Original Article

Comparison the effects of two different dose of intrathecal morphine adjunct to ultra-low dose of naloxone on pain intensity after cesarean section: A double-blind randomized clinical trial

Mohammad Reza Habibi[1], Zohreh Ghahari[2], Ali Habibi[3], Afshin Gholipour Baradari[4], Saloumeh Peivandi[5]*

ABSTRACT

Objective

The aim of this study was to evaluate and compare the effects of two different dose of intrathecal morphine adjunct to ultra-low dose of naloxone on pain intensity after cesarean section.

Methods

In this double-blind randomized clinical trial, 78 women over 18 years of age who referred to the Imam Khomeini Hospital in Sari for elective cesarean section were allocated randomly to receive either intrathecal morphine with doses of 100 µg or 200 µg, adjunct to ultra-low dose of naloxone (20 ng). Patients' pain intensity were assessed using the VAS at 2, 4, 6 and 24 hours postoperatively. Also, the occurrence of adverse effects (pruritus, nausea, vomiting and ileus) in two groups were evaluated during the study period.

Results

The findings of this study indicated a significant difference in pain intensity between the two groups throughout the study period ($p<0.05$). Ileus was not significantly different between the two groups ($P=0.48$). However, using morphine at a dose of 200 µg with naloxone was associated with significantly lower rate of nausea and pruritus ($P<0.001$).

Conclusion

In the present study, patients receiving morphine at a dose of 200 µg with naloxone (20 ng) experienced significantly less pain intensity than the group receiving morphine at a dose of 100 µg with naloxone. In addition, the rate of nausea and pruritus in the group receiving morphine at a dose of 200 µg with naloxone was significantly lower than the other group.

Keywords

Morphine; naloxone; cesarean section; nause

INTRODUCTION

Acute postoperative pain is related to the extent and area of the operation, psychological and physiological background of the patient and the tissue manipulation and injury [1]. Pain is an unpleasant sensory and psychological experience with actual or potential tissue damage [2]. Poorly controlled postoperative pain can cause several physiological side effects, including postoperative paralytic ileus, and nausea and vomiting [3]. Cesarean section (CS) is a frequently performed major surgery that often leads to significant postoperative pain. Inadequate management of this pain after CS

1. Mohammad Reza Habibi, Department of Anesthesiology, Faculty of Medicine, Cardiovascular Research Center, Fatemeh Zahra Hospital, Mazandaran University of Medical Sciences, Sari, Iran.
2. Zohreh Ghahari, Department of Anesthesiology, Faculty of Medicine, Cardiovascular Research Center, Fatemeh Zahra Hospital, Mazandaran University of Medical Sciences, Sari, Iran.
3. Ali Habibi, Student Research Committee, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran.
4. Afshin Gholipour Baradari, Department of Anesthesiology, Faculty of Medicine, Cardiovascular Research Center, Fatemeh Zahra Hospital, Mazandaran University of Medical Sciences, Sari, Iran.
5. Saloumeh Peivandi, Department of Obstetrics and Gynecology, Faculty of Medicine, Clinical Research Development Unit of Imam Khomeini Hospital, Mazandaran University of Medical Sciences, Sari, Iran and Sexual and Reproductive Health Research Center, Mazandaran University of Medical Sciences, Sari, Iran.

Correspondence

Dr. Salomeh Peivandi; Assistant Professor, Department of Obstetrics and Gynecology, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran.
Email: dr.s.peivandi50@gmail.com

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can result in decreased patient mobility, a higher risk of venous thrombosis, hindered bonding between mother and baby, and increased susceptibility to pneumonia. Therefore, appropriate pain control after CS using safe and effective analgesic modalities is a universal concern [4,5].

Today, spinal anesthesia is the right choice for most elective and emergency CSs. A number of studies in the last 25 years have reported the improvement of the quality of analgesia by adding opiates to lidocaine or bupivacaine in regional anesthesia [6, 7]. Some evidence even suggests that intraspinal opioids reduce the incidence of post-dural puncture headache [8].

Numerous studies have demonstrated that combining local anesthetics with opioids offers enhanced analgesia, either through additive or synergistic effects, while minimizing the adverse effects typically associated with higher doses of each drug [9-10].

Intrathecal morphine was described in the early 1980s for obstetric analgesia. Previous research has shown that intrathecal morphine sulfate effectively provides long-lasting pain relief following a Cesarean section [11-12]. However, it may also lead to side effects such as nausea, vomiting, itching, constipation, sedation, and respiratory depression. Furthermore, the effectiveness of the analgesia and the incidence of side effects can vary based on the dosage of intrathecal morphine used [13-14]. Considering that morphine is one of the opioids commonly used for spinal anesthesia in patients undergoing CS and its potential side effects, this study aimed to evaluate two different dose of intrathecal morphine adjunct to ultra-low doses of naloxone on pain intensity after CS.

METHODS AND MATERIALS

In this double-blind randomized clinical trial, women aged over 18 years, weighing between 60-80 kg, who were having their first or second child, classified as American Society of Anesthesiologists (ASA) grade I–II, at term, and scheduled for elective Cesarean delivery under spinal anesthesia at Imam Khomeini Hospital in Sari, were included in the study. This study was carried out following approval from the institutional ethics committee (code: IR.MAZUMS.IMAMHOSPITAL.REC.1398.086; IRCT20091219002883N6).

Patients with known sensitivity to morphine or naloxone, reluctance to continue with the study, failure of spinal anesthesia, prolonged duration of surgery (more than 1.5 hours), emergency CS, and in whom unpredicted adverse effects or complications occurred during surgery (such as excessive blood loss as bleeding more than 1,500 ml, pulmonary embolism, uterine artery injury, emergency peripartum hysterectomy or bladder or ureteral injury) were excluded from the study.

Following approval from the institutional ethics committee and the acquisition of informed consent, patients meeting the inclusion criteria were randomly assigned to two equal groups, labeled A and B, with 41 participants in each group, utilizing a simple randomization method. Patients in the group A, received 10 mg bupivacaine 0.5% along with 100 µg of morphine and naloxone 20 ng intrathecally. In the group B, 10 mg bupivacaine 0.5% along with morphine 200 µg and naloxone 20 ng (group B) were administered intrathecally. The process of morphine preparation began by withdrawing 1 ml of morphine solution with a concentration of 10 mg/ml into a 10 ml syringe. This solution was then mixed with 9 ml of 0.9% NaCl solution in the same syringe. After thorough mixing, 9 ml of the resulting mixture was discarded, leaving 1 ml. This 1 ml was then diluted again with 9 ml of 0.9% NaCl solution. After thorough mixing, 1 ml (100 µg) or 2 ml (100 µg) of this final mixture was drawn into a 5 ml syringe.

Clinical and demographic features of every patient were recorded at the beginning of the study. Pain intensity was assessed using the Visual Analog Scale (VAS) at 2, 4, 6, and 24 hours, postoperatively. Additionally, all patients were inquired about the occurrence of nausea and itching throughout the study period. Following the surgical procedure, each patient was connected to a patient-controlled analgesia (PCA) pump. This PCA pump contained 4 grams of Apotel® (Paracetamol), diluted to a total volume of 120 ml with normal saline. The settings for the PCA pumps included a lockout interval of 15 minutes, a continuous infusion rate of 4 cc/h and a bolus dose of 0.5 ml. The total amount of paracetamol consumption were recorded.

In this study, postoperative ileus was defined as absence of first flatus or defecation or absence of bowel sounds after surgery. Patients were asked about flatulence and defecation and checked bowel sounds at 2, 4, 6 and 24 hours after surgery. A collaborating nurse, who was unaware of the group assignments and had received comprehensive training on the study procedures,

conducted the assessment of the aforementioned variables.

Sample size calculation

The initial sample size was determined using GPower 3.1, applying the formula for repeated measures, with an anticipated effect size of 0.3, a statistical power of 80%, and a Type I error rate of 5%. This calculation indicated that a total sample size of 80 participants would be adequate. To accommodate potential dropouts, we ultimately recruited 90 patients.

Statistical analysis

After data collection, statistical analysis was performed using descriptive and inferential statistics via the SPSS v.18 software. Shapiro-Wilk test was used to assess normality of the data. Chi-Square/Fisher exact test and t-test were used for qualitative and quantitative variables, respectively. Repeated Measure Analysis of Variance (ANOVA) or Kruskal-Wallis tests were used to evaluate pain severity, nausea and pruritus, following by a Tukey test as a post hoc analysis. P-value less than 0.05 was considered statistically significant.

ETHICAL CLEARANCE

The present study was conducted after the approval of the institutional ethics committee (code: IR.MAZUMS.IMAMHOSPITAL.REC.1398.086). The researchers explained the study objectives to the participants, and informed consent was obtained from all participants. Also, protocol of this study was registered in the Iranian Registry of Clinical Trials Database (IRCT20091219002883N6).

RESULTS

In this study, 90 patients were assessed, of whom 82 met the eligibility criteria and were assigned to the respective groups. With the exception of one patients in group A and three patients in group B, all remaining participants (n=78) completed the study, and data from these individuals were included in the final analysis (Figure 1).

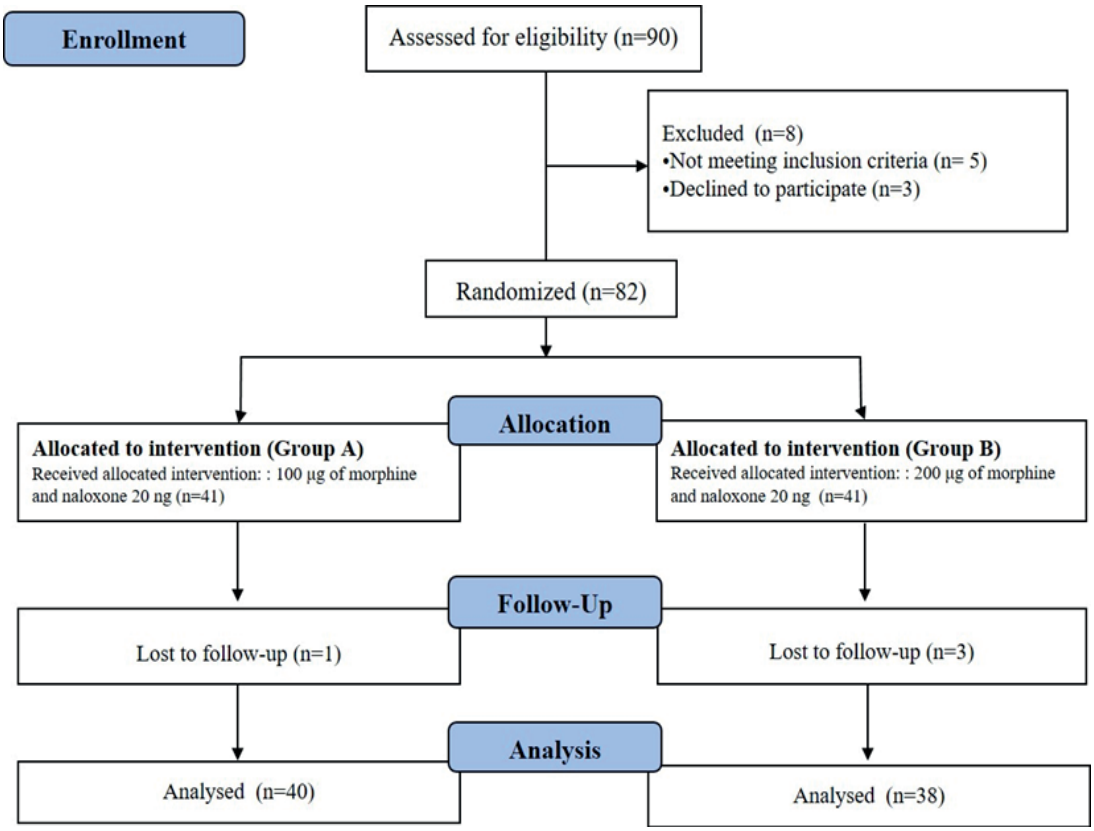

Figure 1: Flowchart of the study

The mean age of the patients in the group A (morphine 100 µg) was 32.63 and in the group B (morphine 200 µg) was 32.2 years (p=0.81). There were no significant differences based on educational level, place of residence or underlying disease between two groups (Table 1).

Table 1: Demographic and clinical characteristics of patients in two groups

Variables		Group A (morphine 100 µg)	Group B (morphine 200 µg)	P-value
Age		32.63±7.89	32.2±7.28	0.81
Educational level	High school	9 (22)	8 (21)	0.93
	diploma	23 (58)	22 (57)	
	Bachelor's degree	6 (15)	4 (11)	
	Masters degree and higher	2 (5)	4 (11)	
Place of residence	Urban	29 (71)	28 (73)	0.96
	Rural	11 (29)	10 (27)	
Underlying disease	Yes	6 (15)	8 (21)	0.26
	No	34 (85)	30 (79)	

The results of this study showed that there was a significant difference in terms of pain intensity during 2, 4, 6, and 24 hours after surgery in two groups (Table 2).

Table 2: Comparison of changes in pain intensity of patients in two groups during the study period

Variable		Group A (morphine 100 µg)	Group B (morphine 200 µg)	P-value
Postoperative pain intensity	2 hour after surgery	0.61±1.17	0.29±0.9	<0.001
	4 hour after surgery	1.55±1.46	1.44±1.69	<0.001
	6 hour after surgery	3.36±1.15	3.67±1.24	0.002
	24 hour after surgery	3.11±0.94	3.17±1.16	<0.001

Also, there was no significant difference between two groups in terms of postoperative ileus (P=0.48). However, the results of the present study showed that patients who received morphine with a dose of 200 µg along with 20 ng of naloxone had significantly lower nausea and pruritus compared to the group receiving morphine with a dose of 100 µg along with 20 ng of naloxone (P<0.001) (Table 3).

Table 3: Comparison of changes in nausea, pruritus and postoperative ileus in two groups during the study period

Variable		Group A (morphine 100 µg)	Group B (morphine 200 µg)	P-value
Nausea	Yes	14 (35)	2 (6)	<0.001
	No	26 (65)	37 (94)	
Pruritus	Yes	17 (43)	3 (8)	<0.001
	No	23 (57)	35 (92)	
Ileus	Yes	2 (5)	1 (3)	0.48
	No	38 (95)	35 (97)	

DISCUSSION

The results of the present study showed that there is a significant difference in the pain intensity between the two groups during the study period, so that the patients receiving morphine with a dose of 200 µg along with naloxone experienced less pain intensity than patients in the other group receiving morphine with the dose of 100 µg. Although the amount of nausea, itching and vomiting in the group receiving morphine with a dose of 100 µg along with 20 ng of naloxone was lower than in the group of morphine with a dose of 200 µg along with naloxone, the difference between the two groups was not statistically significant.

It has been shown that intrathecal administration of morphine alone does not increase pain sensitivity and histone methylation. In contrast, intrathecal administration of low-dose naloxone with morphine significantly reduced pertussis toxin-induced pain and reduced histone methylation. Also, intrauterine administration of low-dose naloxone increases the analgesic effect of morphine by increasing the reuptake of excitatory amino acids (EAA) from the synaptic cleft in the spinal cord of rats [15]. This issue is probably due to the decrease of tumor necrosis factor-α and its receptor expression (TNFR1) and the concentration of excitatory amino acids (EAA) in the dorsal horn of the spinal cord [16]. In the study of Peivandi et al. addition of naloxone to intrathecal morphine, compared to intrathecal morphine

alone, had no statistically significant effect on the reduction of morphine-induced pain. The results of this study showed that the incidence of postoperative nausea and pruritus in the study group was significantly lower than the control group [17], which was different from our study.

A study conducted by Cepeda et al. involving patients undergoing surgeries lasting less than three hours found that incorporating low-dose naloxone (6 mcg/cc) into morphine PCA was significantly linked to higher failure rates. This treatment was associated with increased pain intensity, a greater requirement for opioids, reduced pain relief, and lower patient satisfaction. In this study, no statistically significant differences in morphine-related complications were observed between the two groups, which is consistent with our findings [18]. Additionally, another study by Cepeda et al. indicated that administering naloxone alongside morphine at very low doses via PCA was ineffective in alleviating postoperative pain. However, they did observe lower incidences of nausea and itching in patients receiving the naloxone-morphine combination compared to those treated with morphine alone [19]. In Chen et al.'s study, PCA epidural morphine provided pain control after cesarean section but caused pruritus in more than 22 of 30 patients (73%), which was much higher than in our study. In this study, epidural morphine combined with low-dose intravenous nalbuphine to control itching controlled postoperative pain intensity [20]. In another study involving patients with chronic low back pain, Nekoui et al. found that the combination of intrathecal naloxone and morphine did not significantly enhance the analgesic effects of morphine or reduce complications associated with its use [21]. Meanwhile, Rebel et al. examined patients undergoing radical prostatectomy and reported that administering high-dose intrathecal opioids along with intravenous naloxone significantly alleviated postoperative pain and minimized opioid-related complications [22].

A different study focused on patients undergoing lumbar discectomy demonstrated that administering very low doses of naloxone (0.25 µg/kg/h) in conjunction with morphine via a PCA pump significantly decreased postoperative pain while also reducing nausea and itching caused by morphine [23]. Additionally, it was found that combining low-dose naloxone (ranging from 1/20 to 1/10 of the morphine dose) could temporarily enhance morphine's analgesic effects, though higher doses equivalent to the morphine dose negated these benefits [24].

The complications associated with neuraxial opioids arise from the presence of the drug in the cerebrospinal fluid (CSF) or systemic circulation, or both. Using low-dose naloxone is a proposed approach to mitigate these complications [12, 25]. In our study, for this purpose, naloxone was used to reduce the incidence of these side effects, but the noteworthy point was that these side effects were observed less in the group with a lower dose of morphine, but it was not significant.

CONCLUSION

In conclusion, in the present study, patients receiving morphine with a dose of 200 micrograms along with naloxone felt significantly less pain than the group receiving morphine with a dose of 100 micrograms along with naloxone. Due to the lower dose of morphine in the group receiving morphine with a dose of 100 µ, although the amount of nausea, itching and vomiting in the group receiving morphine with a dose of 100 µ with naloxone was lower than in the group receiving morphine with a dose of 200 µ with naloxone, but the difference There was no significance between the two groups.

Conflict of interest: The authors report no conflicts of interest

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Authors' contribution:

Data gathering and idea owner of this study: MRH, SP

Study design: MRH, AGB, SP

Data gathering: ZG, AH

Writing and submitting manuscript: MRH, AH, SP

Editing and approval of final draft: MRH, ZG, AH, AGB, SP

REFERENCES

1. Small C, Laycock H. Acute postoperative pain management. *Br J Surg*. 2020;**107**(2):e70-e80. https://doi.org/10.1002/bjs.11477.
2. Amzoute E mostafa, Mesfioui A, Mohamed B, Elharas K, Younes Y, Ouissaden A. Postoperative Pain Evaluation: Validity and Applications of the Brief Pain Inventory (BPI). *Bangladesh J Med Sci*. 2025; **24**(2): 465–477. https://doi.org/10.3329/bjms.v24i2.81542.
3. Gholipour Baradari A, Firouzian A, Hasanzadeh Kiabi F, Emami Zeydi A, Khademloo M, Nazari Z, et al. Bolus administration of intravenous lidocaine reduces pain after an elective caesarean section: Findings from a randomised, double-blind, placebo-controlled trial. *J Obstet Gynaecol*. 2017;**37**(5):566-570. https://doi.org/10.1080/01443615.2016.1264071.
4. Zandomenico JG, Perito GZ, Machado JA, Silva HCGE. Postoperative pain management after cesarean delivery: cross-sectional study. *Braz J Anesthesiol*. 2022;**72**(4):533-535. https://doi.org/10.1016/j.bjane.2021.10.020.
5. Ahmad A, Khatoon F, Nishad S, Saambhavi, Sonam S. Exploring the incidence and causes of cesarean Delivery : Partially Mixed Concurrent quantitative and Qualitative analysis from a Medical College. *Bangladesh J Med Sci*. 2022; **21**(2): 284–290. https://doi.org/10.3329/bjms.v21i2.58060.
6. Kim HJ, Choi SH, Kwon H, Park EK, Kwon JY, Yang H, et al. Spinal Versus General Anesthesia for Cesarean Delivery in Pregnant Women With Moyamoya Disease: A Retrospective Observational Study. *Anesth Analg*. 2022; **135**(3):617-624. https://doi.org/10.1213/ANE.0000000000005919.
7. Pırbudak L, Seker B, Mendes E, Emelı Y. Determining Tuffier's Line by Ultrasound in Pregnant and Non-pregnant Female Patients: a prospective cohort study. *Bangladesh J Med Sci*. 2023; **22**(3): 529–535. https://doi.org/10.3329/bjms.v22i3.65316.
8. Imarengiaye C, Ekwere I. Postdural puncture headache: a cross-sectional study of incidence and severity in a new obstetric anaesthesia unit. *Afr J Med Med Sci*. 2006; **35**(1):47-51.
9. Ferrarezi WPP, Braga AFA, Ferreira VB, Mendes SQ, Brandão MJN, Braga F, et al. Spinal anesthesia for elective cesarean section. Bupivacaine associated with different doses of fentanyl: randomized clinical trial. *Braz J Anesthesiol*. 2021; **71**(6):642-648. https://doi.org/10.1016/j.bjane.2021.03.030.
10. Braga Ade F, Braga FS, Hirata ES, Pereira RI, Frias JA, Antunes IF. Association of lipophilic opioids and hyperbaric bupivacaine in spinal anesthesia for elective cesarean section. Randomized controlled study. *Acta Cir Bras*. 2014; **29**(11):752-8. https://doi.org/10.1590/s0102-86502014001800010.
11. Minty RG, Kelly L, Minty A, Hammett DC. Single-dose intrathecal analgesia to control labour pain: is it a useful alternative to epidural analgesia? *Can Fam Physician*. 2007; **53**(3):437-42.
12. Sultan P, Halpern SH, Pushpanathan E, Patel S, Carvalho B. The Effect of Intrathecal Morphine Dose on Outcomes After Elective Cesarean Delivery: A Meta-Analysis. *Anesth Analg*. 2016; **123**(1):154-64. https://doi.org/10.1213/ANE.0000000000001255.
13. Karnjanawanichkul O, Pakpirom J, Pueaksuwan T, Nimmaanrat S, Siripunt N, Kaewsridam S. Different Doses of Intrathecal Morphine on Postoperative Analgesia and Pruritus after Cesarean Section: a Prospective Randomized Triple-Blinded Trial. *PSU Medical Journal*. 2022;**2**(3):109-20. https://doi.org/10.31584/psumj.2022255472.
14. Unlugenc H, Gunduz M, Guzel B, Isik G. A comparative study on the effects of intrathecal morphine added to levobupivacaine for spinal anesthesia. *J Opioid Manag*. 2012; **8**(2):105-13. https://doi.org/10.5055/jom.2012.0103.
15. Yang CP, Cherng CH, Wu CT, Huang HY, Tao PL, Wong CS. Intrathecal ultra-low dose naloxone enhances the antinociceptive effect of morphine by enhancing the reuptake of excitatory amino acids from the synaptic cleft in the spinal cord of partial sciatic nerve-transected rats. *Anesth Analg*. 2011; **113**(6):1490-500. https://doi.org/10.1213/ANE.0b013e31822d39c1.
16. Yang CP, Cherng CH, Wu CT, Huang HY, Tao PL, Lee SO, Wong CS. Intrathecal ultra-low dose naloxone enhances the antihyperalgesic effects of morphine and attenuates tumor necrosis factor-α and tumor necrosis factor-α receptor 1 expression in the dorsal horn of rats with partial sciatic nerve transection. *Anesth Analg*. 2013; **117**(6):1493-502. https://doi.org/10.1213/ANE.0000000000000020.
17. Peivandi S, Habibi MR, Baradari AG, Gholinataj A, Habibi A, Khademloo M, Foladi F. 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):3979-3983. https://doi.org/10.3889/oamjms.2019.852.
18. Cepeda MS, Africano JM, Manrique AM, Fragoso W, Carr DB. The combination of low dose of naloxone and morphine in PCA does not decrease opioid requirements in the postoperative period. *Pain*. 2002;**96**(1-2):73-9. https://doi.org/10.1016/s0304-3959(01)00425-0.

19. Cepeda MS, Alvarez H, Morales O, Carr DB. Addition of ultralow dose naloxone to postoperative morphine PCA: unchanged analgesia and opioid requirement but decreased incidence of opioid side effects. *Pain*. 2004;**107**(1-2):41-6. https://doi.org/10.1016/j.pain.2003.09.011.

20. Chen MK, Chau SW, Shen YC, Sun YN, Tseng KY, Long CY, Feng YT, Cheng KI. Dose-dependent attenuation of intravenous nalbuphine on epidural morphine-induced pruritus and analgesia after cesarean delivery. *Kaohsiung J Med Sci*. 2014; **30**(5):248-53. https://doi.org/10.1016/j.kjms.2014.01.001.

21. Nekoui A, Eldufani J, Mayer P, Blaise G. The Effect of Epidural Morphine-Bupivacaine Combined with a Low Dose of Naloxone on Respiratory Function and Analgesia in Patients with Chronic Low-Back Pain. *J Health Med Informat*. 2018;**9**(1):298.

22. Rebel A, Sloan P, Andrykowski M. Postoperative analgesia after radical prostatectomy with high-dose intrathecal morphine and intravenous naloxone: a retrospective review. *J Opioid Manag*. 2009; **5**(6):331-9. https://doi.org/10.5055/jom.2009.0033.

23. Firouzian A, Gholipour Baradari A, Alipour A, Emami Zeydi A, Zamani Kiasari A, Emadi SA, et al. Ultra-low-dose Naloxone as an Adjuvant to Patient Controlled Analgesia (PCA) With Morphine for Postoperative Pain Relief Following Lumber Discectomy: A Double-blind, Randomized, Placebo-controlled Trial. *J Neurosurg Anesthesiol*. 2018; **30**(1):26-31. https://doi.org/10.1097/ANA.0000000000000374.

24. Song S. The dual effects of naloxone on morphine analgesia: Dose-related different responses on formalin-induced nociception. *J Pain*. 2005;**6**(3):S21.

25. Toljan K, Vrooman B. Low-Dose Naltrexone (LDN)-Review of Therapeutic Utilization. *Med Sci (Basel)*. 2018; **6**(4):82. https://doi.org/10.3390/medsci6040082.