Original Research

Comparison Of Ketamine And Dexmedetomidine In Reducing Complications After Laparoscopic Cholecystectomy Surgery

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Abstract:

Background: Today, the use of less invasive methods for surgery in the hospital is increasing due to less injuries and complications and faster recovery. One of the most important issues after surgery is to find a drug that can provide the longest period of pain relief and sedation for the patient with minimal side effects. This study was conducted with the aim of comparing ketamine and dexmedetomidine in reducing complications after Laparoscopic Cholecystectomy surgery.

Methods: This study was a double-blind randomized clinical trial. 90 patients were evaluated after Laparoscopic Cholecystectomy surgery. Patients were randomly divided into three control groups, intervention group with ketamine and intervention group with dexmedetomidine. The level of sedation, pain, shivering and nausea and vomiting of the patients after the operation were evaluated.

Result: frequency of patient sedation at the time of entering recovery was significantly different between ketamine, dexmedetomidine and control groups ($p=0.006$). The comparison of pain in ketamine, dexmedetomidine and control groups showed that the average pain in 15 minutes later, 30 minutes later, 45 minutes later, 60 minutes later, at the time of entering recovery and leaving recovery in the dexmedetomidine group (0%), It was significantly lower than the ketamine and control groups ($p<0.001$). Comparison of shivering in ketamine, dexmedetomidine and control groups showed that the frequency of shivering at the time of entering recovery in dexmedetomidine group (0%) was significantly lower than ketamine and control groups ($p<0.001$). frequency of nausea at the time of entering recovery in dexmedetomidine group (0%) was significantly higher than control and ketamine groups ($p<0.001$).

Conclusion: Based on the results of the present study, the use of dexmedetomidine in Laparoscopic Cholecystectomy surgery causes relaxation, reduces pain and shivering after the operation compared to ketamine. Therefore, this drug can be used as an anesthetic aid in surgery.

Keywords: Ketamine, Dexmedetomidine, Laparoscopic Cholecystectomy, Shivering, Pain, Nausea, Vomiting.

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Introduction

Today, the use of less invasive methods for surgery in the hospital is increasing due to fewer injuries and complications and faster recovery, among which the laparoscopic cholecystectomy surgery method can be mentioned (1). Laparoscopy is used to diagnose and treat many diseases. Pneumoperitoneum, which is created during laparoscopy, can stimulate the vagus nerve and increase the possibility of nausea and vomiting (2). The types of treatment methods available for the treatment of postoperative pain include systemic anesthesia (such as narcotics and non-narcotics) and regional anesthesia (3). One of the most important issues after surgery is to find a drug that can provide the longest period of pain relief and relaxation for the patient with minimal side effects (4). Dexmedetomidine is one of the alpha-2 agonist drugs, which, in addition to anesthetic and sedation effects, also has analgesic effects and has less side effects than other drugs and also has less effect on the hemodynamics of patients (5-7). Dexmedetomidine is usually used as a sedative and pain reliever (8), to reduce nausea and vomiting (9) after surgery and to Maintaining Hemodynamic Stability in laparoscopic surgery (10). Dexmedetomidine has various effects throughout the nervous system. The sedative effects of this drug are caused by its activity in the brain stem (11-13). In their study, Ghaedi et al. compared ketamine and dexmedetomidine in maintaining hemodynamic stability in Laparoscopic Cholecystectomy surgery with general anesthesia. The results of this study showed that the use of dexmedetomidine compared to ketamine causes hemodynamic stability (14). Ketamine is a phencyclidine derivative. It acts by inhibiting the NMDA receptor complex and by blocking glutamate receptors in the thalamus region of the brain, it prevents the transmission of pain messages to the limbic system (15). The results of the conducted studies indicate that ketamine has reduced the need to use analgesics after surgery and increased the time interval until the first analgesic appointment (16-18). In their study, Saryazdi et al investigated the effect of two drug combinations metoclopramide-acetaminophen and metoclopramide-ketamine on pain, nausea and vomiting after deep vitrectomy surgery. The results of this study showed that both the combination of acetaminophen-metoclopramide and ketamine-metoclopramide effectively reduced pain, nausea and vomiting; although overall, ketamine-metoclopramide had better results (19). Considering the above information and considering the importance of reducing postoperative complications in laparoscopic cholecystectomy surgery, this study was conducted with the aim of comparing ketamine and dexmedetomidine in reducing complications after laparoscopic cholecystectomy surgery.

Method

This study is a double-blind randomized clinical trial study. This study was approved by the ethics committee of Jahrom University of Medical Sciences with the ethics code "IR.JUMS.REC.1398.045" and the clinical trial code (RCT) with the number "IRCT20210415050976N5". Patients were examined after obtaining informed consent to cooperate in the study. The Inclusion criteria the study include: ASA I, II and the exclusion criteria also include: a history of allergy to the anesthetics used in the study, a history of high blood pressure, a history of taking antihypertensive drugs, a history of severe cardiovascular diseases, severe liver dysfunction and Kidneys, drug abuse and diabetes are not controlled. The patients were divided into three control groups, intervention with ketamine, and intervention with dexmedetomidine by random allocation method and using a table of random numbers. Before starting anesthesia, the patient's vital

signs were checked. Anesthetic induction drugs were the same in all three groups: midazolam (40 μg/kg), fentanyl (2 μg/kg), morphine (.15 mg/kg), propofol (2 mg/kg) and atracurium (0.5 mg/kg) was given to all patients. Anesthesia was maintained by continuous iv infusion of propofol. In the control group, a bolus dose of distilled water was given as a placebo at the same time as anesthesia. In the intervention group, a bolus dose (1 μg /kg) and then an infusion dose (0.5 μg /kg/hour) was prescribed at the same time as anesthesia with dexmedetomidine. In the intervention group with ketamine, a bolus dose (0.25 mg/kg) and then an infusion dose (5 μg /kg/min) were prescribed at the same time as anesthesia. The level of sedation of the patients was measured at the time of entering and leaving the recovery room. The pain level of the patients was measured at the time of entering the recovery, 15, 30, 45 and 60 minutes of being in the recovery and also leaving the recovery. The level of pain was assessed based on the pain assessment ruler. In this way, zero means no pain and 10 is unbearable pain. The rate of nausea and vomiting of the patients was measured at the time of entering the recovery, 15, 30, 45 and 60 minutes of being in the recovery and also leaving the recovery. Frequency of nausea and vomiting based on the absence of nausea and vomiting was given a score of 0, having nausea a score of 1, if having nausea + 2 or less than 2 times of vomiting a score of 2 and in case of nausea + 3 or more than 3 times of vomiting a score of 3. If a score of 3 was obtained, 4 mg of ondansetron was given intravenously (20). The amount of shivering of the patients was measured at the time of entering the recovery, 15, 30, 45 and 60 minutes of being in the recovery and also leaving the recovery. The amount of shivering was measured in the form of no significant tension, mild tension in the muscles, shivering in the upper limbs and visible tremors throughout the body. The anesthesiologist who was responsible for administering the patient's anesthesia administered the drug injection through the previously prepared coded syringes; So that when injecting, the patient was not aware of the type of injectable drug, and the medical student who was responsible for collecting the patient's information and variables was not aware of the type of prescribed drug. Data analysis was done by descriptive statistics (mean, percentage and standard deviation) and inferential statistical tests (Chi-square, Friedman and Kruskal–Wallis) using SPSS version 21 software.

Result

90 patients aged 18 to 44 (in three groups of 30) were evaluated with ASA I, Π during general anesthesia. The study groups were matched in terms of age and body mass index variables. Comparison of patient sedation in ketamine, dexmedetomidine and control groups showed that the frequency of patient sedation at the time of entering recovery was significantly different between ketamine, dexmedetomidine and control groups (p=0.006). In the ketamine and control groups, 23.3% and 23.3% of patients were anxious and restless, respectively. Meanwhile, the frequency of patient sedation at the time of recovery was lower in the dexmedetomidine group (10%). The frequency of patient sedation in the study groups was not significant (p=0.062). At the exit from recovery. The majority of patients were cooperative.

The comparison of pain in the ketamine, dexmedetomidine and control groups showed that the average pain at 15 minutes, 30 minutes, 45 minutes, 60 minutes, at the time of entering recovery and leaving recovery in the dexmedetomidine group (0%) was significantly less than Ketamine and control groups were (p<0.001). The average pain in the majority of patients in the ketamine group was in the range of 3 and 4, and after entering recovery, it increased up to 45 minutes, but then it decreased. The control group had the

highest average pain at the time of entering recovery and 15 minutes, but it decreased after that (Table 1).

Comparison of shivering in ketamine, dexmedetomidine and control groups showed that the frequency of shivering at the time of entering recovery in dexmedetomidine group (0%) was significantly lower than ketamine and control groups ($p<0.001$). So that only 6.7% of the patients had mild tension in the muscles, and tremors in the upper limbs and visible tremors throughout the body were negative. In the ketamine group, 3.3% of the patients had mild tension in the muscles and 3.3% of the patients had tremors in the upper limbs. At 15 minutes, 30 minutes, 45 minutes, 60 minutes, there was no significant difference between the ketamine, dexmedetomidine and control groups in the time of entering recovery and leaving recovery ($p<0.05$). In 15 minutes and 30 minutes after entering recovery, the frequency of shivering in the ketamine group has increased compared to entering recovery. From the time of entering recovery to 30 minutes after entering recovery, the frequency of shivering in the dexmedetomidine group has increased compared to entering recovery.

Comparison of nausea in ketamine, dexmedetomidine and control groups showed that the frequency of nausea at the time of entering recovery in dexmedetomidine group (0%) was significantly higher than control and ketamine groups ($p<0.001$). So that all patients in the dexmedetomidine group had nausea at different times. Nausea in the patients of the ketamine group was less than that of the dexmedetomidine group (Table 2).

Discussion

Further, the comparison of patient sedation in ketamine, dexmedetomidine and control groups showed that the frequency of patient sedation at the time of entering recovery was significantly different between ketamine, dexmedetomidine and control groups. In the ketamine and control groups, 23.3% and 23.3% of the patients were anxious and restless, respectively, while the frequency of patient sedation at the time of recovery was less in the dexmedetomidine group (10%). The frequency of patient sedation in the study groups was not significant at the exit from recovery and the majority of patients were calm and cooperated. In the study of Tosun et al., "the combination of dexmedetomidine-ketamine and propofol-ketamine for anesthesia in respiratory disease of children with cardiac catheters" was investigated. Although sedation was effective in both groups, the propofol-ketamine combination was superior. Patients who received dexmedetomidine-ketamine required more ketamine. In addition, recovery time was longer with dexmedetomidine and ketamine (21). Koruk et al (2010) compared sedation using dexmedetomidine and ketamine with midazolam and ketamine during extracorporeal shock wave lithotripsy in a group of 50 pediatric patients ranging in age from 2 to 15 years. Sedation was equally effective in both groups without significant clinical changes in hemodynamic and respiratory parameters (22). Mester et al (2008) retrospectively reviewed the use of dexmedetomidine and ketamine during cardiac catheterization in 16 children with congenital heart disease, ranging in age from 16 months to 15 years. None of the patients showed any reaction during the procedure and sedation was reported to be effective in both groups (23). Qiu et al. (2019) compared dexmedetomidine and ketamine in pediatric dental surgery. Based on the reported results, dexmedetomidine and ketamine have shown similar sedation (24). In the present study, sedation was reported to be more effective in the dexmedetomidine group. Among the reasons for this difference, we can refer to the review of other studies on children, and it seems that ketamine causes more relaxation in children than in adults. Further, the comparison of pain variables between the three groups of ketamine, dexmedetomidine

and control at the time of entering recovery and exiting recovery showed that the average pain at the time of 15 minutes later, 30 minutes later, 45 minutes later, 60 minutes later, at the time of entering recovery And exiting from recovery in the dexmedetomidine group (0%) was significantly less than the ketamine and control groups, and at the time of entering recovery, 15 minutes and 30 minutes after entering recovery, the amount of narcotic required in the dexmedetomidine group was The significance is lower than the ketamine and control groups. Kayyal et al. (2014) investigated the therapeutic effects of dexmedetomidine and ketamine on analgesia after cleft palate repair. Although no significant difference was reported between the two groups, consistent trends regarding lower opioid requirements during the first 24 hours were observed for both drugs (25).

Garg et al (2016) investigated and compared low doses of ketamine and dexmedetomidine for postoperative analgesia in spine surgery. The average pain-free periods in the ketamine group (860 minutes) and the dexmedetomidine group (580 minutes) were longer than the saline group (265 minutes). During the 48-hour follow-up period, a significant decrease in the need for rescue analgesics was observed in both ketamine and dexmedetomidine groups (26), which is not consistent with the results of the present study. One of the reasons for this difference can be pointed to the type of society under investigation and surgery. Chen et al. (2013) compared the effects of dexmedetomidine, ketamine and placebo after strabismus surgery in children. Based on the reported results, dexmedetomidine is significantly more effective than ketamine in controlling postoperative pain in children undergoing strabismus surgery (27), which is consistent with the results of the present study. The mechanism of the analgesic effect of dexmedetomidine as a α2 agonist is not yet fully understood, but it seems that the spinal cord is the most important site of its action. A2-adrenergic receptors of the gelatinous substance are activated in the dorsal horn of the spinal cord. This suppresses peripheral Aδ and C fiber neurotransmission, and subsequently, wide dynamic range neurons are also suppressed, and stimulates the release of acetylcholine and the serotonergic system, and suppresses the release of substance P, and as a result, has an analgesic effect. 28-30). Further, the comparison of shivering in the three groups of ketamine, dexmedetomidine and control at different times showed that the frequency of shivering at the time of entering recovery in the dexmedetomidine group (0%) was significantly lower than the ketamine and control groups. Alvarez et al. (2015) compared the effectiveness of dexmedetomidine, meperidine and ketamine in the prevention of postoperative shivering. According to the reported results, the effectiveness of meperidine was better than ketamine and dexmedetomidine and there was no significant difference between dexmedetomidine and ketamine (31). Sherif et al. (2019) compared dexmedetomidine, ketamine, or dexmedetomidine-ketamine combination to control shivering during spinal anesthesia. There was no significant difference in shivering control between the three groups (32). In the present study, there was no significant difference between the ketamine, dexmedetomidine and control groups at 15 minutes later, 30 minutes later, 45 minutes later, and 60 minutes later, when leaving recovery. Ameta et al. (2018) compared the prophylactic use of ketamine, tramadol, and dexmedetomidine for the prevention of shivering after spinal anesthesia. Based on the reported results, shivering after spinal anesthesia was better controlled in the group receiving dexmedetomidine compared to other groups (33). In the present study, the frequency of shivering at the time of recovery in the dexmedetomidine group (0%) was

significantly lower than the ketamine and control groups. The anti-shivering effects of dexmedetomidine are caused by binding to α2-adrenergic receptors that mediate vasoconstriction and anti-shivering effect. In addition, dexmedetomidine has thermoregulatory effects of the hypothalamus. Dexmedetomidine reduced vasoconstriction and shivering thresholds without altering sweating thresholds, suggesting an effect on the central thermoregulatory system rather than peripheral actions. Therefore, dexmedetomidine may improve hypothermia and still be an effective treatment for postoperative chills (34). Finally, the comparison of nausea in the ketamine, dexmedetomidine and control groups showed that the frequency of nausea at the time of entering recovery in the dexmedetomidine group was significantly higher than the control and ketamine groups. So that all patients in the dexmedetomidine group had nausea at different times. Nausea in the patients of the ketamine group was less than that of the dexmedetomidine group. Although nausea and vomiting are rare side effects of dexmedetomidine (36-35) and some studies have shown that the use of dexmedetomidine reduces the use of antiemetics (37). However, in the present study, the rate of nausea in the dexmedetomidine group was significantly higher than the other two groups. In their study, Koruk et al (2010) stated that the incidence of nausea and vomiting was lower with dexmedetomidine-ketamine than with dexmedetomidine-midazolam (4.7% vs. 32%) (22). Raaya et al. (2020) also stated in their study that the rate of nausea and vomiting in the dexmedetomidine and ketamine group was significantly lower than the ketamine and normal saline group (38). One of the reasons for the difference between these results and the present study is the type of surgery investigated in the present study, because nausea and vomiting are common complications of laparoscopic cholecystectomy surgery.

Conclusion

Based on the results of the present study, the use of dexmedetomidine in l laparoscopic cholecystectomy surgery compared to ketamine causes relaxation, reduces pain and shivering after the operation.

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Tables

Table 1: Comparison of pain variables between three groups of ketamine, dexmedetomidine and control

Pain	Groups			P-value
	Control	Dexmedetomidine	Ketamine	
	Median (First quartile (Third = quartile	Median (First quartile Third = quartile	Median (First quartile Third = quartile	
Entering recovery	(1-9) 5/7	(0-0) 0	(1-4) 3	0.001>
15 minutes	(3-7) 4	(0-0) 0	(2-4) 3	0.001>
30 minutes	(1-6) 3	(0-0) 0	(2-5) 4	0.001>
45 minutes	(1-5) 5/2	(0-0) 0	(3-5) 4	0.001>
60 minutes	(1-3) 2	(0-0) 0	(3-4) 3	0.001>
Leaving recovery	(0-3) 2	(0-0) 0	(3-4) 3	0.001>

Table 2: Nausea & Vomiting rate in three groups of ketamine, dexmedetomidine and control

Nausea & Vomiting	Level	Frequency	%	Frequency	%	Frequency	%	P-value
Entering recovery	No	25	83.3	0	0.0	29	96.7	0.001
	Yes	5	16.7	29	100.0	1	3.3	
15 minutes	No	27	90.0	0	0.0	30	100.0	0.145
	Yes	3	10.0	29	100.0	0	0.0	
30 minutes	No	29	96.7	0	0.0	27	90.0	0.51
	Yes	1	3.3	29	100.0	3	10.0	
45 minutes	No	30	100.0	0	0.0	29	96.7	0.44
	Yes	0	0.0	29	100.0	1	3.3	
60 minutes	No	30	100.0	0	0.0	28	96.6	0.14
	Yes	0	0.0	29	100.0	1	3.4	
Leaving recovery	No	30	100.0	0.0	0	28	96.6	0.37
	Yes	0	0.0	100.0	29	1	3.4	