Archives of Anesthesiology and Critical Care (Autumn 2025); 11(4): 486-495.

Available online at http://aacc.tums.ac.ir

Research Article

Investigating the Role of Ultra-Low Dose Naloxone in Modulating Postoperative Pain after Laparoscopic Cholecystectomy: A Double-Blind Randomized Controlled Trial

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ARTICLE INFO

Article history:
Received 27 December 2024
Revised 18 January 2025
Accepted 01 February 2025

Keywords:
Laparoscopic Cholecystectomy;
Naloxone;
Pain;
Nausea and vomiting;
Pruritic

ABSTRACT

Background: Considering the importance of controlling post-surgical pain in individuals and the limitation in number, in addition to the variations in the results of the clinical research studies focused on pain management outcomes of very low dose naloxone, the present evaluation aims to investigate the role of ultra-low dose naloxone on the severity of pain after the procedure, nausea, vomiting and pruritic.

Methods: In this double-blind controlled randomized clinical trial, 60 patients were selected for laparoscopic cholecystectomy surgery, with class 1 and 2 anesthesia (ASA) by available method, and were allocated to the intervention and control groups using randomization. Every participant underwent general anesthesia with a specific anesthesia protocol. After the operation, PCA was implanted for all patients to control pain. The internal composition of the PCA pump included 20 mg of morphine and naloxone at a specified dosage of 0.25 μg/kg for the intervention group and 20 mg of morphine and placebo for the control arm. Pain intensity, episodes of nausea and emesis and pruritic of patients were evaluated and compared based on VAS criteria within the two groups being analysed, during the immediate postoperative period and then 2, 6, 12 and 24 hours following the surgical procedure.

Results: There was no meaningful variation between therapeutic and standard arms in terms of age, sex, BMI, duration of surgery, duration of anesthesia, and dose of intra-operative fentanyl injection. Also, with respect to the level of pain during the immediate postoperative period and 2, 6, 12, and 24 hours following the surgical procedure, and the intensity of nausea, vomiting, and pruritic during recovery, statistical analysis revealed no remarkable discrepancy between the arms. In both groups, the severity of pain showed a significant decline at each of the examined time points in comparison with the pre-intervention phase ($p < 0.001$, for both groups). Comparing the trend of changes in pain intensity during the postoperative period between the two study groups did not show a statistically meaningful variation ($p = 0.569$).

Conclusion: The simultaneous prescription of naloxone and morphine in patients undergoing laparoscopic cystectomy does not demonstrate a meaningful influence on achieving relief from post-surgical pain levels, nausea and vomiting and pruritic compared to morphine alone, so the use of naloxone to reduce postoperative pain and complications of opioids is not recommended.

The authors declare no conflicts of interest.

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DOI: 10.18502/aacc.v11i4.19359

Introduction

Among surgical techniques, minimally invasive approaches are expanding at a remarkable pace. Since Eric Moh's first laparoscopic cholecystectomy in the year 1985, this method has remained the leading approach for managing symptomatic cholelithiasis [1]. Laparoscopic surgeries are increasing due to less postoperative pain and faster recovery than open cholecystectomy. Post-surgery problems like pain, nausea, and vomiting, while less common than with the open procedure, can still be serious enough to slow down recovery and keep patients longer within the recovery room following anesthesia area. They delay [2-4]. Pain is the major factor influencing recovery duration. Often, there is no effective treatment for pain after laparoscopic cholecystectomy [5]. Pain of this nature is often treated with opioids administered by injection or taken orally. Although the use of these medications have an immediate therapeutic effect, they are often accompanied by side effects like post-surgical drowsiness, nausea and vomiting, constipation, and respiratory depression, which lead to postponed release from the hospital [6-7]. For this reason, different approaches of pain alleviation have been investigated over time to reduce inpatient duration and at the same time enhancing patient contentment. Pain after laparoscopic cholecystectomy comes from three main areas: the incision site, the gas used during the procedure that causes changes in the body, and the wound in the liver from the surgery. After laparoscopic cholecystectomy, abdominal pain is common, with most of it (50-70%) coming from the incision site, then some from pneumoperitoneum (20-30%), and a smaller amount from the cholecystectomy itself (10-20%). Afterward Postoperative pain following laparoscopic cholecystectomy may arise from the surgical incision (incision pain), internal organs (pain originating from the abdomen), or be transmitted from the area below the diaphragm as shoulder discomfort. The intensity of shoulder pain is often low, with a duration of up to 24 hours [8-9]. The intensity of cutting pain is usually low to moderate, peaking right after surgery and fading away over time [10]. Severe Postoperative abdominal discomfort after LC can be present for several reasons:

- Expansion of the parietal peritoneum caused by blowing gas intraperitoneal.
- Release of soft tissue inflammatory mediators.
- The liver bed undergoes gallbladder dissection.

The cause of considerable differences in pain levels among individuals is not yet known, however, this may result from various factors, such as the dimensions of the incisions, the duration of the procedure, and the presence of blood, bile, or gas at the conclusion of the operation. This may also be modified by the procedural duration, the operating physician' s expertise, and the overall blood loss. Research has looked into using nonsteroidal anti-inflammatory drugs and local anesthetics to help with pain after laparoscopic cholecystectomy, in order to prevent the negative effects of opioids that could slow down recovery and discharge from the hospital. Research has revealed that the combination of NSAIDs and local anesthetics provides effective pain relief [11-12]. While studies have demonstrated that both NSAIDs and local anesthetics offer opioid-sparing effects, most of these studies most have not confirmed their ability to act as effective analgesics when used alone after LC [11–14]. This is primarily due to the different pain mechanisms occur following laparoscopic surgery. As a result, a comprehensive approach appears to be effective in managing postoperative pain.

Intravenous infusion of naloxone

Naloxone is a potent antagonist of the Mu-opioid receptor. Naloxone administration has been applied to mitigate the occurrence of symptoms such as nausea, emesis, impaired respiration, and urinary hesitancy following epidural [15-16] and intrathecal [17-18] opioids. This treatment may lead to the reversal of opioid analgesia [19]. Administering naloxone at a dosage of 10 μg/kg/h decreased both the length and efficacy of pain relief produced by epidural morphine or fentanyl [15-16]. Giving naloxone at a dose of 1 μg/kg/h helped reduce pain for individuals who were given intrathecal diamorphine after lumbar laminectomy [18]. At a dosage of 5 μg/kg/h, naloxone infusion led to remarkable analgesia, while adverse effects remained rare and minor [20]. The success of naloxone infusion in lessening adverse effects associated with neuraxial opioid led a team of researchers to explore how naloxone infusion affects morphine PCA [21]. Researchers divided patients undergoing hysterectomy into three arms in a randomized double-blind study:

1. Morphine PCA, 1 mg/ml, along with saline fluid replacement.
2. Administration of PCA morphine in combination with an infusion of naloxone at low dosage (0.25 μg/kg/hour).
3. Administration of PCA morphine in combination with an infusion of naloxone at high dosage (1 μg/kg/h).

It was noted that both naloxone doses had an equal effect in reducing the occurrence of nausea, vomiting, and pruritus compared to a placebo. No significant differences in pain scores were observed across the three groups, though the cumulative amount of morphine used was notably superior within the arm treated with the reduced dosage (42.3 ± 24.1 mg) as opposed to the placebo condition (59 ± 27.4 mg) or those administered the higher dosage (64.7 ± 33 mg) was significantly less.

The occurrence of respiratory depression was absent. Across the groups, sedation assessments, respiratory rate, hemodynamic status, and antiemetic administration showed no notable statistical variations [21]. According to a separate research, a team of researchers investigated the influence of low- concentration naloxone for 24 hours among 90 individuals following hysterectomy. The researchers observed that the administration of naloxone resulted in a significant decrease in morphine use during the first postoperative day in comparison with the control (saline) group. Furthermore, the occurrence and intensity of nausea and vomiting were notably reduced in the naloxone group, consistent with the outcomes reported in a prior study [22]. Naloxone's dose-dependent action enables it to alleviate postoperative pain. While reduced dosages of naloxone produced pain relief in rats, greater dosages increase in pain sensitivity [23]. The study indicated that naloxone Generates pain relief in a dose-dependent way at first, then leads to an increase in pain sensitivity [24]. Other researchers have observed this dual or biphasic modulatory effect of naloxone [25-27]. The pain-relieving role of naloxone might stem from the stimulation of endorphins or their competitive binding to pain receptors [28]. An alternative possibility is the enhanced function of opioid binding sites, notwithstanding that this up-regulation effect has been observed following long-term naloxone infusion (7 days) and in animal studies. At elevated dosages, naloxone disrupts the action of endorphins that have been released or moved to the postsynaptic receptor [29-30]. Administering naloxone through IV PCA does not provide any extra advantage [31–33]. The altered pharmacokinetics behavior of the drug explain the lack of additional benefit when it is administered on an intermittent schedule as opposed to a continuous infusion method. Naloxone exhibits a biphasic elimination pattern, with an initial half-life of approximately 4 minutes and a second phase half-life ranging between 55 and 60 minutes. As a result, naloxone's continuous infusion ensures stable plasma concentrations, providing a more consistent therapeutic effect [34-35]. At present, IV infusion of naloxone is primarily indicated for managing the side effects associated with neuraxial opioid use. Some research, including Gan [21] et al. and Movafegh et al. [22], indicated that administering low-dose naloxone can reduce opioid usage. Additional controlled studies should investigate the increased clinical use of naloxone for postoperative analgesia in different surgical procedures.

State the problem

Gallstones are one of the common diseases of the digestive system. Most of these stones remain without symptoms throughout the patient's life. Some patients, for unknown reasons, progress to a symptomatic stage, where they experience biliary colic pains due to the blockage of the cystic duct by gallstones, potentially leading to related complications. Therefore, cholecystectomy surgery is necessary in cases of gallstones, if the gallstones are symptomatic, or if a person is likely to experience these symptoms. You can perform the cystectomy surgery using either an open method or a closed method known as laparoscopic [36-37]. Considering the many advantages that laparoscopic surgery has over the open method, the use of this method is growing day by day, so it has replaced the open method as the method of choice [38-39]. Despite many benefits, a frequently observed complications after laparoscopic cholecystectomy surgery is postoperative pain. Pain after laparoscopic surgery is a multidimensional and complex phenomenon that includes shoulder pain, abdominal pain, tissue damage, and regional pain [40]. Various factors include phrenic nerve stimulation as a result of carbon dioxide gas (CO_2) entering the peritoneal cavity, acidosis caused by CO_2 gas, stretching of the abdominal wall, increased release of inflammatory mediators, incision of the port site, trauma related to the exit of the gallbladder, and other factors contribute to pain after laparoscopic cholecystectomy [41-42].

Uncontrolled postoperative pain may lead to a range of detrimental physiological responses, such as shallow breathing and ineffective clearance of respiratory secretions, which can contribute to atelectasis and other pulmonary complications. Additionally, it may trigger cardiovascular responses including tachycardia and elevated blood pressure, thereby increasing the risk of myocardial ischemia. Gastrointestinal dysfunction like ileus, combined with extended periods of immobility, may further raise the likelihood of deep vein thrombosis. In addition, it can trigger stress responses, affect the immune system, and delay wound healing. Each of these circumstances can lead to increased inpatient duration and ultimately the surgery costs and change the patient's feeling of recovery and the result of the surgery [43-45]. Therefore, finding a way to create the greatest feeling of pain reduction and relaxation for the patient with as few adverse effects is a crucial concern following the surgical procedure [46-47]. There are different methods to achieve a suitable analgesia after surgery, including laparoscopic cholecystectomy surgery, which may involve utilizing systemic painkillers such as opioid drugs, anti-inflammatory medications lacking steroidal structure, or the use of local anesthetic drugs with different methods, mentioned regional nerve block drugs, epidural catheters, etc., each of which has its own advantages and disadvantages, and despite the use of these methods, the lack of proper pain control after surgery is still one of the most important issues after surgery [42,48]. Opioids are the first choice of treatment for spanning moderate to intense levels of pain after surgery. Notwithstanding, the use of these drugs appears to be linked with harmful reactions in particular itching,

nausea, vomiting, confusion, insomnia, breathing problems, urinary retention, and constipation, which limit their use in hospitals. In addition, the side effects necessitate the use of symptomatic treatments, including anti-nausea and vomiting drugs, as well as antihistamines, to mitigate them. Therefore, it seems logical to use compounds that can reduce the effective pain intensity of patients without causing side effects caused by the use of opioids [49-50]. Naloxone, an opioid μ receptor inhibitor, is one of the drugs used to potentiate the pain alleviation consequences of narcotics after surgery. In vitro studies [51-53] as well as various clinical studies on the effects of minimal naloxone concentrations combined with narcotic analgesics on perceived pain levels and the amount of narcotic drug use and side effects. There have been narcotic drugs that have led to contradictory results, so the results of some studies indicate a significant effect of adding naloxone with a very low dose in reducing pain after surgery and also minimizing postoperative opioid-related adverse effects [20, 22, 54-56]. while some other studies have not shown such effects [32-33, 57-58]. In another study that was conducted on patients undergoing laparoscopic cholecystectomy surgery, the findings showed that the concurrent use of naloxone at minimal doses and morphine significantly reduced the complications caused by opioids but had a notable influence on the severity of pain after the operation of the patients. did not have [59]. Given the aforementioned information, the significance of pain relief for patients following laparoscopic cholecystectomy surgery, the paucity of research in this area, and the relative safety of naloxone, this study aims to investigate the effect of ultra-low-dose naloxone on pain intensity after laparoscopic cholecystectomy surgery. Took in a study conducted by Movafegh et al. with the aim of investigating the effects of ultra-low-dose naloxone infusion on pain intensity and analgesia resulting from the use of morphine using the PCA method, the number of 90 patients was 35-55, who were candidates for abdominal hysterectomy surgery and met the conditions to participate in the research, were randomly allocated to two arms of 45 participants, intervention and control. All patients underwent general anesthesia using a standard protocol. After the operation and during the immediate postoperative period, morphine was used to control the pain of the patients using the PCA method. In addition, for the patients in the intervention group, naloxone infusion with a very low dose was used for 24 hours after the operation, and in the control group, normal saline infusion was done for 24 hours. After surgery, pain intensity, amount of morphine consumption, amount of nausea and vomiting, itching, and the amount of anti-nausea and emesis medication requests were evaluated at 30 minutes, 1, 4, 8, 16, 20, and the end of the first postoperative day. Data analysis revealed that within 24 hours after the operation, the amount of morphine consumed in the naloxone infusion arm was notably reduced as opposed to the participants in the placebo arm. Also, the incidence and severity of nausea and vomiting in the group receiving naloxone infusion was notably reduced as opposed to the participants in the placebo arm ($P<0.05$), although data showed equivalence across the arms in the severity of pain and itching in the two groups. ($P < 0.05$) [22].

In the research conducted by Toolabi et al., which was conducted with the aim of assessing the influence of administering low-dose naloxone on pain levels and the frequency of nausea, emesis, itching, and urinary retention in patients undergoing laparoscopic cholecystectomy, 60 patients required laparoscopic cholecystectomy surgery. and after surgery, they were randomly allocated to two arms:

- Naloxone arm (0.25 μg/kg/hour naloxone plus 20 μg/kg/hour morphine).
- Placebo arm (rate of morphine 20 μg/kg/h).

Patients were evaluated 2, 4, 8, and 16 hours after entering the recovery room, and the degree of pain experienced and the frequency of negative outcomes, such as nausea, emesis, itching, and urinary retention, was documented by a nursing professional. Study outcomes demonstrated that despite the fact that the prevalence of nausea, vomiting, itching, and urinary retention at 2, 4, 8, and 16 hours following the surgical procedure was considerably inferior in individuals treated with naloxone as opposed to the non-treatment group, in terms of severity, there was no noteworthy distinction in pain after surgery across both participant groups [58]. An analysis led by Jun Zheng et al. on 90 patients undergoing laparoscopic cholecystectomy in China with the purpose of examining the impact of simultaneous administration of naloxone and fentanyl through the PCA pump compared to the administration of fentanyl alone concerning the magnitude of pain, nausea, and emesis. Individuals underwent the procedure. The findings of this research indicated that naloxone in minimal doses can increase the analgesic effect of fentanyl, which is a fentanyl receptor agonist, and on the other hand, reduce nausea and vomiting [59]. In the experiment conducted by Cepeda et al., which focused on examining the impact of the combination of low-dose naloxone and morphine and its administration through PCA on the amount of opioid consumption and pain intensity after surgery, the number of 136 patients aged 18-65 who underwent They underwent surgery with a duration of less than 3 hours and were in ASA class I-II. We randomly divided them into case and control groups. For patients in the case group, morphine 1 mg/cc using PCA plus naloxone 6 micrograms/cc, and for the control group, morphine 1 mg/cc using PCA plus normal saline was employed as a placebo. The amount of opioid consumption, pain intensity, and complications caused by the use of opioids were evaluated every 4 hours after surgery and for 24

hours after surgery. Also, the satisfaction level of the patients was evaluated after 24 hours. The study's conclusions revealed that the patients receiving morphine + naloxone had significantly Increased levels of pain, increased opioid intake, less pain relief, and reduced satisfaction than the control group (>0.05) compared to the control group (p). Furthermore, the two groups showed no notable variation in the occurrence of complications [31]. According to the research conducted by Maxwell et al., with the objective of seeing how low-dose naloxone affects complications from opioids, 46 patients who had orthopedic and neurosurgery and were in severe to moderate pain after surgery were included. They met the analysis requirements and were assigned at random to a group receiving the treatment (20 people) and a group not receiving it (26 people). PCA containing morphine with the same dose and amount was used for all patients to control pain. In addition, for the case group, naloxone was provided at a rate of 0.25 μg/kg over 24 hours, and normal saline was provided as a placebo for the control group. During the study period, pain intensity and complication rates were evaluated every 4 hours. The study's conclusions revealed that the incidence and intensity of itching and nausea in the group receiving naloxone was substantially diminished ($p<0.05$), although the amount of opioid used and the intensity of pain while resting and coughing in the two groups, no notable difference was detected. In conclusion, the study found that using low-dose naloxone helps lessen the side effects of opioids, like itching and nausea, without affecting their pain-relieving benefits, so it is highly recommended for patients taking opioids. They controlled the pain [55].

In a study by Sartain et al. that randomly assigned 92 patients needing hysterectomy surgery to two groups, researchers looked at how a mix of naloxone and morphine given through PCA compared to morphine alone in terms of side effects and pain relief. Participants in the reference arm were given 60 mg of morphine per ml and normal saline through PCA. In the case group, in addition to morphine, patients also received 0.8 mg of naloxone through the PCA pump. The level of pain, nausea, vomiting, and pruritus experienced by the patients in the two study groups was evaluated at 6 and 24 hours post-operation utilizing the VAS scale. The amount of morphine consumed by the patient was also recorded. The results of the research indicated that one day post-study, there was no significant difference in the intensity of pain, nausea and vomiting, and itching, as well as the amount of morphine consumed among the two examined groups ($P<0.05$). Finally, the study concluded that using PCA to combine naloxone and morphine [32].

Methods

This study was designed as a double-blind controlled randomized clinical trial to evaluate the consequence of ultra-low dose naloxone on postoperative pain intensity following laparoscopic cholecystectomy. A total of 80 patients scheduled for elective laparoscopic cholecystectomy with ASA physical status classes I and II were selected using a convenient sampling method and randomly assigned to two groups of 40 participants each: the intervention group (naloxone) and the control group (placebo). All patients underwent general anesthesia based on a standardized anesthesia protocol. Postoperatively, patient-controlled analgesia (PCA) devices were installed for all patients for pain management. The PCA pump content for the intervention group consisted of 20 mg of morphine combined with naloxone at a dose of 0.25 μg/kg, while the control group received 20 mg of morphine with a placebo. Pain intensity, nausea and vomiting, and pruritus were assessed using the Visual Analog Scale (VAS) in the immediate postoperative care setting and at 2, 6, 12, and oneday post-experiment. Statistical analyses were performed using appropriate tests to compare outcomes among two treatment arms, with a significance threshold fixed $p < 0.05$. We received approval from the university ethics committee (IR.IUMS.FMD.REC.1401.659) and registered our clinical trial (IRCT20230424057986N1).

Results

In this randomized controlled double-blind clinical trial, 80 patients were examined in the form of two groups of 40: intervention (naloxone) and control (control). The average age is 56.80 years with a standard deviation of 9.15, and the lower and upper limits are 42 and 73 years, of which 60% (48 people) are men. The average BMI of the patients is 25.07 kg/m² with a standard deviation of 2.88, and the lower and upper limits are 21.05 and 20.64 kg/m². The mean and standard deviation of the duration of the operation and the duration of anesthesia are 113.50 ± 19.26 minutes and 143.50 ± 19.26 minutes, respectively. The mean and standard deviation of pain intensity in the recovery phase and at 2, 6, 12, and 24 hours following the procedure are, respectively, 8.00 ± 0.85, 6.75 ± 0.78, 5.05 ± 0.75, and 94.05 ± 0.75. The reported values ranged from 3.40 to 0.79. The mean and standard deviation of PONV severity at the time of recovery were 0.45 ± 1.09, and it was zero at other times. The mean and standard deviation of itching intensity during recovery were 0.50 ± 1.05, and it was zero at other times. All patients needed NSAIDs or opioids for postoperative pain after recovery, and 27 patients required NSAIDs or opioids two hours after surgery (Table 1).

Analytical statistics

In order to analyze the quantitative data, initially, the normality of the dataset was determined with the Kolmogorov-Smirnov test and its findings showed that the variables of age, BMI, duration of operation, and duration of anesthesia have a normal distribution, so for other quantitative variables Equivalent non-parametric statistical tests were used. The results of the independent t-test, Mann-Whitney, and chi-square in comparing the background information of the patients between the two study groups showed that there was a significant difference between the groups in terms of age, gender, BMI, length of operation, duration of anesthesia, and the dose of fentanyl injected during the operation. (Table 2) does not show any differences between the intervention and control groups. The results of the Mann-Whitney test revealed that there is no statistically meaningful variation across the treatment and control arms in terms of pain intensity at the time of recovery and 2, 6, 12, and one day post-experiment, and the intensity of PONV and itching at the time of recovery. The two groups had similar amounts of NSAIDs or opioids 2 hours post-op (Table 3).

Table 1- Background and clinical characteristics of all study patients

		Abundance	**Percentage**
sex	man	48	60
	woman	32	40
		Average	Standard deviation
Age (Years)		56.80	9.15
BMI (kg/m^2)		25.07	2.88
Duration of operation (minutes)		113.50	19.26
Duration of anesthesia (minutes)		143.50	19.26
Intraoperative prescription dose of fentanyl (micrograms)		225.00	25.64
intensity of pain	Recovery	8.00	0.85
	2 hours subsequent to the procedure	6.75	0.78
	6 hours subsequent to the procedure	5.05	0.75
	12 hours subsequent to the procedure	3.40	0.94
	24 hours subsequent to the procedure	2.00	0.79
NSAIDs or opioids at times recovery		80	100
NSAIDs or opioids at times 2 hours after the operation		27	33.8
Severity of PONV	Recovery	0.45	1.09
intensity of itching	Recovery	0.50	1.05

Table 2- Comparison of background and health-related characteristics across both study arms

		Arms		**P value**
		Intervention (Naloxone)	**Control (Placebo)**	
Age (Years)		56.90 ±9.80	56.70 ± 8.98	0.963
sex	man	(55%) 22	(60%)24	0.989
	woman	(45%)18	(40%)16	
BMI (kg/m2)		25.07 ± 3.05	25.06 ± 2.87	0.997
Duration of operation (minutes)		106.16 ±17.66	114.00 ± 21.70	0.750
Duration of anesthesia (minutes)		135.15 ± 14.49	144.19 ± 18.55	0.767
Intraoperative prescription dose of fentanyl (micrograms)		20.16±220.00	25.81±230.00	0.383

Table 3- Comparison of intensity of pain, PONV and itching at different times between two study groups

		Group		**Group**
		Intervention (Naloxone)	**Control (Placebo)**	
intensity of pain	Recovery	8.10 ± 0.87	7.90 ± 0.87	0.602
	2 hours subsequent to the procedure	6.80 ± 0.63	6.70 ± 0.94	0.596
	6 hours subsequent to the procedure	4.90 ± 0.87	5.20 ± 0.63	0.394
	12 hours subsequent to the procedure	3.30 ± 1.05	3.50 ± 0.84	0.691

	24 hours subsequent to the procedure	2.00 ± 0.81	2.00 ± 0.81	1.000
NSAIDs or opioids at times Recovery	Yes	40 (100%)	40 (100%)	-
	No	0	0	
NSAIDs or opioids at times 2 hours after the operation	Yes	15 (37.5 %)	12 (30%)	0.47
	No	25 (62.5 %)	28 (70%)	
Severity of PONV	Recovery	0.6 ± 1.26	0.3 ± 0.94	0.542
intensity of itching	Recovery	0.5 ± 1.08	0.5 ± 1.08	1.000

The paired t-test results indicated that both study groups experienced a significant reduction in pain intensity at all checked times compared to before (P<0.001 for both the intervention and control groups). Based on the repeated measures ANOVA test, there was no significant difference in pain intensity changes during the recovery period among the experimental arms (P=0.569) (Figure 1).

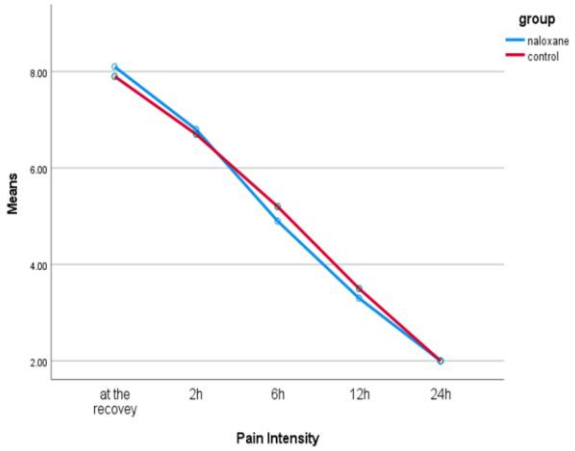

Figure 1- Comparison of pain intensity changes during the postoperative period between the two study arms

Discussion

The findings of our study showed that the use of naloxone along with morphine to relieve complications after laparoscopic cholecystectomy surgery did not show a significant difference in reducing pain intensity within 24 hours after the operation compared to placebo. Also, the results of our study showed that the effect of using naloxone along with morphine is not much different from placebo in reducing itching and nausea and vomiting experienced following surgery, and in both groups, there was a significant reduction in the intensity of pain, nausea and vomiting, and itching after surgery. The action clearly demonstrated this effect. Although the naloxone group experienced a similar slope of pain reduction in the first hours after the operation as the placebo group, both groups experienced similar pain intensity at the end of the postoperative period.

The limited studies conducted in the field of the effect of naloxone administration in reducing the intensity of pain and other postoperative complications have been accompanied by conflicting results.

In a research performed by Movafegh et al. [22] in order to examine the therapeutic implications of minimal-dosage naloxone infusion on the intensity of pain and analgesia resulting from the use of morphine using the PCA method, it was shown that within 24 hours after the operation, the amount of morphine consumed in the naloxone infusion arm was notably less as opposed to that in participants receiving standard treatment. Also, the frequency and intensity of nausea and vomiting in the naloxone infusion arm was notably less as opposed to that in participants receiving standard treatment, although no meaningful variation was detected in the severity of pain and itching in the two arms.

In the research conducted by Toolabi et al. [58], which intended to examine the influence of naloxone delivery at minimal doses on pain levels and the incidence of nausea, vomiting, itching, and urinary retention in patients undergoing laparoscopic cholecystectomy, it was found that despite the prevalence of nausea , vomiting, itching, and urinary retention at 2, 4, 8, and 16 hours after surgery being notably less in the group receiving naloxone in comparison the arm receiving placebo, there was an absence of significant variation in levels of perceived pain across both trial arms after surgery.

Also, in the research conducted by Maxwell et al. [55] with the aim of evaluating the effect of prophylactic infusion of naloxone with a low dose on the incidence of complications caused by the use of opioids in orthopedic and neurosurgery, the incidence and severity of itching and nausea in the naloxone-receiving group compared with placebo was significantly less (P>0.05). However, there were no observable statistical discrepancies in the administered opioid levels and the intensity of pain while resting and coughing in the two groups.

On the other hand, Jun Zheng et al. [59] conducted a study on 90 patients undergoing laparoscopic cholecystectomy, the aim was to investigating the effect of simultaneous administration of naloxone and fentanyl through the PCA pump compared to administration of fentanyl alone on the intensity of pain and nausea and vomiting. It was found that a low naloxone dose boosts fentanyl's analgesic effect and reduces nausea and vomiting.

Furthermore, in the research carried out by Cepeda et al. [31], with the objective of examining the influence of the combination of low-dose naloxone and morphine and

its administration through PCA on the amount of opioid consumption and pain intensity after surgery, patients receiving morphine + Compared to the control group, naloxone had significantly more pain intensity, more opioid consumption, less pain reduction, and less satisfaction than the control group. In addition, both groups showed a comparable rate of complications, with no meaningful variation.

In a randomized clinical trial study conducted by Sartain et al. [32] with the purpose of analyzing the influence of the combination of naloxone and morphine through PCA and comparing it with the use of morphine alone on the incidence of side effects and their analgesic effects, there was a significant difference in the severity of pain, nausea and vomiting, itching, and the amount of morphine used between the two study groups did not exist 24 hours after the operation, and it was concluded that the use of naloxone in combination with morphine using PCA does not have a beneficial effect.

In another study [58], which examines the effect of naloxone administration in reducing postoperative pain intensity, it was found that the concurrent intraoperative administration of minimum concentration naloxone and high-dose remifentanil in participants undergoing elective thyroid procedure reduces the action but does not affect the intensity of the pain.

In all the studies mentioned above, the use of intravenous naloxone during surgery, either in standard doses or in very low doses, has been associated with conflicting results in alleviating the intensity of pain, nausea, vomiting, and complications.

In another study by Ahmed et al. [14], the influence of ultra-low-dose naloxone administration through ultrasound-guided transverse abdominal plane block on postoperative pain reduction in patients undergoing laparoscopic cholecystectomy was investigated. Patients in two study groups (naloxone + bupivacaine) and control (bupivacaine) were compared in relation to the requirement for extra analgesia and pain intensity after surgery. The results of this clinical trial showed that the use of very low-dose naloxone in TAP block significantly reduces pain scores and postoperative opioid consumption in patients who have undergone laparoscopic cholecystectomy. By connecting to the inhibitory protein G complex (o/Gi) and μ μ-opioid receptor, opioids prevent the release of excitatory neurotransmitters from nociceptive neurons and cause pain relief. Studies have shown that the effect of naloxone on pain is dose-dependent. Thus, a high dose of naloxone reduces the analgesic effect of opioids and causes an increase in pain, while a low dose of naloxone does not increase the need for opioids [60-61]. Naloxone has the ability to counteract both the pain-relieving effects and adverse reactions of opioids when administered at doses exceeding 0.06 μg/kg/h [31], so lower doses may be preferred to obtain selective antinociceptive effects without affecting analgesia. be given as a result, the lack of effect of naloxone on reducing pain intensity and other postoperative complications in the patients of our study can be due to the higher dose of naloxone received in this study compared to other studies.

Conclusion

The Evidence of the current research demonstrated that the simultaneous prescription of naloxone and morphine in participants undergoing laparoscopic cholecystectomy has no significant effect in reducing the intensity of pain, nausea, vomiting, and itching after the operation compared to morphine alone. Therefore, we do not recommend using naloxone to reduce postoperative pain and opioid side effects.

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