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Effects of Intraoperative Low Dose Ketamine on Hemodynamic Changes and Postoperative Opioid Consumption in Patients Undergoing Laparoscopic Cholecystectomy

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ABSTRACT

Background: Laparoscopic Cholecystectomy (LC) as a minimally invasive surgery has become extremely common in recent decades. Despite being less invasive, these surgeries require postoperative analgesia. In this regard Ketamine, can reduce postoperative pain and opioid consumption.

Owing to the wide heterogeneity of studies on efficacy of ketamine in pain management in different operations, anesthetics methods, and the way and dose of consumption, the present study sought to evaluate the effects of intraoperative low-dose ketamine on postoperative pain, opioid consumption, and hemodynamic changes of patients undergoing LC in the 5th Azar hospital of Gorgan in 2019.

Methods: 66 patients with the need for LC were randomly selected. After induction of anesthesia and intubation, and before surgical incision, 0.5 mg/kg of Ketamine was injected as a bolus for target group (n=33), and the equivalent volume of normal saline for control group (n=33). Systolic, diastolic and mean arterial pressure were recorded before, during, after anesthesia and during surgery at 5-minute intervals. Postoperative pain was evaluated through Visual Analog Scale(VAS). We recorded the time of the first dose of opioid, total amounts of opioid consumption during the first 24 hours after surgery and doses of antihypertensive drug.

Results: VAS score (opioid requirement) were lower in the intervention group only in the recovery period (p=0.049). There was no difference between two groups in total amounts of opioid consumption during 24 hours even in cases with increase of the length of surgery (p= 0.742). Blood pressure trend increased from the beginning of induction to the end of anesthesia (p-value<0.001); however, there was no statistically significant difference between two groups (p=0.786). The need for labetalol was higher in control group (p<0.0001).

Conclusion: Although 0.5 mg/kg ketamine could not reduce overall opioid consumption within 24 hours after surgery, it had significant pain relief during awakening and recovery. Additionally, it reduced the need for further interventions, such as labetalol and other drugs and therefore was associated with lower costs.

In all surgeries, postoperative pain is a major challenge for anesthesiologists and surgeons [1] for this reason minimally invasive surgeries have become more common in recent decades. Laparoscopic surgeries are one of them [2-3]. LC is a golden standard surgical procedure for gallstone management even in the elderly [4], The occurrence of pain after laparoscopic surgery is less frequent than the open method; Most

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patients experience moderate pain after LC: 4-6 degrees from the VAS score [5]. however, the same amount may increase the duration of hospitalization, and the time to return to normal activity in patients. Unfortunately, the mechanism of pain after laparoscopic surgery is unclear. Investigator such as Vecchio [6], have investigated the causes of pain after laparoscopic surgery and its treatment [7-8].

Due to the involvement of several mechanisms, including somatic pain, visceral pain, and inflammatory system activation [9-12], researchers have agreed to the multimodal treatment of LC pain [13-14]. In other words, the combination of multimodal analgesics with different functional mechanisms improves the analgesic effects and reduces the incidence of side effects due to the high dose of opioids [15].

Existing studies demonstrate that administration of ketamine during surgery has beneficial effects on the control of acute postoperative pain, and it can have more analgesic effects and fewer side effects, particularly if a multimodal approach is used [16].

The existence of variable results with ketamine can be due to various reasons, such as dose of the drug, time of administration, duration of postoperative administration, method of administration (intravenous, epidural, …), type of the drug (racemic mixture or S+), length of postoperative evaluation, and adjuvant or single-drug ketamine [17].

Saxena et al. concluded that low-dose ketamine was an effective analgesic, even in long-term laparoscopic gynecological procedures, and it could stabilize intraoperative hemodynamics and reduce the need for other anesthetics and antihypertensive drugs [18]. Atashkhouei also found that low-dose ketamine in patients undergoing laparoscopic gynecological procedures could lead to fewer hemodynamic changes, a lower overall dose of Propofol, and improvement of postoperative analgesia [19].

Harsimran Singh et al. considered a dose of 0.5 mg/kg Ketamine effective in reducing postoperative LC pain in Punjab [20] and Nesek-Adam also confirmed this issue in another study [21]. Two meta-analyses by Jiang Zhu [22] and Fan Ye [23], and one study by Mi Hyeon Lee [24] also confirmed the effect of ketamine on reducing the postoperative pain of LC, while studies like the one conducted by Moro [25] dismissed this claim.

we assumed that low-dose ketamine would improve the patient's recovery quality after LC, and would also be effective in controlling complications during surgery by better control of hemodynamic changes. Since the effective dose of ketamine in pain control varies in different studies, the present study aimed to evaluate the effect of intraoperative low dose ketamine on postoperative pain control, intraoperative hemodynamic changes in LC, and drug use rate compared to the control group.

Methods

The present study was a completely double-blind randomized clinical trial.

One study conducted by Atashkhoyi et al. [19] was employed to calculate the sample size. The number of samples required for each group was calculated by comparing the indices. Given the percentage of reduction in the mean arterial pressure equal to 37% for the control group and 0.07% for the intervention group, and considering a type I error of 0.05 and a test power of 80%, the minimum sample size was 29 individuals per group and a total of 58 individuals. Due to the 10% loss of samples, 33 individuals in each group and a total of 66 individuals were studied in the present research. A list of random patient assignments to the control and intervention groups was prepared using 6-sided dice.

After entering the operating room, systolic and diastolic blood pressures, and the mean arterial pressure were non-invasively recorded by the operator. All participants received 0.15 mg/kg Midazolam and 3 mic/kg fentanyl as premedication. Afterward, they were injected with 0.5 mg/kg Lidocaine for reducing their pain caused by propofol injection, 2 mg/kg propofol as an anesthetic, and 0.5 mg/kg Atracurium for intubation. After intubation and fixation of the endotracheal tube, vital signs were recorded again. We recorded vital signs every 5 minutes until the end of the surgery. After preparing the surgical site and one minute before making a skin incision to pass the laparoscopic trocar and the CO_2 insufflation, 0.5 mg/kg of ketamine was injected as a bolus in the target group (by a drug-conscious anesthetist). Normal saline with an equal volume was injected into the control group. After gas insufflation into the peritoneal cavity, the intra-abdominal gas pressure was increased to 12 to 14 mmHg. For maintenance of anesthesia, isoflurane gas at a maximum volume of 1.5% in combination with oxygen and air was used to maintain arterial oxygen saturation of more than 98%. Standard monitoring in the study included capnography, pulse oximetry, electrocardiogram, NIBP (non-invasive blood pressure), and nerve stimulator with a TOF mode. It should be noted that all surgeries were performed by a surgeon completely familiar with the design. During anesthesia, if systolic blood pressure increased by 25% compared to baseline levels (before anesthesia), 10 mg of Labetalol was administered intravenously, and every 10 minutes if necessary, up to a maximum of 120 mg/h in both groups by maintaining a heart rate above 50 beats per minute. If the operation lasted for more than an hour, ketamine with half the previous dose (0.25 mg/kg) in the target group, and normal saline with an equal volume in the control group were injected by an anesthesiologist aware of the type of the drug. At the end of the surgery and after suctioning excess gas inside the abdomen, with TOF>0.85, the relaxing effect was reversed with 0.05 mg/kg of Neostigmine and 0.02 mg/kg of Atropine.

At the end of the operation, all data were collected, including the amount of labetalol consumed, and the parameters of vital signs, and then the amount of pain was measured based on VAS. The test was evaluated in recovery by an anesthesiologist in charge of recovery, and by nurses trained for the use of this tool in the surgical unit. Meperidine at a dose of 0.25 mg/kg with a maximum daily dose of 2 mg/kg was used in patients of both groups if analgesics (VAS≥4) were requested to reduce VAS (<4). During these stages, the time of the first dose of opioids use, and then every 4 hours, the total amount of opioids used during the first 24 hours after the surgery were recorded.

Inclusion criteria

- Patients classified in ASA I&II (American Society of Anesthesiologists) who had signed the informed consent form to enter the study.
- The age range of 18 to 60 years

Non-Inclusion criteria:

- The drug, opioid, or psychoactive substance abuse
- A history of seizures or taking anticonvulsant medications
- A history of allergies to ketamine and anesthetic drugs
- Increased Intracranial Pressure (ICP)
- Patients with obesity (BMI>40)

Exclusion criteria

- Changing the surgery from laparoscopic cholecystectomy to open cholecystectomy
- Complications, such as capnothorax and pneumothorax
- The operation time longer than two hours

Data analysis

The independent t-test was used if the normality assumptions were observed, and the Mann-Whitney test was employed in case of non-compliance. Data normality was performed using the Shapiro-Wilk test. Comparing blood pressure at 5-minute intervals, the effect of time and type of intervention were analyzed using the repeated-measures analysis of variance. The significant difference level was considered to be 0.05 during the tests.

The proposal of the present study was approved with an ethical code of IR.GOUMS.REC.1398.186 and was registered at the Iranian Registry of Clinical Trials (IRCT): IRCT20170413033408N2.

Results

In the study, the participants were in the age range of 18 to 60 years, and the mean age was obtained to be 35.33±12.32. The age distribution of both groups was almost the same, so that the participants' mean age was 36.18±13.41 in the control group. On the contrary, the participants' mean age was 34.48±11.26 in the ketamine group.

Only two out of 66 participants were male, and the rest were female.

According to the results of recovery, 28 individuals in the ketamine group (84%), and 21 individuals in the control group (63.6%) did not need the opioid injection. According to the Chi-square test and the p-value=0.049, the difference was statistically significant. The need for opioids in the ketamine group was felt only in one patient with an operation time longer than one hour (patients who required repeated ketamine doses).

The need for opioids between the two groups was not statistically significant at 8, 12, and 24 hours after the surgery, and none of the participants in both groups received opioids after 24 hours.

The normality of drug consumption was assessed in two groups. The result of the Shapiro-Wilk test indicated that the assumption of normality was not established.

Tests of Normality

	Group	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
		Statistic	Df	Sig.	Statistic	Df	Sig.
Total.opioid	Ketamine	0.264	16	0.004	0.867	16	0.024
	Control	0.201	21	0.027	0.888	21	0.021

a. Lilliefors Significance Correction

According to studies, we observed no need for opioids in 17 individuals in the ketamine group (51.5%), and 12 individuals in the control group (36.4%). Among 16 patients in the ketamine group, who received opioids, a total dose of 41.25 ± 12.17 mg of meperidine was used per person. The rate was 45.95±21.36 for 21 patients in control group. The difference (0.742) was not significant according to the results of the Mann-Whitney test.

A total of 5 individuals in the ketamine group received opioids. In this group, 22 operations required more than one hour and needed the repetition of ketamine. The study of opioid consumption indicated that 2 individuals (18%) received opioids from the subgroup of less than one hour (n=11), and 3 individuals (13%) received opioids from the subgroup of longer than one hour (n=22). Despite the decrease in the measure of opioid consumption in individuals with repeated doses of ketamine, the difference was not statistically significant according to the Chi-square test. The operation time parameter was also examined in the control group. The operation lasted longer than one hour in 14 patients, among whom 3 received opioids (21.4%). 9 (47.4%) out of 19 patients with an operation time less than one hour received opioids. According to the results, increasing the length of surgery did not lead to an increase in opioid use in patients undergoing laparoscopy.

Regarding patients' hemodynamics, as presented in Table 1, the first 3 parameters in each patient were statistically analyzed, and the mean of all three blood pressures was compared in the two groups; however, there was no significant difference.

During the study, using the repeated-measures analysis of variance (F), we assessed the effects of time and group on blood pressure. Given the non-acceptance of the sphericity hypothesis, the time trend in the mean systolic blood pressure was significantly different regardless of the study group (F=4.69, p-value<0.001) using the Mauchly's Test of Sphericity and the Greenhouse-Geisser method. The results also indicated that the type of intervention was not significantly different in the mean systolic blood pressure irrespective of the intervention times (F=0.30, p-value=0.58). Like the systolic pressure, the time trend was significantly different in the mean diastolic pressure (F=3.55, p-value=0.004); however, the difference in the mean pressure was not significant between the two groups (F=0.002, p-value=0.96). Likewise in the mean arterial pressure (MAP), the time trend difference was significant (F=4.69, p-value<0.001); however, the mean pressure between the two groups did not differ significantly (F=0.075, p-value=0.786).

Figures 2 to 4 present the diagram of hemodynamic changes in both groups. The results indicated that 6.1% of patients in the intervention group and 66.7% in the control group needed to consume labetalol in at least one of the 5, 10, ..., 70 minutes, and the difference was statistically significant according to the Chi-square test (p-value<0.0001).

Figure 1- depicts the sampling status of the study using the CONSORT diagram

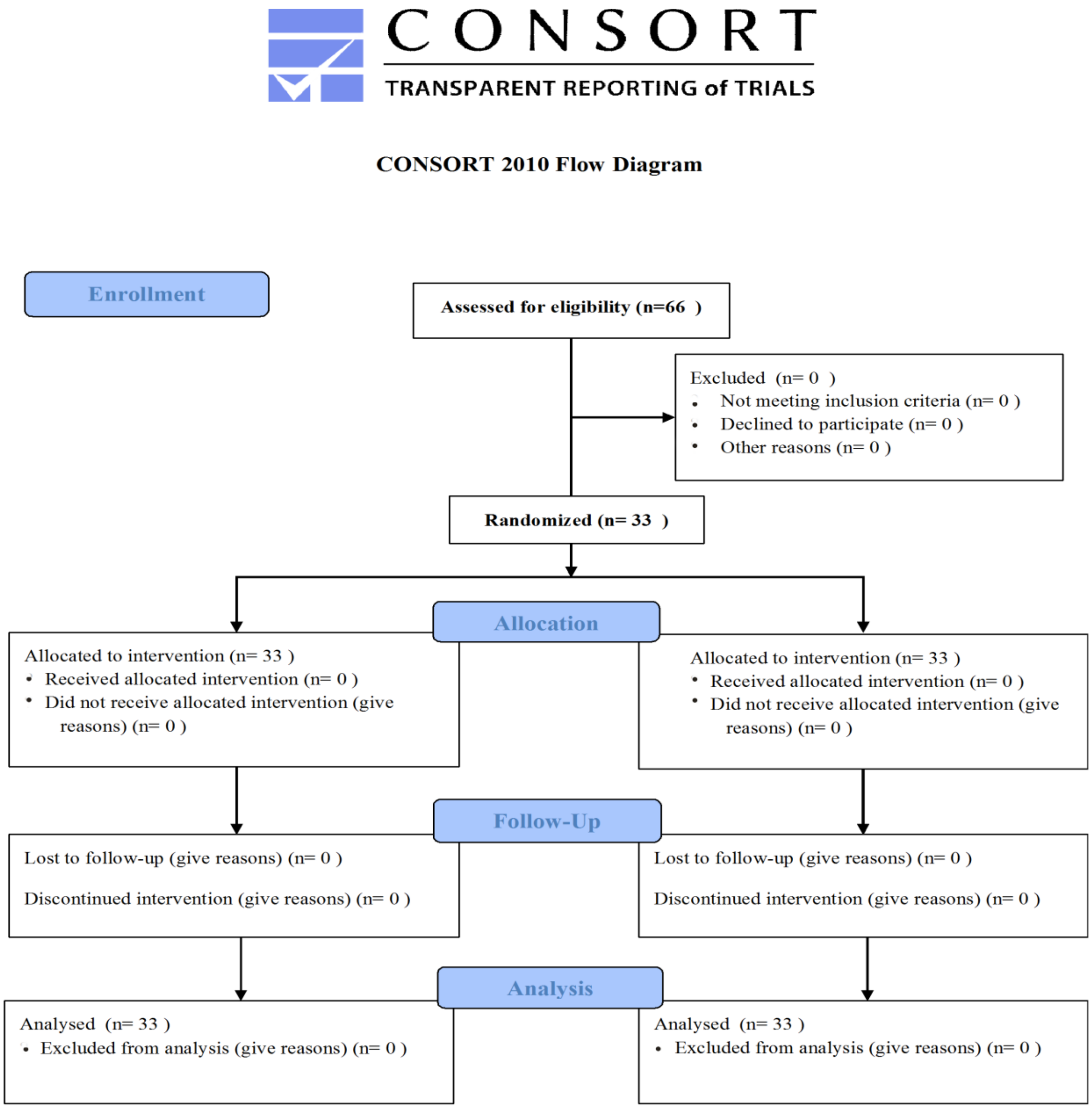


Figure 2- Trend of mean systolic pressure during LC (time: every number demonstrate 5 minutes in horizontal axis)

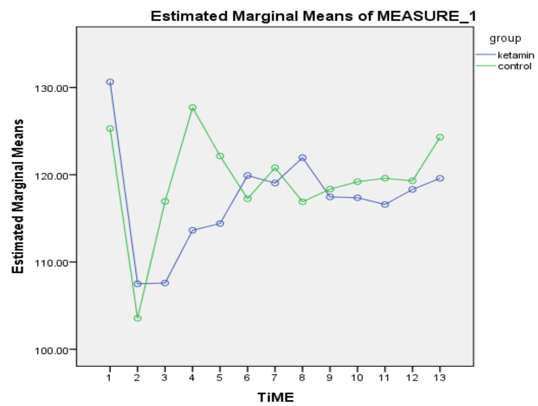


Figure 3- Trend of mean distolic pressure during LC (time: every number demonstrate 5 minutes in horizontal axis)

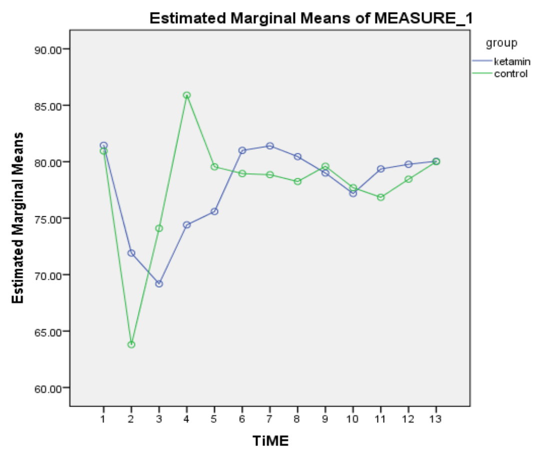
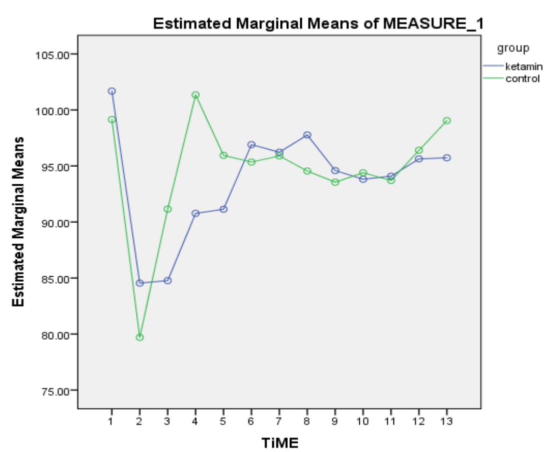


Figure 4- Trend of mean arterial pressure during LC (time: every number demonstrate 5 minutes in horizontal axis)



Discussion

Several studies have examined the control of pain caused by laparoscopic operations, and different results have been obtained. In our review of various sources, most studies have used ketamine in combination with other drugs to control pain after laparoscopic surgery, and few studies have investigated the effectiveness of ketamine alone.

The present study aimed to evaluate the effects of intraoperative low dose ketamine on postoperative pain, the amount of opioid use, and hemodynamic changes in patients undergoing laparoscopic cholecystectomy.

The research results indicated that ketamine at the recommended dose (0.5 mg/kg) was associated with lower pain and the need for opioids in recovery. Consistent with this finding, Saxena [18] and Atashkhouei [19] found that ketamine with the same dose affected the reduced need for opioid use after surgery.

Although the rate of opioid use after surgery and recovery decreased in the ketamine group in our study, the 24-hour postoperative examination did not exhibit any reduction of opioid use by this dose of ketamine compared to the control group. The findings of this study were consistent with one study conducted by Mi Hyeon Lee [24]. In studies conducted by Nesek Adam [21] and Sung Kwan Choi [26], the use of ketamine was effective in reducing pain, but Moro et al. [25] found that 0.2 and 0.4 mg/kg of ketamine did not reduce pain after LC. Two simultaneous meta-analyses in China (Zhu and Fan Ye) confirmed the significant effect of ketamine on reducing pain and improving recovery in patients [22-23]. Singh (20) specifically demonstrated that all three doses (0.5, 0.75, and 1 mg/kg) of ketamine were involved in reducing opioid use after LC.

In addition to pain, we also examined the hemodynamic status of patients during surgery. Most studies did not report the effect of ketamine on patients' hemodynamics. Only one study conducted by Saxena [18] mentioned the hemodynamic stabilization of ketamine during laparoscopy. Our findings also revealed that ketamine at a certain dose could act well as a hemodynamic stabilizer and prevent hemodynamic fluctuations during laparoscopy.

Although nausea and vomiting are among the side effects of ketamine and these complications are the reasons for the general disagreement to use this drug in laparoscopic patients, the results of the present study indicated that the incidence of nausea and vomiting was even lower in the ketamine group than in the control group; however, the difference was not statistically significant. The important point in this regard was the safe use of ketamine in laparoscopic procedures without being concerned about its side effects, and this result was consistent with one study conducted by Moro [25].

Conclusion

According to the research results concerning the use of 0.5 mg/kg of ketamine in patients undergoing LC, it can be concluded that the use of this dose could not reduce the total opioid consumption within 24 hours after surgery. Nevertheless, it was associated with positive results, such as a significant reduction in pain in the time of waking up and recovery, and reduction of the need for further interventions like labetalol, or the use of other drugs including opioids, or balanced anesthesia, leading to reduction of costs by better maintenance of hemodynamic stability.

Suggestions:

1- Given the higher prevalence of gallbladder inflammation in women and its significant effect in the present study, further studies can be conducted with a larger sample size and both sexes to examine the results in two sex groups.

2- In addition to the bolus dose of ketamine, low-dose ketamine infusion can be used to continue anesthesia in order to assess postoperative pain control that requires the design of another study.

3- Since the use of ketamine was not associated with higher PONV in the patients, conducting a study on a larger sample size or other intraperitoneal surgeries can examine the assumption that whether the use of ketamine in intraperitoneal surgery is preferable to other methods of pain prevention and control.

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