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Preincisional intravenous low-dose ketamine and local infiltration with ropivacaine reduces postoperative pain after laparoscopic cholecystectomy

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Abstract
Background: The preincisional use of ketamine combined with local tissue infiltration with Ropivacaine may reduce noxious input during surgery. The goal of this study was to examine whether this combination improves postoperative pain control after laparoscopic cholecystectomy.
Methods: A total of 55 patients were randomly assigned to one of three groups. Group 1 received placebos preincisional. Group 2 received preincisional saline IV and local infiltration with 20 ml ropivacaine (10 mg/ml). Group 3 received preincisional ketamine 1 mg/kg IV and local infiltration with 20 ml ropivacaine (10 mg/ml). Postoperative pain was rated at 0, 3, 6, 12, 24, and 48 h postoperatively by visual analogue scale scores (VAS). Cumulative analgesic consumption and time until first analgesic medication request were recorded.
Results: Group 3 experienced significantly ($p < 0.05$) less pain than group 2 at 6 h and 12 h postoperatively. Groups 2 and 3 did not differ significantly by VAS at 0 h, 3 h, 24 h, and 48 h. Group 1 had significantly higher VAS scores than groups 2 and 3 at 0 h, 3 h, 6 h, 12 h, and 24 h postoperatively. The consumption of analgesics was significantly higher in group 1 than in groups 2 and 3. Although the consumption of analgesics was higher in group 3 than in group 2, this difference did not reach statistical significance. The time to first request for analgesics was significantly longer in groups 2 and 3 than in group 1, with no statistical difference between groups 2 and 3.
Conclusion: Preincisional treatment with low-dose IV ketamine and local infiltration with ropivacaine 1% reduces postoperative pain after laparoscopic cholecystectomy.

Key words: Preemptive pain therapy — Ketamine — Ropivacaine — Laparoscopic cholecystectomy — Cholecystectomy — Pain control

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The optimal management of postoperative pain is essential to minimize patient discomfort and reduce the need for a hospital stay after laparoscopic cholecystectomy.

Peripheral tissue injury during the operation produces two kinds of modification in the responsiveness of the central nervous system. The first is an increase in the sensitivity of the high-threshold nociceptive neurons caused by inflammatory mediators and other chemical substances deliberated by, or in reaction to, tissue damage (peripheral sensitization) [16]. The second is an increased excitability of spinal cord neurons, triggered by nociceptive afferent inputs (central sensitization). This sensitization process, caused by the operative tissue damage, leads to an increase in the response to pain and a decrease in the pain threshold.

The N-methyl-D-aspartate (NMDA) receptor represents the main receptor for glutamate, the most important neurotransmitter of pain. The activation of this receptor plays a major role in the sensitization processes. Clinical and experimental studies have shown that ketamine is the most potent NMDA-receptor inhibitor, thus blocking neuronal transmission and inhibiting sensitization processes [2, 3, 15].

Recent efforts to improve postoperative pain management have concentrated on pain preventive regimens directed at decreasing noxious stimuli input and sensitization in pain pathways [10]. The underlying principle is that therapeutic intervention should be done in advance of the pain rather than in reaction to it (preemptive analgesia). Pain preventive therapy could be directed at the periphery, at inputs along sensory axons, or at central neurons. A number of different options are available to achieve this: local anesthetics to block sensory inflow, nonsteroidal antiinflammatory drugs (NSAID) to reduce the activation/sensitization of nociceptors, and centrally acting drugs such as opiates or ketamine [12, 16].

Treatment regimes that act at different levels of the pain transmission could maximize the prevention of pain.

Methods

After we received the approval of the ethics committee and informed consent from the patients, 55 patients undergoing elective laparoscopic cholecystectomy under general anesthesia were enrolled in this randomized prospective double-blinded study. The patients were randomly assigned to one of three groups. Group 1 received preincisional placebos. Group 2 received preincisional saline IV and local infiltration with 20 ml ropivacaine (10 mg/ml). Group 3 received preincisional ketamine 1 mg/kg IV and local infiltration with 20 ml ropivacaine (10 mg/ml).

Exclusion criteria included contraindications to any of anesthetic or study drugs used; age <18 years or >75 years; weight <45 kg or >120 kg; evidence of severe cardiovascular, renal, hematologic or hepatic disease; physical status (according to the American Society of Anesthesiologists [ASA] classification) >III; preexisting neurological or psychiatric illnesses; chronic pain syndromes; alcohol or drug abuse; and difficulties in communication and cooperation between doctor and patient.

All perioperative conditions were similar for the three groups. During the preoperative visit, the patients were introduced to the concept of the visual analogue scale (VAS), which ranges from 0 = no pain to 10 = most imaginable pain. On the day of surgery, patients were premedicated with oral diazepam 0.15 mg/kg 1 h preoperatively.

In all 55 patients, anesthesia was induced with fentanyl 3–5 μg/kg and propofol 2–3 mg/kg, followed by cisatracurium 0.1 mg/kg to facilitate tracheal intubation. All patients were given an IV injection of midazolam 2 mg and Ondansetron 4 mg 5–10 min prior to anesthesia.

The creation of the pneumoperitoneum was achieved with open laparoscopy according to the Hasson technique, utilizing a cone-shaped 10–12-mm trocar (Ethicon, Cincinnati, Ohio, USA). The cholecystectomy was perfomed according to the American variable; in addition to the Hasson trocar, we used one 10-mm and two 5-mm trocars. Before skin incision, all trocar insertion sites were infiltrated with ropivacaine (10 mg/ml) to a total of 20 ml, which was divided proportionally according to the length of the skin incision (7 ml for the 10-mm trocars and 3 ml for the 5-mm trocars).

The anesthesia was maintained with sevoflurane 1–2%. Muscle relaxation was maintained throughout the operation with intermittent doses of cisatracurium. Pain intensity, visual analogue scale scores, verbal rating scale scores, and analgesic consumption were recorded at 0 h, 3 h, 6 h, 12 h, 24 h, and 48 h postoperatively.

A standardized plan for postoperative analgesia was prepared. If VAS scores were >3, nonsteroidal anti-inflammatory drugs (diclofenac 50–100 mg) were administered in suppository form. In case of pain persistence, parenteral dextropropoxyphene (75 mg) was given. If pain relief with dextropropoxyphene was not adequate, meperidine 50 mg IM was administered. The patients were specifically asked about the occurrence of side effects such as nausea and dizziness, as well as the side effects known to be associated with ketamine (unusual dreams, hallucinations).

Data are expressed as mean ± standard deviation (SD). Parametric data were compared between groups by analysis of variance (ANOVA) and post hoc testing. Statistical significance was assumed if $p < 0.05$. Nonparametric data were analyzed using chi-square tests between groups. Analysis was performed with the Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL, USA).

Results

There were no significant differences among the groups regarding demographic data, duration of anesthesia, or duration of surgery (Table 1). Of the 55 patients enrolled, two had to be withdrawn from the study because of difficulties in communication between patient and doctor in the postoperative period.

The VAS scores in group 3 (ketamine + ropivacaine) were significantly lower than group 2 (ropivacaine) and group 1 (placebo) at 6 h and 12 h postoperatively. At 0 h, 3 h, and 24 h, the VAS scores did not differ significantly between groups 2 and 3, but they were significantly lower compared with group 1 ($p < 0.01$) (Table 2). Group 2 had significantly lower VAS scores than group 1 at 0 h, 3 h, 6 h, 12 h, and 24 h postoperatively. At 48 h postoperatively, no statistically significant differences were noted among the three groups (Fig. 1).

Table 1. Patient characteristics

	Group 1 (placebo) (n = 18)	Group 2 (ropivacaine) (n = 17)	Group 3 (ketamine + ropivacaine) (n = 18)
Age (yr)	43.9 ± 13.6	47.9 ± 16.7	41.3 ± 13.6
Weight (kg)	71.5 ± 14.6	73.4 ± 13	68.5 ± 8.3
Gender (m/f)	5/13	4/13	6/12
ASA I/II/III	11/7/0	9/7/1	7/9/2
Duration of surgery (min)	48.2 ± 11.4	55.8 ± 8.7	47.7 ± 7.5
Duration of anesthesia (min)	63 ± 29	70 ± 28	71 ± 25

Values given as mean ± SD

Table 2. VAS scores for the three groups

	Group 1	Group 2	Group 3
0 h	3.06 ± 1.3	1.4 ± 1.6	0.89 ± 1.3
3 h	3.8 ± 0.7	2.41 ± 1.7	2.1 ± 1.1
6 h	2.5 ± 0.5	1.6 ± 0.9	0.94 ± 1
12 h	2.3 ± 0.4	1.2 ± 0.8	0.6 ± 0.3
24 h	1.78 ± 1	0.5 ± 1.3	0 ± 0
48 h	0.3 ± 0.1	0 ± 0	0 ± 0

Values given as mean ± SD

The time to first analgesic request was comparable for group 3 (132 ± 34 min) and group 2 (121 ± 18 min) ($p = 0.12$), but it was significantly lower in group 1 (72 ± 12 min) when compared with groups 2 and 3 ($p < 0.05$).

Group 1 received significantly higher doses of all kinds of analgesics (diclofenac, dextropropoxyphene, meperidine) than groups 2 and 3 ($p < 0.05$) (Fig. 2). Although group 3 consumed higher doses of analgesics than group 2, this difference did not reach statistical significance (Table 3).

The incidence of postoperative nausea and vomiting was similar in all three groups (group 1; four of 18 [22.2%]; group 2; four of 18 [23.5%]; group 3; five of 18 [27.7%]). None of the patients in group 3 (ketamine + ropivacaine) reported any psychological events that could have been attributed to ketamine.

Discussion

The goal of this study was to determine whether the combination of IV low-dose racemic ketamine (1 mg/kg) and local infiltration with ropivacaine in patients undergoing laparoscopic cholecystectomy could improve the postoperative control of pain when added to an otherwise optimal anesthetic plan. Successful early discharge after this laparoscopic procedure is highly dependent on optimal postoperative pain control with nonopiod analgesic drugs. When such drugs are taken together with specific antiemetic prophylaxis, such as Ondansetron, a high success rate can be achieved. Our study showed that this combination enhanced pain relief and decreased the demand for analgesics. Our

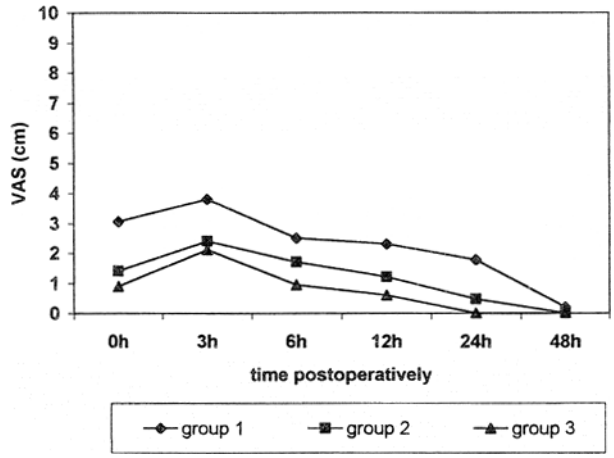

Fig. 1. Visual analogue scale (VAS) (0 = no pain–10 = intolerable pain) during the first 48 h after the operation in the placebo group (group 1), the saline and local infiltration group (group 2), and the preemptive ketamine and local infiltration group (group 3).

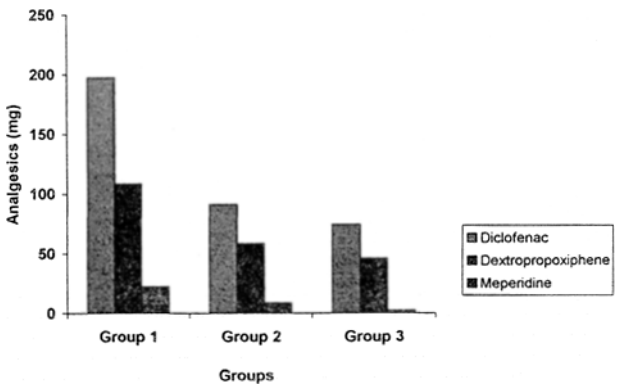

Fig. 2. Consumption of analgesics (supp. diclofenac, IM dextropropoxyphene, and IM meperidine) at 48 h postoperatively. Group 1 received higher doses of all kinds of analgesics than the other two groups

Table 3. Need for analgesics in the three groups

	Group 1 (n = 18)	Group 2 (n = 17)	Group 3 (n = 18)
No analgesia required	3	6	8
Sup. diclofenac (50 mg) (n)	8	6	5
Dose per patient (mg)	197.2 ± 32	91.6 ± 23	75 ± 20
IM dextropropoxyphene (75 mg) (n)	8	5	4
Dose per patient (mg)	108.3 ± 21	58.3 ± 7.4	45.8 ± 10.3
IM meperidine (50 mg) (n)	4	2	1
Dose per patient (mg)	200/100/50/50	100/50	50

Values given as mean ± SD

analysis focused on the first 48 h after the operation, when most patients experience a peak pain level.

The pain in laparoscopic cholecystectomy is multifactorial. The pneumoperitoneum contributes to postoperative pain by increasing the intraabdominal pressure intraoperatively, causing irritation of the diaphragm. Other factors that contribute significantly to the intensity of postoperative pain include the irrigating effect of CO_2, the intraoperative use of electrocautery, and finally the possible spillage of bile in the peritoneal cavity.

The visceroperitoneal organs are innervated multiply by the spinal nerves T5–T12 [13], the vagus nerve [5, 6, 14], and the phrenic nerve (C3–C5) [8, 13] in the upper abdomen. All of these nerves are closely associated with visceroperitoneal nociception. These facts suggest that central sensitization is induced not only segmentally but also heterosegmentally. In upper abdominal surgery, therefore, multiple blockades of afferent nociception may be necessary to attain definitive preemptive analgesia. Although previous studies have shown that preemptive application of low-dose IV ketamine reduces postoperative pain and the consumption of opioids [8, 10], we were not able to find any study examining the effect of the combination we used (ropivacaine + ketamine).

We observed that the ketamine group (group 3) experienced less pain than groups 1 and 2, but significantly lower VAS scores were recorded only at 6 h and 12 h postoperatively compared to group 2. Perhaps this delayed onset in the action of ketamine means that a period of time is necessary for the effects of the sensitization caused by the surgery to become evident. Another possible explanation is that in the first postoperative hours, the preemptive effect of the local infiltration with ropivacaine, (which is proven by the significant difference between groups 2 and 1) partially covers the preemptive action of intravenous ketamine. In any case, this difference cannot be attributed directly to the analgesic action of ketamine, since the pharmacological duration of a single intravenous injection of ketamine is significantly shorter [11]. The fact that the VAS scores did not differ among the three groups at 48 h postoperatively could be explained by a reduction in the input of noxious stimuli from the operated area.

The most persuasive mechanism to explain the analgesic action of low-dose ketamine is related to NMDA–receptor blockade. The NMDA receptor antagonist ketamine not only attenuates peripheral afferent inputs by noxious stimuli, but also prevents a process called central sensitization [1]. Central sensitization is an activity-dependent increase in the excitability of the spinal neurons which may cause increased postoperative pain [9].

The increased pain relief in our study reflects the potential complementary antinociceptive action of the two drug classes used. Local anesthetics do not block all pain-sensitizing mechanisms, and IV ketamine does not completely abolish hyperalgesia when used alone in abdominal surgery. Local infiltration blocks C-fiber input to the dorsal horn and thereby may inhibit central sensitization [10]. Bisgaard et al. have shown that local infiltration with ropivacaine reduces incisional pain but has no effect on deep intraabdominal pain [4]. Dahl et al. [7] and Illkajer et al. [8] found that IV low-dose ketamine had no significant preemptive effect. This may be the result of the low dosage in addition to the insufficient effect of IV ketamine when it is used alone as a preemptive analgesic regimen. Some different preemptive effects observed in previous studies may be attributable to differences in the surgical area and the surgical manipulations.

In conclusion, the dual blockade of nociceptive input

and NMDA activation using local infiltration with ropivacaine and IV low-dose ketamine may be necessary for preemptive analgesia in laparoscopic cholecystectomy.

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