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

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Background: Lumbar discectomy is one of the most commonly performed neurosurgical procedures. Many patients experience postoperative pain after lumbar discectomy. This study evaluated the effect of ultra–low-dose naloxone infusion on pain intensity after lumbar discectomy in individuals receiving patient-controlled analgesia (PCA) with morphine.

Materials and Methods: In a double-blind, randomized, controlled trial, a total of 80 patients scheduled for open discectomy was randomly assigned to receive naloxone (group N) or placebo (group P). After surgery, all patients were connected to a morphine PCA pump. Both groups received 500 mL of normal saline using a continuous infusion pump through a separate intravenous line for 24 hours. However, group N received a total dose of 0.25 μg/kg/h naloxone, which was added to the normal saline infusion. All patients were asked to grade the intensity of their pain, severity of nausea, vomiting, and pruritus on a 0 to 10 visual analog scale before being discharged from the post-anesthesia care unit and at 1, 6, 12, and 24 hours postoperatively.

Results: It was observed that both groups had a statistically significant ($P < 0.01$) time trend difference for pain, nausea, and pruritus scores. A significant difference was found between the 2 groups in terms of intensity of pain, nausea, and pruritus, with the naloxone group experiencing a lower level in comparison with the placebo group. Moreover, the median (interquartile range) of morphine consumption after surgery for patients who received naloxone was 26 (24.25 to 28) mg, which is significantly ($P < 0.001$) lower than for the placebo group, which had a median (interquartile range) of 34 (32 to 36) mg.

Conclusions: It is concluded that infusion of ultra–low-dose naloxone (0.25 μg/kg/h) along with morphine PCA can significantly reduce pain intensity, morphine consumption, and opioid-induced nausea and pruritus after lumbar discectomy.

Key Words: naloxone, discectomy, postoperative pain, nausea, pruritus

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One of the most commonly performed neurosurgical procedures is lumbar discectomy.[1,2] Many patients experience postoperative pain following lumber discectomy, which, may persists for several days after surgery.[3] Therefore it is responsibility of the anesthesiologist to manage patients' postoperative pain effectively. This can alleviate patients' discomfort, increase their satisfaction, and reduce postoperative morbidity. In addition, appropriate postoperative pain control can lead to several other benefits, including earlier restoration of mobility, shorter hospital stays, lower hospital costs, and lower risk of developing chronic pain.[2,3]

Numerous analgesics have been used after spinal surgery, but no gold standard exists.[4] Currently, morphine may be the most commonly used analgesic agent for postoperative pain management. However, the use of morphine is associated with various side effects including respiratory depression, nausea, vomiting, pruritus, hypotension, and sedation.[5,6] These side effects often lead to insufficient treatment of postoperative pain.[7] Multimodal analgesia techniques, in which adjuvant analgesics are added to opioids, have been introduced to achieve better pain control with fewer adverse effects. But, the adjuvants have their own side effects and limitations.[5,8,9]

Recently, ultra–low-dose naloxone has been suggested as a useful analgesic adjuvant that can enhance the antinociceptive effect of morphine.[10] Naloxone is an antagonist of the μ-opioid receptor and inhibits the effects of morphine at high doses. However, by blocking signals

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of excitatory opioid receptors in dorsal root ganglion neurons, inhibiting microglia neuroinflammation, and enhancing the release of enkephalin, naloxone may improve the analgesic effect of morphine at ultra-low doses.[10,11] Some earlier studies advocated that ultra–low-dose naloxone has a positive effect on reducing postoperative pain and opioid-induced side effects.[12,13] Nonetheless, these propositions have not been evaluated through properly randomized and controlled studies.[14–16] Furthermore, the authors' literature search did not reveal any clinical studies that used ultra–low-dose naloxone along with morphine patient-controlled analgesia (PCA) for postoperative pain relief following lumbar discectomy. Therefore, we hypothesized that concomitant administration of ultra–low-dose naloxone infusion with morphine PCA, can reduce pain intensity, morphine consumption, and opioid-induced side effects.

The present study was carried out to evaluate the usefulness of ultra–low-dose naloxone infusion along with morphine PCA on postoperative pain intensity and other side effects of PCA morphine in patients following lumbar discectomy.

MATERIALS AND METHODS

To carry out the study, approval was obtained from the ethics committee of Mazandaran University of Medical Sciences, along with informed consent from patients before the study. A total of 80 adult patients of both sexes (age, 35 to 70 y) with lumbar disk herniation confirmed by magnetic resonance imaging (class I or II according to the classification of the American Society of Anesthesiologists) who were scheduled for elective, single level open discectomy under general anesthesia were enrolled in this prospective, double-blind, randomized, placebo-controlled study. The study was carried out between September 2013 and October 2014.

Patients with a history of prior spinal surgery, previous hypersensitivity reactions to the drugs used in the study, epilepsy, alcohol and drug abuse, more than single level or emergency discectomy, inability to understand the visual analog scale (VAS) and/or how to operate the PCA device, and any complication during the surgical procedure were excluded from the study.

During the next step, with the help of a nurse anesthetist who was blind to the study groups and using a sealed envelope technique with a computer-generated random numbering system, patients who fulfilled the inclusion criteria were randomly divided into groups N and P (n = 40 for each group). All patients in both groups were instructed on how to use the PCA device and on how to use the VAS to rate the intensity of their pain, nausea, and pruritus on a scale from 0 to 10 (with 0 denoting the lowest level of intensity of the symptom and 10, the worst imaginable intensity) one day before surgery. All patients were also asked to rate their pain intensity on VAS before surgery.

In the operating room, upon establishing venous access in the forearm of the nondominant hand, patients in groups N and P received an infusion of 500-mL isotonic normal saline solution over a period of 30 minutes using infusion pumps. A similar anesthesia administration protocol was used for both groups of patients. All patients received intravenous (IV) midazolam (0.02 mg/kg) and fentanyl (3 μ/kg) before anesthesia induction for premedication. We induced general anesthesia with sodium thiopental (5 mg/kg), and atracurium (0.5 mg/kg) and maintained anesthesia with 50% nitrous oxide (N_2O), isoflurane (1 to 1.5 MAC), and morphine (0.1 mg/kg). During surgery, all patients in both groups received continuous intravenous remifentanil infusion 0.1 to 0.3 μg/kg/min. A bispectral index was used at a score of 45 to 55 to ensure adequate depth of anesthesia in all patients. During the surgery all patients received an infusion of 5 mL/kg/h isotonic normal saline. Half an hour before extubation, ondansetron 4 mg/IV was administered to patients as antiemetic prophylaxis. The same surgeon (K.H.) performed all surgeries using the standard posterior approach.

Patients were connected to a PCA pump after being transferred to the neurosurgical ward. The PCA solution contained 40-mg morphine in 80-mL normal saline. The PCA was set to administer a bolus dose of 0.5 mL with a lockout interval of 15 minutes and a background infusion rate of 2 mL/h.

In group N, 500 mL normal saline plus a total dose of 0.25 μg/kg/h naloxone was administered using an infusion pump (JMS OT-701) through a separate IV line for 24 hours (infusion rate: 21 mL/h). Patients in group P (control) received only normal saline (rather than saline with naloxone), with every other aspect of how saline was administered being identical. In addition to this, in both groups a continuous rate of 1.5 mL/kg/h of normal saline were infused as maintenance fluid.

Before being discharged from the postanesthesia care unit, and 1, 6, 12, and 24 hours after surgery, both groups of patients rated the intensity of their pain, nausea, and pruritus using the VAS 1 to 10 scale. An anesthesiology resident who was blinded to the study groups then evaluated the recorded intensity of patients' pain, nausea, and pruritus. The amount of morphine used during the 24-hour study period was also recorded.

The primary outcome of the study was to compare total morphine consumption at 1, 6, 12, and 24 hours after surgery between the 2 groups. The secondary outcomes were to compare the intensity scores of pain, nausea and pruritus at 1, 6, 12, and 24 hours after surgery, and record the incidence of any side effects between the 2 groups. This study is registered in the Iranian Registry of Clinical Trials Database (IRCT201312126803N5).

Statistical Analysis

Using a meaningful mean group difference of 1 point on the 10-point scale, an expected common SD of 1.3 points, 80% power, and 2-tailed level of significance at $P < 0.01$, the predicted minimum required sample size was 40 per group. To confirm the normality of the data, the Shapiro-Wilk test was performed. Comparisons were

tabulated as mean ± SD, median (interquartile range), or as percentages for the descriptive baseline characteristics of the 2 groups (naloxone and placebo). To statistically compare the categorical data, a χ^2 or Fisher exact test was performed, while the *t* test and Mann-Whitney *U* test were carried out to statistically compare the continuous data. Using a general linear model, the 2 groups' VAS 1 to 10 scale scores were compared using a repeated-measurement analysis of variance test. Mauchley's Sphericity test was performed to test the compound symmetry assumption. A *P*-value of 0.05 or less was considered statistically significant. Data were analyzed using IBM (Armonk, NY) SPSS statistics version 16 and Stata version 10.

RESULTS

A total of 96 patients were screened during the study period. Of these, 9 patients did not meet the inclusion criteria and 7 patients declined to participate in the study. The characteristics of the remaining 80 patients are presented in Figure 1 and Table 1. There are no statistically significant differences between patient's demographic and clinical characteristics in for the 2 groups (Table 1). The mean values of pain, nausea, and pruritus on the VAS preintervention and postintervention scores for each group are presented in Table 2. As illustrated in Table 2, a significant within-subject difference or time effect exists ($P < 0.001$) in the nausea scores of the 2 groups. This suggests that nausea scores in both groups initially increased but then decreased over time. There was significantly less nausea in naloxone group ($P = 0.001$) compared with the control group. The naloxone group had a greater reduction slope than the control group, with a significant difference between the groups (interaction effect) ($P = 0.042$).

The median (interquartile range) of morphine consumption after surgery in patients who received naloxone was 26 (24.25 to 28) mg, which was significantly ($P < 0.001$) lower than the placebo group, with 34 (32 to 36) mg. No naloxone-related adverse side effects were observed in this study.

DISCUSSION

We evaluated the effect of ultra–low-dose naloxone infusion as an adjuvant to enhance the antinociceptive effect of morphine on pain intensity after lumbar discectomy. One of the major findings of this study was that patients receiving ultra–low-dose naloxone infusion had significantly lower pain intensity and morphine consumption postoperatively in comparison with the control group. Patients in the naloxone group also had significantly lower nausea intensity and morphine-induced pruritus than patients in the control group. In addition, no naloxone-related adverse effects were observed in this study.

Opioids are the most frequently used analgesics for postoperative pain control after spinal surgery.[17] Irrespective of their route of administration, they are generally problematic in terms of their undesired side effects (eg, pruritus, nausea, and vomiting).[11] It was proven by Gan et al[18] that a fixed-rate naloxone infusion (0.25 μg/kg/h) combined with IV PCA morphine significantly reduced opioid consumption and side effects after abdominal

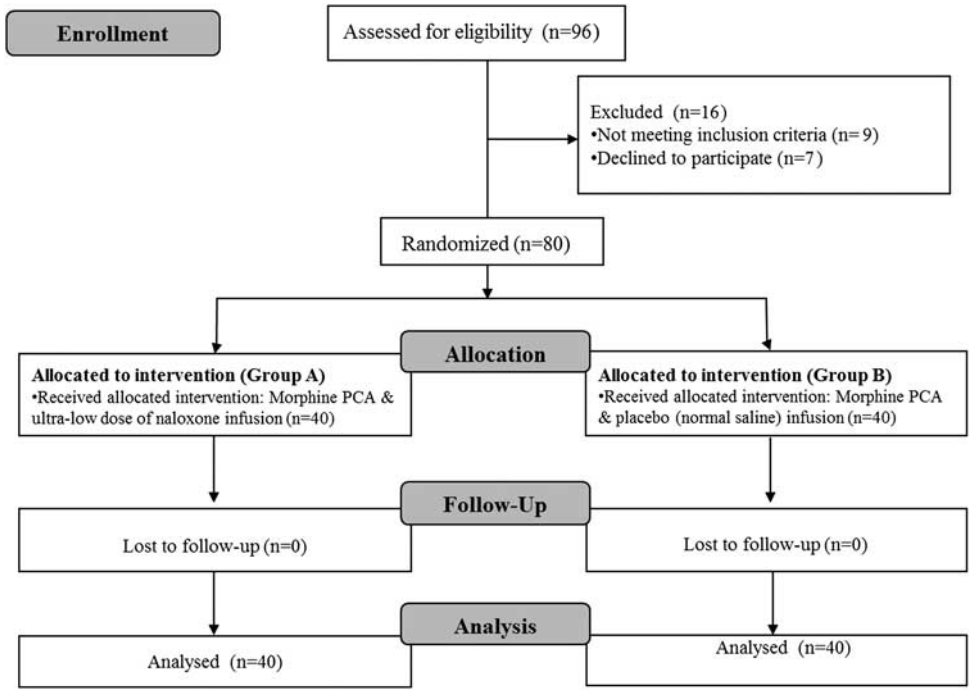

FIGURE 1. Flow diagram of the study. PCA indicates patient-controlled analgesia.

TABLE 1. Demographic and Clinical Characteristics of Patients in the 2 Groups

Variables	Group		*P*
	Naloxone (N = 40)	Placebo (N = 40)	
Age (y) (mean ± SD)	36.63 ± 7.85	38.5 ± 8.96	0.32
Sex (female/male) (No.)	16/24	19/21	0.65
BMI, (mean ± SD)	27.98 ± 2.67	27.66 ± 2.98	0.26
Surgical site (No. [%])			
L4-L5	34 (85)	31 (77.5)	0.57
L5-S1	6 (15)	9 (22.5)	
Surgery time (median [inter-quartile range])	47.5 (45-50)	45 (45-50)	0.94
Anesthesia time (median [inter-quartile range])	62 (60-68.75)	60 (60-65)	0.71
Preoperative pain score (mean [SD])	7.92 (1.07)	7.71 (1.15)	0.42
Pain VAS score before intervention (median [interquartile range])	6 (5-7)	6 (5-7)	0.26
Nausea VAS score before intervention (median [interquartile range])	0 (0-0.75)	0 (0-1)	0.23
Itching VAS score before intervention (median [interquartile range])	0 (0-0)	0 (0-0)	0.31

BMI indicates body mass index; VAS, visual analog scale.

hysterectomy. In addition, Maxwell et al[12] demonstrated that postoperative continuous infusion of small-dose naloxone (0.25 μg/kg/h) significantly ameliorates the severity and incidence of morphine-induced side effects without affecting its analgesic effectiveness. Results of a study by Sadeghi et al[19] confirmed that postoperative pain intensity and morphine consumption after cesarean section was significantly reduced by administering an IV bolus of ultra–low-dose naloxone before spinal anesthesia. In the same vein, Movafegh et al[20] found that adding an ultra-low dose of naloxone to lidocaine for axillary brachial plexus block extended the time to onset of postoperative pain. Furthermore, patients who received an ultra-low dose of naloxone by infusion within the first 24 hours after abdominal hysterectomy were found to have significantly lower morphine consumption, incidence, and severity of opioid-induced nausea and vomiting.[13]

Adding ultra–low-dose naloxone to lidocaine or fentanyl for peribulbar anesthesia can extend the duration of postoperative analgesia without excessive side effects.[21] Similarly, Jia et al[22] proved that tramadol-induced side effects would be significantly alleviated by a low–dose-naloxone infusion without affecting its analgesic effect, potentially resulting in more comfort for patients after cervical spine surgery.

Several mechanisms have been proposed to elucidate why an opioid antagonist might improve analgesia instead of regularly reversing it. It is believed that the functions of the μ-opioid receptor excitatory G-protein complexes (Gs) are antagonized by naloxone at ultra-low doses, leading to a reduction in side effects such as nausea and vomiting. The other empirical justification is that ultra–low-dose naloxone may cause excessive release of endogenous opioids through blockade of presynaptic autoinhibition of enkephalin release.[18,23,24]

In addition, the current study provides significant support for decreasing morphine-induced pruritus by administering ultra–low-dose naloxone infusion. One of the adverse effects of opioid treatment in patients with acute postoperative pain is opioid-induced pruritus. As such, managing side effects is relatively challenging for clinicians to ensure patients' comfort.[25] The mechanism and reason for opioid-induced pruritus is not clearly defined. However, researchers have proposed a centrally mediated mechanism using the μ receptor.[25,26] Thomas et al[27] have proposed that the medullary dorsal horn is a site where morphine acts on μ-opioid receptors and causes pruritus. Therefore, the antagonistic effect of naloxone on μ-opioid receptors can reduce opioid-induced pruritus.

TABLE 2. Pain, Nausea, and Pruritus Scores Trend (According to Visual Analog Scale) 1, 6, 12, and 24 Hour After Intervention in the 2 Groups

	Time After Intervention				*P*		
	1 h	6 h	12 h	24 h	Time Effect	Group Effect	Interaction Effect
Pain							
Naloxone	5.95 ± 1.2	3.26 ± 1.02	2.43 ± 1.08	0.75 ± 0.93	< 0.001	0.046	0.035
Placebo	6.3 ± 1.38	4.2 ± 1.23	2.78 ± 1.42	0.9 ± 1.03			
Nausea							
Naloxone	0.33 ± 0.66	0.8 ± 1.09	0.3 ± 0.72	0 ± 0	< 0.001	< 0.001	0.042
Placebo	0.6 ± 0.98	1.55 ± 1.43	0.93 ± 1.05	0.08 ± 0.35			
Pruritus							
Naloxone	0.03 ± 0.16	0.28 ± 0.64	0.3 ± 0.69	0 ± 0	< 0.001	0.002	0.016
Placebo	0.08 ± 0.27	0.9 ± 1.15	0.65 ± 1	0.05 ± 0.22			

Another possible mechanism for opioid-induced pruritus is the release of histamine through mast cells and the serotonergic system.[28] Furthermore, naloxone might reduce the incidence of pruritus by inhibiting the release of histamine.[29] The findings of a meta-analysis revealed that intravenous naloxone can reduce postoperative pruritus without any increase in pain intensity.[30] In contrast to these findings, several studies have found that infusion of ultra–low-dose naloxone has no value in the prevention of opioid-induced side effects or in augmenting analgesia.[14–16,31] The method used to prepare morphine and naloxone and then coadminister them may be one potential explanatory factor in this failure. The aforementioned studies mixed morphine and naloxone together and administered them using a PCA pump. Therefore, patients might have received only small intermittent doses of naloxone when the PCA pump button was pressed. This indicates that administered doses of naloxone (and the duration of administration) were different among the patients in these studies.[11]

The current study is not without limitations. First, infusion of a single low dose of naloxone in patients undergoing lumbar discectomy was investigated in this study. Hence, there is a need for further studies to confirm the different effects of infusion of higher or lower doses of naloxone. Second, neither naloxone nor morphine plasma concentration was measured in this study. Thus, it is recommended that future studies identify an optimal dose of administration based on measuring naloxone plasma concentration. Third, efforts were made to use similar anesthetic protocols for the 2 groups of patients. However, variances in patients' body weights require different dosages. This confounding issue demands further clarification in future studies.

In conclusion, the study findings indicate that administering ultra–low-dose naloxone (0.25 μg/kg/h) infusion, together with IV morphine PCA, can significantly reduce pain intensity, morphine consumption, and opioid-induced nausea and pruritus after lumbar discectomy. It is recommended that clinicians should consider administering concomitant ultra–low-dose naloxone infusion when initiating IV morphine PCA for postoperative pain management. However, further well-designed randomized controlled trials are required to test the effectiveness of ultra–low-dose naloxone as an adjunct to morphine for postoperative pain control.

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