RESEARCH ARTICLE

Evaluation of the Postoperative Analgesic Efficacy of Intraperitoneal Ketamine Compared with Bupivacaine in Laparoscopic Cholecystectomy

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Background: This randomized controlled study was designed to compare the postoperative analgesic efficacy of intraperitoneal ketamine versus bupivacaine in patients undergoing laparoscopic cholecystectomy.

Methods: We randomly divided 60 patients undergoing elective laparoscopic cholecystectomy into two groups. The intervention group patients received intraperitoneal ketamine (0.5 mg/ kg) diluted in 30ml normal saline and the control group received intraperitoneal bupivacaine 30 ml 0.25% (75mg) at the end of the procedure, before removal of the trocars. The primary end point of this study was, time to tracheal extubation and the intensity of postoperative pain by using visual analogue scale (VAS) score at 5-15min, 6, 12 and 24 h after surgery. The secondary outcome included time to the first request of analgesia in the postoperative period, total dose of analgesic used in first 24 h postoperative period and any postoperative complication.

Results: Time to tracheal extubation was higher in ketamine group compared to bupivacaine group that caused prolongation of anesthetic duration in this group. During the first 6 h after surgery, the pain scores were significantly lower in patients receiving ketamine compared with bupivacaine group. Pain scores in the subsequent time were low but were not different between the two groups. Time to first request of analgesia was longer in ketamine group (21.43±0.50 min) compared to bupivacaine group (6.32±0.64 min) (p=0.001). Total meperidine consumption was also lower in ketamine group compared to bupivacaine group.

Conclusion: Intraperitoneal instillation of 0.5mg/kg ketamine in elective laparoscopic cholecystectomy significantly reduces the postoperative pain and the analgesic requirement in the first 6 h after surgery as compared to bupivacaine but it increased extubation time.

Keywords: bupivacaine; intraperitoneal; ketamine; postoperative pain; laparoscopy

Laparoscopic cholecystectomy is presumed to be the method of choice for gallbladder surgery. While laparoscopic cholecystectomy is concerned to induce less pain than open surgery, pain is the principal cause of delayed hospital discharge after outpatient laparoscopic cholecystectomy [1].

Pain may result from distending of the parietal peritoneum, peritoneal inflammation, and diaphragmatic irritation caused by accumulated carbon dioxide in the peritoneal cavity [2]. Many methods have been proposed to relieve postoperative pain following laparoscopic cholecystectomy. Administration of local anesthetics into the abdomen may be an effective way of decreasing the pain after laparoscopic cholecystectomy [3]. N-methyl–D-aspartate (NMDA) receptor activation is considered one of the mechanisms of postoperative pain, and hypersensitivity through both peripheral and central effects [4]. Ketamine is a non specific NMDA receptor antagonist with hypnotic and analgesic activity, which can be administrated in many ways [5]. It simply crosses from most tissue membranes that lead to easy absorption. It also has early onset and short duration of action and because of peripheral action at both opioid and NMDA receptor, its peripheral application has been recently evaluated in many studies [6]. It seems that intra peritoneal administration of ketamine could be an acceptable surrogate to local anesthetics such as bupivacaine as a postoperative analgesic in laparoscopic surgery [7]. The aim of this study was to compare the anti-nociceptive effects of intraperitoneal ketamine instillation with intraperitoneal bupivacaine alone in patients undergoing laparoscopic cholecystectomy.

Methods

After obtaining approval from the Institutional Review Board (IRB) of Tehran University of Medical Sciences, this

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prospective randomized blinded clinical study was conducted in our center from June 2014 to December 2015. A total of sixty, ASA I-II patients aged 18-60 years without cardiovascular, pulmonary, psychological or neurological diseases, who were scheduled for elective laparoscopic cholecystectomy under general anesthesia were enrolled. Patient who were allergic to local anesthetic and study drugs, patients with acute cholecystitis, patients with severe cardiac, pulmonary, and neurological diseases and those in whom the procedure had to be converted to open cholecystectomy were excluded from the study. Before anesthesia written informed consent was obtained from the participants. Routine monitoring system was used including electrocardiography, noninvasive arterial blood pressure (NIBP), pulse oximetry, and capnography.

Pre-oxygenation with 100% oxygen was done for 3 min. General anesthesia was induced with an injection of fentanyl (2 µg/kg), midazolam (0.05 mg/kg), propofol (1-2mg/kg) followed by atracurium (0.5mg/kg) to facilitate orotracheal intubation. Anesthesia was maintained using isoflurane in an air/oxygen mixture and a bolus injection of fentanyl (2 µg/kg) every hour. Intermittent boluses of atracurium were used to achieve muscle relaxation. Minute ventilation was adjusted to maintain normocapnia (end tidal carbon dioxide; EtCO2, between 34 and 38 mm Hg). Patients were placed in 15-20° reverse Trendelenberg's position with the left side tilt position. During laparoscopy, intra-abdominal pressure was maintained at 11-15 mm Hg. The CO2 was removed carefully by manual compression of the abdomen at the end of the procedure with open trocar.

Patients were randomized into the two groups using a computer-generated table of random numbers, the intervention group patients received intraperitoneal ketamine (0.5 mg/ kg) diluted in 30ml normal saline. The control group received intraperitoneal bupivacaine 30 ml 0.25% (75mg). Study drugs were prepared by a nurse anesthesiologist not involved in the study. Anesthesiologist who observed the patient and the surgeon were unaware of the study group until the end of the study. At the end of the surgery, the drug was instilled intraperitoneally before removal of trocar in trendelenberg's position, into the hepato-diaphragmatic space, on gall bladder bed and near and above hepatoduodenal ligament. For neuromuscular blockade reversal, neostigmine 0.05 mg/kg combined with atropine 0.01 mg/kg were used then trachea was extubated and the patient was transferred to post anesthesia care unit (PACU).

The primary outcome variables were time to tracheal extubation and postoperative pain based on visual analogue scale (VAS) score. The secondary outcomes included time to the first request of analgesia in the postoperative period, total dose of analgesic used in first 24 h postoperative period and any postoperative complication. The intensity of postoperative pain was recorded for all the patients using VAS score at 5-15min, 6, 12, 24 h after surgery. All the study patients were instructed about the use of the VAS score before induction of anesthesia. Patients who reported VAS>3 were given meperidine 0.5mg/kg intravenously as rescue analgesia. Patients were also observed for postoperative nausea and vomiting. Patients who had nausea or vomiting were given ondansetron 4 mg IV. A total sample size of 60 patients was calculated, assuming 30% improvement in pain scores with an α error of 0.05 and a power of 80%. For the statistical analysis, the statistical software SPSS version 16 (SPSS Inc., Chicago, IL) was used. P values of 0.05 or less were considered statistically significant. Demographic data were analyzed by chi-square test. Normally scattered data were measured using unpaired Student's t-test. Comparison was carried out using Chi-square ($\chi 2$) test with a p-value reported at 95% confidence level. Results were expressed as mean ± standard deviation, number and percentage (%).

Results

Demographic data of patients were comparable between the two groups, with no significant differences noted (Table 1).Time to tracheal extubation was higher in ketamine group compared to bupivacaine group (Table 2). During the first 6 h after surgery, the pain scores were significantly lower in patients receiving ketamine compared with bupivacaine group (Table 2). Pain scores in the subsequent time were low but were not different between the two groups. Time to first request of analgesia was longer in ketamine group (21.43±0.50 min) as compared to group bupivacaine (6.32±0.64 min). Total meperidine consumption was also lower in ketamine group compared to bupivacaine group. Overall analysis showed that postoperative complication such as nausea and vomiting were not statistically significant between the two study groups (Table 3).

Table 1- The comparison of patient's characteristics between two groups

Variable	Ketamine group(30)	Bupivacaine group(30)	p-value
Age (years)	36.80±8.96	37.52±9.01	0.7
Male/Female	11/19	10/20	0.6
ASA I/II	17/13	20/10	0.8
Anesthesia time (min)	78.1±9.40	67.00±10.21	0.002
Duration of surgery (min)	55.56±10.94	56.00±10.89	0.5

ASA: American society of anesthesiologists

Table 2- Postoperative VAS score in both studied groups

Time	ketamine	Bupivacaine	p-value
5 min	2.0±0.74	4.0±1.60	0.002
15 min	1.54±0.50	1.80±0.64	0.02
6hr	2.12±0.90	4.78±1.22	0.001
12hr	3.0±0.86	3.50±0.84	0.1
24hr	3.0±0.86	3.50±0.84	0.1

VAS: Visual analogue scale, Mean± Standard deviation

Table 3- post operative analgesic requirements, time to first request of analgesia and recovery outcome

variable	ketamine	Bupivacaine	p-value
Time to tracheal Extubation(min)	18.96±4.9	13.72±3.2	0.012

Table 3- post operative analgesic requirements, time to first request of analgesia and recovery outcome (continued)

variable	ketamine	Bupivacaine	p-value
Time to first request of analgesia in postoperative period (min)	21.43±0.50	6.32±0.64	0.001
Total dose of Meperidine (mg) in 24 h	23.2 ±0.90	44.78±1.22	0.001
Recovery time(min)	3.0±0.86	31.50±0.84	0.1
Nausea &vomiting	7(23%)	8(26%)	0.2

Mean± Standard deviation

Discussion

Our data showed that peritoneal ketamine infiltration was associated with reduction of both postoperative pain, and the analgesic requirements in patients undergoing laparoscopic cholecystectomy. Intra peritoneal ketamine administration led to more effective pain control than the intra peritoneal bupivacaine instillation especially in the early postoperative period.

Postoperative pain after laparoscopic cholecystectomy consists of three components, visceral, parietal and referred shoulder pain distinguishable from each other in the intensity, latency and duration [8]. Combined analgesic regimens with different mechanisms of action as a multimodal approach is becoming popular, with the aim of reducing postoperative opioids, consumption, complications and reliance on them [9].

Multimodal efforts like intraperitoneal instillation of local anesthetic agents has become an important method to control postoperative pain, nausea, vomiting and reduced hospital stay [10]. Intra peritoneal local anesthetics block the visceral afferent signals and modify visceral nociception [11].

Golubovic et al. assessed the analgesic effects of intra peritoneal instillation of bupivacaine in patients undergoing laparoscopic cholecystectomy and came to this result that intraperitoneal instillation of bupivacaine is an effective method for management of pain after laparoscopic cholecystectomy and it significantly reduces postoperative analgesic and antiemetic medication [12]. In a systematic review that was done by Gurusamy et al. intra-abdominal local anesthetic administration was associated with a low serious adverse event and could control pain sooner after surgery but the clinical importance of this reduction in pain is likely to be small [13].

N-methyl –D-aspartate (NMDA) receptor activation is considered to be one of the mechanisms of postoperative pain, and the hypersensitivity through both peripheral (intraperitoneal), and central effects (intravenous route) [14]. Peripheral NMDA receptors are important in normal visceral pain transmission, and this finding may offer us a new measure to understand development of peripheral sanitization, and subsequent visceral hyperalgesia [15].

Ketamine, a non-competitive NMDA antagonist, prevents central sensitization of nociceptors at sub anesthetic doses through the elimination of peripheral afferent noxious stimulation [16]. Recently, several studies have shown that the pre-incisional treatment of the wounds with subcutaneous infiltration of ketamine would decrease mean pain score after surgery, prolong the time before the first analgesic requirement and reduce the total amount of analgesics consumed [17].

Borner et al. suggested that the administration of intra articular S (+) ketamine (antagonism of peripheral NMDA receptors) after arthroscopic knee operation may lead to a substantial reduction in postoperative pain killer need [18]. Goma et al. in a similar study found that intraperitoneal ketamine, which blocks peripheral NMDA receptors, may reduce the postoperative analgesic needs in morbidly obese patients following bariatric surgery in compare with intraperitoneal lidocaine [7].

One of the drawbacks of the present report is prolongation of extubation time in ketamine group. It seems intraperitoneal ketamine leads to systemic absorption that could potentiate the effect of anesthetic drugs [19]. Nadeson et al. concluded that ketamine may enhance analgesia of fentanyl through a synergistic effect at the level of the spinal cord even when ketamine was given through the intra peritoneal route in rats [20].

Conclusion

We conclude that intraperitoneal instillation of 0.5mg/kg ketamine in elective laparoscopic cholecystectomy significantly reduces the post-operative pain and the analgesic requirement in post-operative period as compared to bupivacaine 0.25% but it increased extubation time versus bupivacaine.

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