J Orthop Spine Trauma. 2024 December; 10(4): 160-5. DOI: 10.18502/jost.v10i4.17358

Research Article

Effects of a Very Low Dose Naloxone Addition to Intraoperative Remifentanil Infusion on Postoperative Pain in Patients Undergoing Total Hip Replacement Surgery: A Randomized Clinical Trial

Mohsen Sabermoghaddamranjbar[1], Saeid Jamalie Bastami[1], Alireza Sharifian Attar[1], Seyed-Hossein Khademi[1], Mohammad Alipour[1], Mahdieh Samei[2], Omid Shahpari[3,*]

[1] Anesthesiologist, Department of Anesthesiology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[2] Master in Immunology, Orthopedic Research Center, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
[3] Orthopedic Surgeon, Orthopedic Research Center, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran

[*] Corresponding author: Omid Shahpari; Orthopedic Research Center, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran. Tel: +98-5138413494
Email: omidshahparidr@gmail.com

Received: 08 July 2024; **Revised:** 12 September 2024; **Accepted:** 01 October 2024

Abstract

Background: The objective of this study was to assess the effect of adding a very low dose of naloxone to a remifentanil infusion on postoperative pain in patients undergoing hip replacement surgery in the lateral position.
Methods: This randomized clinical trial involved 80 patients who underwent hip replacement surgery under general anesthesia and were randomly assigned into two groups through block randomization: group 1 received remifentanil at a dose of 0.3 µg/kg/minute, while group 2 received remifentanil at a dose of 0.3 µg/kg/minute with a very low dose of naloxone administered at 0.05 µg/kg/hour following injection. Postoperative pain [measured using the visual analog scale (VAS)], drowsiness caused by narcotics and analgesics in recovery, and the duration of getting out of bed were all monitored and recorded in the ward.
Results: The median [interquartile range (IQR)] of time to administration of the first sedative drug was 0 (0, 4) hours in the control group and 4 (0, 4) hours in the intervention group. The difference between the groups was statistically significant ($P < 0.0001$). The frequency of pain after surgery at 0, 4, and 8 hours was significantly different between the control and intervention groups ($P = 0.003$, $P < 0.0001$, and $P = 0.021$, respectively).
Conclusion: Based on the results, we recommend using a very low dose of naloxone along with remifentanil infusion in patients undergoing complete hip replacement surgery to reduce their pain and the need for painkillers.

Keywords: Naloxone; Remifentanil; Pain; Randomized Controlled Trial; Hip

Citation: Sabermoghaddamranjbar M, Jamalie Bastami S, Sharifian Attar A, Khademi SH, Alipour M, Samei M, et al. **Effects of a Very Low Dose Naloxone Addition to Intraoperative Remifentanil Infusion on Postoperative Pain in Patients Undergoing Total Hip Replacement Surgery: A Randomized Clinical Trial.** *J Orthop Spine Trauma* 2024; 10(4): 160-5.

Background

Orthopedic surgeries, such as total hip joint replacement, commonly have side effects, and among these, pain is a significant issue that affects various aspects of surgeries. It is necessary to take measures to prevent or reduce the severity of this complication during and after surgery. To minimize these problems and expedite patient recovery, anesthesiologists use analgesics like remifentanil (1-4). Remifentanil is a potent analgesic with a short-term effect, making it widely used during the intraoperative period and other treatment periods due to its favorable pharmacokinetic characteristics, including rapid onset and analgesic effects. Additionally, this medication reduces the risks of patient hypoventilation or delayed recovery from surgery (1). There is strong evidence suggesting that high doses of intraoperative remifentanil infusion lead to acute opiate tolerance (the effects of narcotic overdose). However, the findings of numerous clinical investigations are controversial (5).

Many studies have shown that low-dose naloxone is associated with tolerance and hyperalgesia caused by narcotics (6). However, our search does not yield significant clinical studies on the effect of opioid antagonists on remifentanil-induced tolerance. Naloxone is a selective µ-opioid receptor antagonist [similar to morphine receptors (µ)], commonly used in clinical practice to counteract the effects of narcotic overdoses, such as morphine, nalbuphine, and pentazocine. It can be administered in very low doses (0.08 to 1 mg) in combination with opioids to enhance the analgesic effect (7). Naloxone is also used to prevent the development of acute narcotic tolerance, increasing the duration of narcotic impact relative to the amount of drug used, and preventing side effects like hypoventilation, headache, nausea and vomiting, itching, urinary retention, ileus, and constipation caused by medication (8). Furthermore, by affecting pain receptors, naloxone prolongs the onset of pain after surgery (9, 10).

Therefore, due to the effects of naloxone, adding a low dose as a complementary drug during surgeries that require high doses of narcotics may help anesthesiologists reduce pain (11). The aim of this study was to assess the impact of adding a very low dose of naloxone to a remifentanil infusion on postoperative pain in patients undergoing hip replacement surgery.

Methods

Study Design and Setting: Between 2019 and 2021, this clinical trial study included patients who had been admitted for complete hip replacement at Ghaem and Imam Reza Hospitals, Mashhad City, Iran. The study was registered with the Iranian Registry of Clinical Trials (IRCT) under the identification number

IRCT20220111053694N1 and ethics approval number IR.MUMS.MEDICAL.REC.1399.624.

Participants: The participants consisted of 80 patients who had undergone total hip replacement surgery, were between 18 and 65 years old, had American Society of Anesthesiologists (ASA) I-II physical status (based on the physical status grading of the ASA), and had filled out the informed consent form.

The exclusion criteria included a body mass index (BMI) of ≥ 30 kg/m^2, pregnancy [based on beta-human chorionic gonadotrophin (B-HCG)], addiction to drugs and alcohol based on direct questioning, use of any pain relievers in the last 24 hours, unusual bleeding, cardiac ischemia, seizure history, a decrease or increase in blood pressure by more than 30% of the baseline value, and surgical complications such as prosthesis fracture or surgery expansion due to a large pelvic bone fracture. Additionally, patients with contraindications to anesthesia, previous chronic pain, and those who had received any narcotics about 12 hours before the operation were not included in the study. Postoperative exclusion criteria consisted of reoperation, excessive bleeding, and prolonged ventilation (> 12 hours).

Surgical Procedure: In this study, the intervention group received naloxone infusion at a rate of 0.05 µg/kg/hour. All patients were not allowed to use medicine and food for at least eight hours. Baseline heart rate (HR) and mean arterial pressure (MAP) were defined as the mean of the lowest measurements recorded during the 3- to 5-minute interval before induction of anesthesia. General anesthesia was initiated with propofol (2-2.5 mg/kg), fentanyl (2 µg/kg), and atracurium (0.5 µg/kg), while anesthesia depth was maintained via an infusion of propofol (150-300 µg/kg/minute) and remifentanil (0.3 µg/kg/minute). MAP, HR, and oxygen saturation (SPO2) were continuously monitored. Once spontaneous breathing resumed, neostigmine (0.04 µg/kg) and atropine (0.02 µg/kg) were administered for reversal, followed by extubation.

When hypotension (MAP < 60 mmHg) or bradycardia (HR < 45 beats/minute) occurred for more than five minutes, the patient was treated with ephedrine 10 mg or atropine 0.5 mg. Muscle relaxation was maintained by bolus doses of atracurium every 20-30 minutes, and after extubation, the patients were transferred to the recovery department, where they were given oxygen at a rate of five l/minute through a face mask. All patients were prescribed 1000 mg of apotel in the last half hour of the operation. The remifentanil infusion was continued until the end of the operation.

Values from all anesthesia monitors were recorded at five-minute intervals during surgery.

During the recovery of the patients, in cases of nausea and vomiting, treatment with ondansetron was performed.

Randomization: Before entering the operating room, the patients were randomly divided into groups in a ratio of 1:1 in two equal parts using the block randomization method.

Outcome: The primary outcome was a 10-point visual analog scale (VAS) for assessing pain. The pain of the patients was evaluated with the VAS pain scale after they were fully awake and able to answer the questions. A score of 0 indicated no pain, 1 to 4 indicated mild discomfort, 5 to 6 indicated moderate pain, and 7 to 10 indicated severe pain.

If the VAS score was below 4 and the patient did not express the need, they did not receive painkillers. If it was 5 or 6, 500 mg of morphine was used per kilogram of weight. If it was 7, 8, or 9, narcotics were prescribed according to the doctor's opinion. Post-surgery pain, when the VAS score of the patients was higher than 4, was treated by nurses who were not aware of the classification of patient groups, with common painkillers in the department, such as apotel, etc.

Secondary outcomes included the average time to the first sedative and cumulative dose of sedative medication.

Sample Size: A sample size of 40 patients in each group was calculated according to the mean difference of the postoperative pain based on the VAS in patients receiving naloxone and patients receiving naloxone plus fentanyl reported in the Zheng et al. study (12) using α= 0.05, β= 0.1, and a 15% drop-out rate.

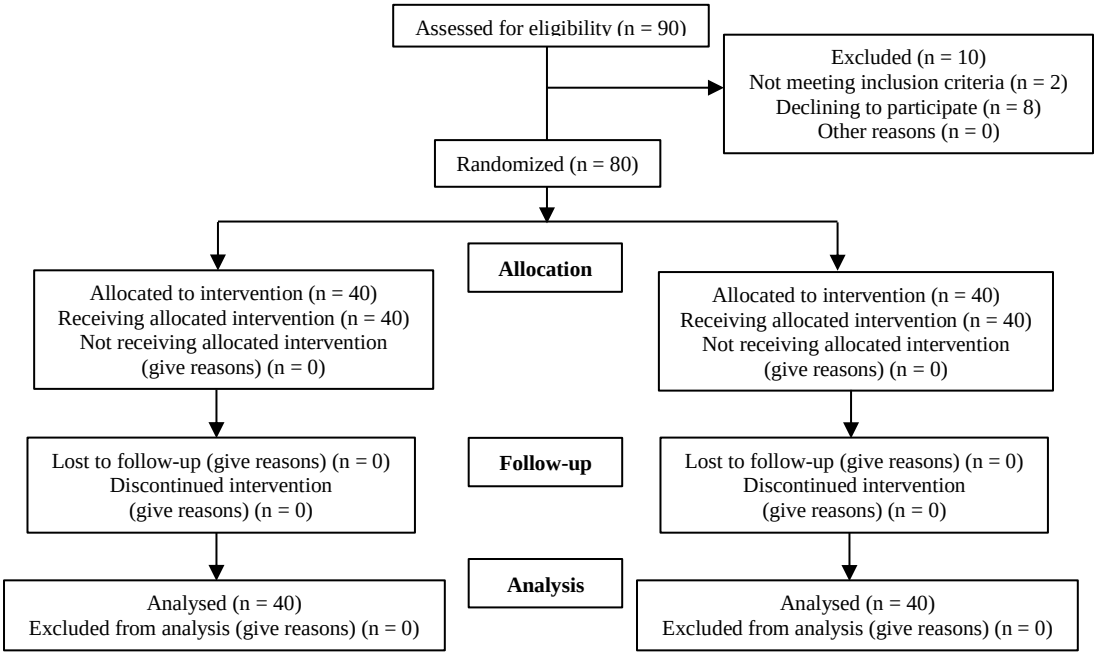

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the evaluated and included patients

Table 1. Comparison of the frequency of pain scores at different hours after surgery in the intervention and control groups

Variable		Intervention group [n (%)]	Control group [n (%)]	P-value
Pain (0 hours)	Without pain	7 (17.5)	0 (0)	0.003
	Mild	22 (55.0)	16 (40.0)	
	Moderate	11 (27.5)	21 (52.5)	
	Severe	0 (0)	3 (7.5)	
Pain (4 hours)	Without pain	2 (5.0)	0 (0)	< 0.001
	Mild	15 (37.5)	0 (0)	
	Moderate	17 (42.5)	18 (45.0)	
	Severe	6 (15.0)	22 (55.0)	
Pain (8 hours)	Without pain	1 (2.5)	0 (0)	0.021
	Mild	7 (17.5)	2 (5.0)	
	Moderate	24 (60.0)	36 (90.0)	
	Severe	8 (20.0)	2 (5.0)	
Pain (12 hours)	Without pain	4 (10.0)	2 (5.0)	0.648
	Mild	27 (67.5)	27 (67.5)	
	Moderate	9 (22.5)	11 (27.5)	
Pain (24 hours)	Without pain	20 (50.0)	20 (50.0)	> 0.990
	Mild	20 (50.0)	20 (50.0)	

Statistical Analysis: The SPSS software (version 26, IBM Corporation, Armonk, NY, USA) was used to analyze data. Normal distribution was checked using the Kolmogorov-Smirnov test. For normal distribution, data were described as mean ± standard deviation (SD), otherwise as median (quartile 25, quartile 75). Qualitative data were described as frequencies (percentages). The chi-square test was used to examine the relationship between qualitative variables. The comparison between two groups was done using an independent t-test or its non-parametric equivalent. A significance level of $P < 0.05$ was considered significant.

Results

Patient Characteristics: This study involved 80 patients admitted to Ghaem and Imam Reza Hospitals, who were separated into two groups: one group receiving remifentanil plus a very low dose of naloxone (n = 40), and the other group receiving only remifentanil (n = 40) during surgery (Figure 1). The average age of the participants was 47.08 ± 19.48 years (intervention group: 47.15 ± 19.43, control group: 47.02 ± 19.53). There was no statistically significant difference in age between the two groups ($P = 0.97$). In terms of gender distribution, the intervention group consisted of 18 men (45%) and 22 women (55%), whereas the control group had 28 men (70%) and 12 women (30%), showing a significant difference between the groups in gender composition ($P = 0.024$). Based on the collected data and the chi-square test, the number and type of drugs used (morphine, methadone, apotel, pethidine) were similar between the control and intervention groups at 0, 4, 8, 12, and 24 hours. There was no significant difference between the two groups in this respect ($P > 0.990$).

Pain Scores: The data in table 1 indicate a significant difference in the pain score frequencies between the two groups immediately after surgery (at 0 hours) ($P = 0.003$).

This indicates that a very low dose of naloxone effectively reduced postoperative pain at 0 hours. Additionally, the frequency of pain after surgery at 4 and 8 hours showed a significant difference between the two groups ($P < 0.0001$, $P = 0.021$, respectively). However, no significant differences were found between the control and intervention groups during the other hours of the study ($P > 0.05$).

According to the data in table 2, the frequency of pain after surgery in women was significantly different between the control and intervention groups only at 4 hours after the operation ($P = 0.006$). No significant difference was observed between the two groups during the remaining hours examined ($P > 0.05$).

According to table 3, the frequency of pain scores after surgery in men at 0 and 4 hours was significant between the two groups ($P = 0.031$, $P = 0.001$, respectively), indicating the effect of very low dose naloxone in reducing postoperative pain at this time points. However, no significant difference was observed between the control and intervention groups for the remaining hours under investigation ($P > 0.05$).

Additionally, by using logistic regression to analyze the influence of gender on pain scores in both groups, we found that after accounting for gender effects, there was a significant difference in pain intensity frequency between the two groups. Importantly, the intervention group demonstrated a notably lower frequency of pain scores compared to the control group ($P = 0.003$).

Average Time to the First Sedative: According to the data in table 4, the median [interquartile range (IQR)] of time to administration of the first sedative drug was 0 (0, 4) hours in the control group and 4 (0, 4) hours in the intervention group. The difference between the two groups was statistically significant ($P < 0.0001$), suggesting that the time to the first sedative in the intervention group was significantly longer than in the control group. Additionally, when examining the average time to the first sedative for women, no significant difference was found between the groups ($P = 0.061$). However, among men, there was a significant difference, with the intervention group experiencing a notably longer time before receiving the first sedative compared to the control group ($P < 0.0001$).

Table 2. Comparison of the frequency of pain scores in different hours after the operation in the intervention and control groups in women

Variable		Intervention group [n (%)]	Control group [n (%)]	P-value
Pain (0 hours)	Without pain	4 (18.2)	0 (0)	0.120
	Mild	11 (50.0)	4 (33.3)	
	Moderate	7 (31.8)	7 (58.3)	
	Severe	0 (0)	1 (8.3)	
Pain (4 hours)	Mild	9 (40.9)	0 (0)	0.006
	Moderate	10 (45.5)	5 (41.7)	
	Severe	3 (13.6)	7 (58.3)	
Pain (8 hours)	Without pain	1 (4.5)	0 (0)	0.221
	Mild	4 (18.2)	0 (0)	
	Moderate	13 (59.1)	11 (91.7)	
	Severe	4 (18.2)	1 (8.3)	
Pain (12 hours)	Without pain	0 (0)	1 (8.3)	0.278
	Mild	17 (77.3)	7 (58.3)	
	Moderate	5 (22.7)	4 (33.3)	
Pain (24 hours)	Without pain	13 (59.1)	5 (41.7)	0.331
	Mild	9 (40.9)	7 (58.3)	

Table 3. Comparison of the frequency of pain scores at different hours after surgery in the intervention and control groups in men

Variable		Intervention group [n (%)]	Control group [n (%)]	P-value
Pain (0 hours)	Without pain	3 (16.7)	0 (0)	0.031
	Mild	11 (61.1)	12 (42.9)	
	Moderate	4 (22.2)	14 (50.0)	
	Severe	0 (0)	2 (7.1)	
Pain (4 hours)	Without pain	2 (11.1)	0 (0)	0.001
	Mild	6 (33.3)	0 (0)	
	Moderate	7 (38.9)	13 (46.4)	
	Severe	3 (16.7)	15 (53.6)	
Pain (8 hours)	Mild	3 (16.7)	2 (7.1)	0.063
	Moderate	11 (61.1)	25 (89.3)	
	Severe	4 (22.2)	1 (3.6)	
Pain (12 hours)	Without pain	4 (22.2)	1 (3.6)	0.138
	Mild	10 (55.6)	20 (71.4)	
	Moderate	4 (22.2)	7 (25.0)	
Pain (24 hours)	Without pain	7 (38.9)	15 (53.6)	0.331
	Mild	11 (61.1)	13 (46.4)	

Table 4. Comparison of the average time to the first sedative in the intervention and control groups in men and women and in general

Factor		N	Median (q25, q75)	P-value*
Time to first sedative drug				
	Control	40	0 (0, 4)	< 0.0001
	Intervention	40	4 (0, 4)	
Time to first sedative drug				
Men	Control	28	0 (0, 4)	< 0.0001
	Intervention	18	4 (3, 6.5)	
Women	Control	12	0 (0, 3)	0.0610
	Intervention	22	4 (0, 4)	

*Mann-Whitney test
Q: Quartile

Cumulative Dose of Sedative Medication: According to the data in table 5, the average cumulative dose of morphine and methadone received in the first 24 hours was significant between both groups. The control group had a significantly higher cumulative dose of morphine and methadone in the first 24 hours compared to the intervention group ($P < 0.0001$, $P < 0.002$, respectively).

Discussion

Recently, the combination of the μ-receptor antagonist, naltrexone or naloxone, with oxycodone or buprenorphine has been used to enhance the analgesic effects of opioids and prevent the development of physical tolerance. Although naloxone and intermediary receptors are involved in the analgesic effects, they do not have a direct analgesic effect and can cause dysphoria, hallucinations, and respiratory stimulation. Multiple mechanisms have been proposed to explain the effects of very low doses of naloxone when administered simultaneously with remifentanil. Animal experiments have shown that naloxone can prevent microglial activation and superoxide production, thereby protecting neurons from damage. This neuroprotective effect of naloxone may inhibit the growth of drug tolerance, considering that neuronal apoptosis is a pathological process that occurs during the development of drug tolerance (13). Naloxone also binds to a pentapeptide section of the protein filamin A and prevents G protein coupling (Gi/o to Gs) by opioid receptors (9).

This mechanism may explain the inhibition of tolerance to drugs due to desensitization of the opioid analgesic system (14). Additionally, naloxone affects the toll-like receptor 4 (TLR4) receptor and inhibits neuroinflammation, which plays a role in inhibiting the development of tolerance caused by drugs (15).

The results of our study indicated a significant difference in pain frequency after surgery at 0, 4, and 8 hours between the control and intervention groups. This indicates that administering a very low dose of naloxone can help lower pain intensity within the first 8 hours following total hip replacement surgery. However, at 12 and 24 hours post-surgery, there was no significant difference in the frequency of pain between the intervention and control groups, suggesting both groups experienced comparable levels of pain intensity during that period. A study conducted by Peivandi et al. found that adding a very low dose of naloxone to intrathecal morphine did not significantly reduce the intensity of postoperative pain (16). However, Makarem et al. concluded that adding a low dose of naloxone to remifentanil was effective and useful in reducing the frequency and intensity of postoperative pain and hyperalgesia in patients under general anesthesia for laparotomy hysterectomy (17), which is in line with the results of our study.

Several mechanisms, including drug-induced hyperalgesia, tolerance, and withdrawal syndrome, have been suggested to increase pain intensity after drug administration. Pain from drug tolerance usually occurs at the site of tissue damage and can be relieved with additional analgesics. On the other hand, opioid-induced hyperalgesia (OIH) is perceived in distant areas from the site of tissue damage and is experienced throughout the body. The intensity of OIH pain increases with the administration of additional analgesics. However, OIH can be managed by reducing the dose of the drug or using N-methyl-D-aspartate (NMDA) receptor antagonist drugs such as ketamine. Nevertheless, sudden discontinuation of remifentanil infusion may cause acute withdrawal syndrome. Various mechanisms contribute to OIH, such as central sensitization resulting from reduced reuptake or heightened release of excitatory neurotransmitters (like glutamate and aspartate), a decrease in opioid receptors within the gray matter, heightened pain responses, and genetic factors. However, few studies have quantitatively examined these mechanisms.

Table 5. Comparison of the average cumulative dose of sedative medication received in the first 24 hours between the control and intervention groups

Variable		N	Mean ± SD	Minimum	Maximum	P-value
Cumulative dose of morphine in the first 24 hours	Control	32	13.43 ± 4.10	5.0	20.0	< 0.0001
	Intervention	38	9.40 ± 3.36	2.5	15.0	
Cumulative dose of pethidine in the first 24 hours	Control	2	17.50 ± 3.53	15.0	20.0	0.0700
	Intervention	3	7.50 ± 4.30	2.5	15.0	
Cumulative dose of methadone in the first 24 hours	Control	3	15.00 ± 5.00	10.0	20.0	0.0020
	Intervention	7	4.63 ± 2.67	2.5	10.0	
Cumulative dose of apotel in the first 24 hours	Control	28	1392.86 ± 727.32	1000.0	3000.0	0.0800
	Intervention	26	1067.92 ± 577.79	500.0	2500.0	

SD: Standard deviation

Naloxone acts as a dual-phase pain modulator, with low doses enhancing analgesic narcotic effects and higher doses reversing narcotic-induced analgesia. The precise mechanism of low-dose naloxone has not been identified, but it is believed to arise from the antagonism or modification of NMDA and opioid receptor activity, which is considered a primary factor in its pain-relieving effects. Movafagh et al. also reported that low-dose naloxone infusion was associated with lower morphine doses following surgery in hysterectomy patients (18).

The notable difference in the average time to the first sedative between the two groups demonstrates the considerable effect of a very low dose of naloxone in minimizing pain and reducing the postoperative need for analgesics. Our study identified a notable gender difference in the timing of postoperative sedative administration. Among women, there was no significant difference between the control and intervention groups in the time of the first sedative. However, in men, the intervention group showed a significantly longer delay before requiring the first sedative compared to the control group. This indicates that naloxone may have a stronger impact on delaying sedation in men. These results could be linked to physiological and hormonal variations between men and women in their response to opioids and opioid antagonists.

Naloxone is an antagonist drug that competitively binds to opioid receptors, and it can reduce the analgesic effects of morphine. Therefore, naloxone is widely used to manage complications related to morphine abuse or excessive use. In our study, the intervention group had significantly lower cumulative doses of sedative drugs, morphine, and methadone in the first 24 hours after surgery compared to the control group. This finding is consistent with other findings in this study, indicating the significant effect of a very low dose of naloxone in reducing the need for sedative drug use after surgery. Another study conducted by Koo et al. demonstrated that combining low-dose naloxone with high-dose remifentanil reduced postoperative hyperalgesia, though it did not lower postoperative pain intensity (19). Naloxone can also inhibit narcotic receptors in both the spinal cord and higher nerve levels, leading to hyperalgesia. Most studies in this field have investigated hyperalgesia caused by chronic opioid administration, and evidence for acute OIH is scarce. Another study has shown that individuals receiving naloxone experienced significantly lower levels of postoperative pain compared to those receiving saline, suggesting that naloxone's ability to block opioid receptors can increase postoperative pain relief. Our study also concluded that the frequency of pain intensity differed significantly between the intervention and control groups, even without considering gender, with the intervention group experiencing significantly lower pain intensity. This demonstrates that a very low dose of naloxone can be used to reduce pain intensity and decrease the need for analgesics in the initial 8 hours after surgery, regardless of gender.

One of the limitations of this study was its relatively small sample size. For better investigations, studies in the form of clinical trials with a larger sample size can be used. Another weakness of this study was that patients in the wards were attended to by various nurses when we monitored them and administered painkillers based on their individually assessed VAS, following the protocol.

Conclusion

Based on the results obtained, we recommend using very low doses of naloxone in conjunction with remifentanil infusion for patients undergoing surgery. This approach effectively reduces pain and minimizes the need for painkillers in these patients. Additionally, it is essential to provide a comprehensive explanation to the patient regarding the benefits and potential complications associated with the surgery.

Studies are recommended to be conducted in the form of clinical trials, particularly in specialized departments like the intensive care unit (ICU), utilizing a distinct pain control protocol. It is also advisable to conduct studies on patients undergoing different types of surgeries.

Conflict of Interest

The authors declare no conflict of interest in this study.

Acknowledgements

This research received no specific grant from any funding agency in the public or commercial secretors.

References

1. Servin FS. Remifentanil: An update. *Curr Opin Anaesthesiol*. 2003;16(4):367-72. doi: 10.1097/01.aco.0000084479.59960.3f. [PubMed: 17021484].
2. Taylor R, Pergolizzi JV, Porreca F, Raffa RB. Opioid antagonists for pain. *Expert Opin Investig Drugs*. 2013;22(4):517-25. doi: 10.1517/13543784.2013.778973. [PubMed: 23484859].
3. Heidari B, Salimi R, Saremi H, Arab GM. Assessment of magnesium sulfate infusion in combination with ketorolac for the pain management in intertrochanteric fractures; a randomized clinical trial. *Arch Bone Jt Surg*. 2023;11(6):414-20. doi: 10.22038/ABJS.2023.64778.3109. [PubMed: 37404294]. [PubMed Central: PMC10314985].
4. Saliminia A, Atef Yekta R, Azimaraghi O, Shamabadi A, Naderi S, Movafegh A. Evaluation of the effect of Transversus Abdominis Plane (TAP) block on post-laparoscopic cholecystectomy stress responses: A randomized controlled trial. *Arch Anesth & Crit Care*. 2022;8(Supp 1):399-406.
5. Gan TJ, Ginsberg B, Glass PS, Fortney J, Jhaveri R, Perno R. Opioid-sparing effects of a low-dose infusion of naloxone in patient-administered morphine sulfate. *Anesthesiology*. 1997;87(5):1075-81. doi: 10.1097/00000542-199711000-00011. [PubMed: 9366459].
6. Crawford MW, Hickey C, Zaarour C, Howard A, Naser B. Development of acute opioid tolerance during infusion of remifentanil for pediatric scoliosis surgery. *Anesth Analg*. 2006;102(6):1662-7. doi: 10.1213/01.ane.0000216036.95705.c2. [PubMed: 16717305].
7. Imasogie NN, Singh S, Watson JT, Hurley D, Morley-Forster P. Ultra low-dose naloxone and tramadol/acetaminophen in elderly patients undergoing joint replacement surgery: A pilot study. *Pain Res Manag*. 2009;14(2):103-8. doi: 10.1155/2009/497217. [PubMed: 19532850]. [PubMed Central: PMC2706645].
8. Maxwell LG, Kaufmann SC, Bitzer S, Jackson EV Jr, McGready J, Kost-Byerly S, et al. The effects of a small-dose naloxone infusion on opioid-induced side effects and analgesia in children and adolescents treated with intravenous patient-controlled analgesia: A double-blind, prospective, randomized, controlled study. *Anesth Analg*. 2005;100(4):953-8. doi: 10.1213/01.ANE.0000148618.17736.3C. [PubMed: 15781505].
9. Wang HY, Friedman E, Olmstead MC, Burns LH. Ultra-low-dose naloxone suppresses opioid tolerance, dependence and associated changes in mu opioid receptor-G protein coupling and Gbetagamma signaling. *Neuroscience*. 2005;135(1):247-61. doi: 10.1016/j.neuroscience.2005.06.003. [PubMed: 16084657].
10. Xiao Y, Wu L, Zhou Q, Xiong W, Duan X, Huang X. A randomized clinical trial of the effects of ultra-low-dose naloxone infusion on postoperative opioid requirements and recovery. *Acta Anaesthesiol Scand*. 2015;59(9):1194-203. doi: 10.1111/aas.12560. [PubMed: 26041316].

11. Kim SH, Lee MH, Seo H, Lee IG, Hong JY, Hwang JH. Intraoperative infusion of 0.6-0.9 microg.kg(-1).min(-1) remifentanil induces acute tolerance in young children after laparoscopic ureteroneocystostomy. *Anesthesiology*. 2013;118(2):337-43. doi: 10.1097/ALN.0b013e31827bd108. [PubMed: 23241726].
12. Zheng J, Han W, Han XD, Ma XY, Zhang P. Effect of naloxone on intravenous fentanyl patient-controlled analgesia after laparoscopic cholecystectomy. *Medicine (Baltimore)*. 2016;95(48):e5074. doi: 10.1097/MD.0000000000005074. [PubMed: 27902584]. [PubMed Central: PMC5134765].
13. Hu S, Sheng WS, Lokensgard JR, Peterson PK. Morphine induces apoptosis of human microglia and neurons. *Neuropharmacology*. 2002;42(6):829-36. doi: 10.1016/s0028-3908(02)00030-8. [PubMed: 12015209].
14. Li Q. Antagonists of toll like receptor 4 maybe a new strategy to counteract opioid-induced hyperalgesia and opioid tolerance. *Med Hypotheses*. 2012;79(6):754-6. doi: 10.1016/j.mehy.2012.08.021. [PubMed: 23062774].
15. Powell KJ, Abul-Husn NS, Jhamandas A, Olmstead MC, Beninger RJ, Jhamandas K. Paradoxical effects of the opioid antagonist naltrexone on morphine analgesia, tolerance, and reward in rats. *J Pharmacol Exp Ther*. 2002;300(2):588-96. doi: 10.1124/jpet.300.2.588. [PubMed: 11805221].
16. Peivandi S, Habibi MR, Baradari AG, Gholinataj A, Habibi A, Khademloo M, et al. The effect of adding low-dose naloxone to intrathecal morphine on postoperative pain and morphine related side effects after cesarean section: a double-blind, randomized, clinical trial. *Open Access Maced J Med Sci*. 2019;7(23):3979-83. doi: 10.3889/oamjms.2019.852. [PubMed: 32165939]. [PubMed Central: PMC7061398].
17. Makarem J, Majedi H, Bahmaee F, Mireskandari SM, Amraei F, Yousefshahi F, et al. Evaluation of the efficacy of low-dose naloxone for the prevention of acute remifentanil-induced hyperalgesia in patients undergoing general anesthesia for laparotomy. *Arch Neurosci*. 2020;7(4):e108836. doi: 10.5812/ans.108836.
18. Movafegh A, Nouralishahi B, Sadeghi M, Nabavian O. An ultra-low dose of naloxone added to lidocaine or lidocaine-fentanyl mixture prolongs axillary brachial plexus blockade. *Anesth Analg* . 2009;109(5):1679-83. doi: 10.1213/ANE.0b013e3181b9e904. [PubMed: 19843808].
19. Koo CH, Yoon S, Kim BR, Cho YJ, Kim TK, Jeon Y, et al. Intraoperative naloxone reduces remifentanil-induced postoperative hyperalgesia but not pain: A randomized controlled trial. *Br J Anaesth*. 2017;119(6):1161-8. doi: 10.1093/bja/aex253. [PubMed: 29029049].