results in a significant decrease in abdominal pain scores at 0, 1, 2, 6, 12, and 24 hours postoperatively. Also, it has proven effective in relieving postoperative shoulder pain at 0 and 6 hours with a significantly lower number of patients who needed rescue analgesics and a significantly lower incidence of postoperative vomiting.

CONCLUSION

Our study shows that the multimodal approach to pain management following laparoscopic cholecystectomy is best achieved with a combination of intraperitoneal spray of 40 mL of bupivacaine 0.25% as a local anesthetic and 200 mg of intravenous ketoprofen as a nonsteroidal anti-inflammatory drug. This combination of 2 drugs acting on 2 different sites by 2 different mechanisms results in a synergistic action that significantly decreases postoperative abdominal and shoulder pain. Also, it decreases the number of patients who require postoperative rescue analgesics, as well as the incidence of postoperative vomiting.

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