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The effect of different doses of naloxone on postoperative hyperalgesia in patients who received high-dose remifentanil during hysterectomy procedures; a double-blind randomized clinical trial

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ABSTRACT

Background: Hyperalgesia is one of the adverse effects of remifentanil, an opioid drug used for reducing pain in surgical procedures. Naloxone is used for reversing the adverse effects of opioids and can reduce this acute and persistent pain after surgery. In the present study, we aimed to investigate the effect of two doses of naloxone (high and low doses) for reducing hyperalgesia after hysterectomy.

Methods: In this single-blinded randomized clinical trial, 72 patients who underwent hysterectomy with ASA class I and II were randomly divided into three groups of 24 participants. All three groups received an intraoperative infusion of 0.4 micrograms/kg/min of remifentanil.

One group received 0.02 μg/kg/min naloxone, the other group received 0.05 μg/kg/min naloxone, and the third group received 0.2 cc/kg normal saline instead of naloxone. The results of the visual analogue scale, Ramsay score, and pressure algometry were completed for all participants half an hour before the surgery, one hour, two, and eight hours after the surgery, pethidine requirement, and postoperative nausea/vomiting and the Ramsay score were recorded. Comparison of variables among the groups was performed using one-way ANOVA and posthoc tests by SPSS software, version 21.

Results: The mean age of the participants was 48.63±9.85 years. The pressure algometry of the right and left forearms and abdomen was different among the three groups after surgery ($P<0.05$). There was no difference in mean pethidine requirement at recovery and in general, visual analogue scale score, Ramsay score 1 hour and 8 h after the surgery, and the frequency of postoperative nausea and vomiting among the three groups ($P>0.05$).

Conclusion: The similar efficacy and adverse effects of the two doses indicate that the low dose of naloxone is suggested for reducing remifentanil-induced hyperalgesia after hysterectomy.

Introduction

Opioids are frequently used during and after surgery for reducing pain, and remifentanil, a potent, selective μ-opioid receptor agonist, is one of the most commonly used ones.[1] The adverse effects of opioids and remifentanil, using for analgesia, include itching, nausea and vomiting, muscle rigidity, bradycardia, and hyperalgesia, which results in a paradoxical condition.[2] The experienced pain can be similar or dissimilar to the underlying pain.[3]

Having not much evidence available on opioid-induced hyperalgesia, its exact mechanism is still not understood. It is generally believed to be the result of neuroplastic changes in the central nervous system, resulting in a sensitivity of pro-inflammatory pathways.[3]Other mechanisms suggested include the central glutaminergic system, spinal cord dynorphins, genetic mechanisms, reduced re-uptake, and increased response to pain.[3] Inflammation at the site of tissue injury triggers the

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activity of afferent nociceptors, which sensitize the peripheral and central nervous systems and cause functional changes in the peripheral nerves, spinal cord, and central pain pathways, in which specific receptors like N-Methyl-D-Aspartate played a role in chronic pain after acute injury. However, other neurotransmitters and secondary messengers such as substance P and γ-C protein kinase also play a major role in spinal sensitization.[4]

Naloxone, a μ opioid receptor antagonist, is commonly used for reversing the adverse effects of opioids.[5] Low-dose naloxone has also been found effective in reducing opioid-induced hyperalgesia without affecting analgesia.[6] Nevertheless, relying on other reports, opioid-induced hyperalgesia results in delayed postsurgical recovery and increases the duration of hospitalization, plus patients' discomfort and increased use of analgesics and therefore requires treatment.[7] The wide application of surgery, and anesthesia, along with hyperalgesia as one of the side effects of opioids' withdrawal, confirm the necessity of research on methods to control this important complication.

In this randomized clinical trial, we aimed to investigate the effect of two doses of naloxone (high and low doses) for reducing hyperalgesia, as a side effect of remifentanil after hysterectomy. We hypothesized that the low doses of naloxone added to remifentanil could reduce the postoperative hyperalgesia compared with remifentanil alone, and used a lower dose of the drug in each prescription, both because of the costs and the side effects. Different methods are available for the measurement of hyperalgesia, such as the pinprick test, von Frey filament, pressure algometry, and cold test.[8] In this study, we used pressure algometry because of its lower bias and higher reliability.

Materials and methods

In this randomized clinical trial, women who underwent a hysterectomy at Rasool Akram Medical Complex, Tehran, Iran, 2019 to 2021, were considered as the study population.

The sample size of the study was calculated at 20 in each group (a total of 60 participants) based on a pilot study performed before main study. For this calculation, Hertzog and colleagues' study helped.[9] Considering 15% chance of lost to follow-up, 24 patients were included in each group, (72 patients in total). Aged 30 to 70 years old with American Society of Anesthesiologists (ASA) class I and II, the women, who did not have hypersensitivity to drugs, substance abuse, and were not alcoholic were included into the study using a simple random sampling method.

All patients underwent general anesthesia using 1.5 to 2 mg/kg intravenous (IV) propofol and 0.2 mg/kg cisatracurium, premedication with 3 μg/kg fentanyl and 0.02 mg/kg midazolam, and maintenance with 50–100 μg/kg/min propofol and infusion of 0.4 μg/kg/min remifentanil (Exir Pharmaceutical Company, Iran) intraoperativly. Then, the patients were intubated with endotracheal tube cuff and placed under mechanical ventilation with 6 to 8 cc/kg TV and maintenance of 30 to35 end-tidal carbon dioxide. At the end of the surgery, the patients were reversed using 0.04 mg/kg neostigmine and 0.02 mg/kg atropine after the patients' respiration returned. If the patient developed bradycardia during surgery (heart rate <50 beats/min), 0.02 mg/kg atropine was prescribed for the patient, and in case of repetition, another dose was prescribed, and if not responding to this treatment, the patient was excluded from the study. When the patients' blood pressure (BP) reduced >20% of the initial BP or mean arterial pressure reached <70 mmHg, a bolus dose of 0.2 mg/kg of ephedrine; if not responding to this treatment, the patient was excluded from the study. Also, if the surgery was prolonged to more than three hours, the patient would be excluded from the study.

Before entering patients operating room the patients were randomized into three groups, based on the block randomization using a random number table, using a simple randomization method by sequence extracted from the computer, 24 in each; one group and after induction in anesthesia samples received 0.02 μg/kg/min naloxone (Caspian Tamin Pharmaceutical Company, Iran), the other group received 0.05 μg/kg/min naloxone, and the third group received 0.2 cc/kg normal saline, as placebo during surgery. Allocation of participants into the three groups was performed. The participants and outcome assessors are unaware of the type of group and intervention. A technician was responsible for random selection of the type of drug and patients, and another was responsible for evaluating the patient for variables. The clinician was blinded.

The patients' demographic characteristics, including age and sex, duration of anesthesia, and ASA class, were recorded, and they were asked to rate their pain based on a ten-point visual analogue scale, one hour and eight hours after the surgery. The patients with a visual analogue scale score ≥4 received 0.2 mg pethidine, and if the score did not reduce, the same dose was repeated; pethidine requirements at the recovery room and in general were recorded. Patients' postoperative nausea and vomiting were also recorded and treated by 10 mg metoclopramide. Moreover, a pressure algometry test was performed using JTECH digital pressure algometer (Australasian Medical & Therapeutic Instruments, Australia), half an hour before the surgery, one hour, two, and eight hours after the surgery by applying increasing variable pressure on 1 cm^2 area at parts away from the surgical site, including middle one-third of the anterior right and left forearms, and 10-cm away from the incision site on the abdomen. The pressure was stopped when the patient-reported pain, and the maximum pressure was recorded by N/m^2 by the device. Ramsay sedation scale score was also recorded by the assessor one hour and eight hours after the surgery by four scores: anxious and restless (score 1), cooperator and aware (score 2), responsive to instructions (score 3), and quick response to stimulations (score 4).

Statistical analysis

Descriptive results of the categorical variables were presented by number (percentage) and compared among the groups using the Chi-square test. Descriptive results of the numeric variables were presented as mean±standard deviation, and compared between two groups, *t*-test or Mann-Whitney U test, according to the normal distribution of the data, and compared among three groups using one-way ANOVA. The effect of time and comparison of variables among the measured intervals were evaluated using mixed-design ANOVA. For the statistical analysis, the statistical software IBM SPSS Statistics for Windows version 21.0 (IBM Corp. 2012. Armonk, NY: IBM Corp) was used. P values <0.05 were considered statistically significant.

Ethics declaration

The study protocol was approved by the Ethics Committee of Iran University of Medical Sciences [code: IR.IUMS.FMD.REC.1398.483) and registered in the Iranian Registry of Clinical Trial https://www.irct.ir/trial/48155 by the number IRCT20180723040570N5 on 27/06/2020. All the ethical considerations of the latest version of Helsinki's declaration were met throughout the study, and patients signed the written informed consent forms after receiving a complete explanation about the study. This study followed the applicable CONSORT guidelines for randomized trials.

Results

A total of 70 patients completed the study in three randomized groups (Fig. 1). The mean age of participants was 48.63±9.85 years, and the demographics of the three groups (with normal distribution) were not statistically different ($P>0.05$).

The results of pressure algometry for the right and left forearms are shown in Table 1. As demonstrated, there was no difference in mean scores before the surgery. In the right forearm. The scores were 50.58±13.08 in the control group, vs. 54.92±14.07 in the low-dose

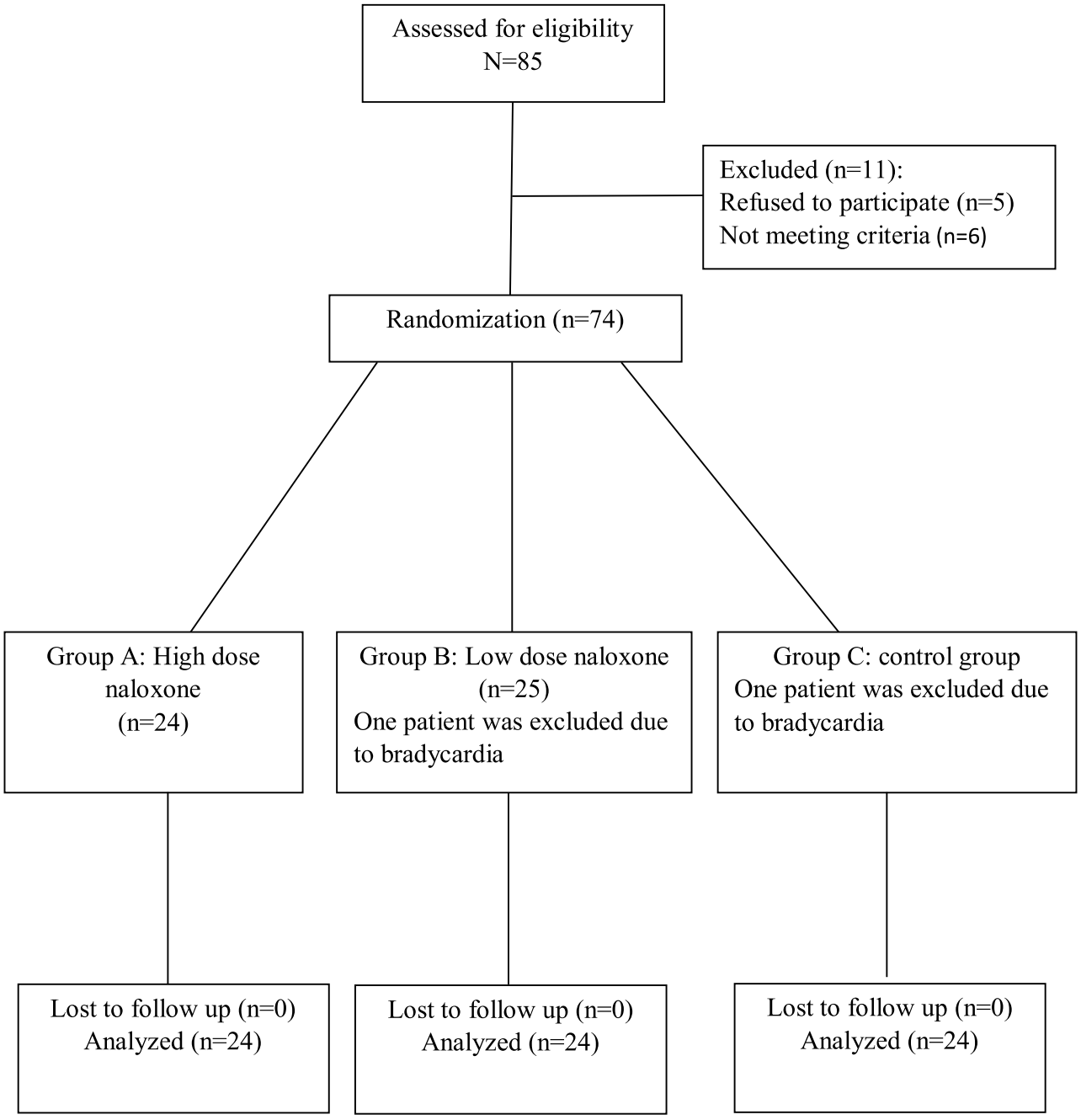

Fig. 1. The chart of patients' enrollment into the study (CONSORT Flow Diagram).

Table 1
Comparison of the results of pressure algometry of the right and left forearm and abdomen among the three study groups.

	Variable	Total	Control group	Low-dose naloxone	High-dose naloxone	P value*
Right forearm	Before surgery	51.43±14.40	50.58±13.08	54.92±14.07	48.79±15.83	0.322
	1 hour after surgery	32.91±11.37	26.58±8.25	38.13±9.84	34.08±12.77	0.001
	2 h after surgery	33.00±11.26	26.25±8.05	38.67±9.90	34.08±12.09	<0.001
	8 h after surgery	46.71±13.25	42.88±11.91	50.79±11.41	46.46±15.40	0.116
Left forearm	Before surgery	51.26±14.96	49.67±13.36	54.00±15.71	50.13±15.93	0.551
	1 hour after surgery	32.89±11.87	26.00±8.18	37.92±11.35	34.75±12.64	0.001
	2 h after surgery	32.60±11.28	26.25±7.96	36.63±10.70	34.92±12.25	0.002
	8 h after surgery	46.47±14.02	41.21±11.50	49.75±13.84	48.46±15.46	0.074
Abdomen	Before surgery	37.76±11.84	34.92±12.45	40.04±10.53	37.76±11.84	0.316
	1 hour after surgery	23.64±9.17	18.25±6.74	27.75±8.14	24.92±9.93	0.001
	2 h after surgery	23.11±7.99	18.71±5.67	26.38±7.72	24.25±8.53	0.002
	8 h after surgery	25.31±9.18	21.13±7.26	28.75±7.62	26.04±10.88	0.012

* The results of one-way ANOVA.

naloxone group and 48.79±15.83 in the high-dose naloxone group; (P = 0.322). There were 49.67±13.36 in the control group, vs. 54.00±15.71 in the low-dose naloxone group, and 50.13±15.93 in the high-dose naloxone group (P = 0.551) in the left forearm; while mean pressure algometry of the right forearm was significantly different among the groups one hour (26.58±8.25 in the control group, vs. 38.13±9.84 in the low-dose naloxone group, and 34.08±12.77 in the high-dose naloxone group; P = 0.001) and 2 h after the surgery (26.25±8.05 in the control group, vs. 38.67±9.90 in the low-dose naloxone group, and 34.08±12.09 in the high-dose naloxone group; P<0.001). Also, in the left forearm, the mean pressure algometry was significantly different among the groups 1hour (26.00±8.18 in the control group, vs. 37.92±11.35 in the low-dose naloxone group and 34.75±12.64 in the high-dose naloxone group; P = 0.001) and 2 h after the surgery (26.25±7.96 in the control group, vs. 36.63±10.70 in the low-dose naloxone group, and 34.92±12.25 in the high-dose naloxone group; P = 0.002). The results of post hoc analysis showed a significant decrease one hour and two hours after the surgery between the low dose naloxone group compared with the control group and between the high dose naloxone group vs. control group in both forearms (P<0.05; Table 2). Eight hours after the surgery, the mean pressure algometry was not different among the three groups in the right (42.88±11.91 in the control group, vs. 50.79±11.41 in the low-dose naloxone group, and 46.46±15.40 in the high-dose naloxone group; P = 0.116) and left forearms (41.21±11.50 in the control group, vs. 49.75±13.84 in the low-dose naloxone group, and 48.46±15.46 in the high-dose naloxone group; P = 0.074).

The mean pressure algometry of the abdomen was not different among the study groups before the surgery (34.92±12.45 in the control group, vs. 40.04±10.53 in the low-dose naloxone group, and 37.76±11.84 in the high-dose naloxone group; P = 0.316); while it was significantly different among the three study groups one hour (18.25±6.74 in the control group, vs. 27.75±8.14 in the low-dose naloxone group, and 24.92±9.93 in the high-dose naloxone group; P = 0.001), 2 h (18.71±5.67 in the control group, vs. 26.38±7.72 in the low-dose naloxone group, and 24.25±8.53 in the high-dose naloxone group; P = 0.002), and eight hours after the surgery (21.13±7.26 in the control group, vs. 28.75±7.62 in the low-dose naloxone group, and 26.04±10.88 in the high-dose naloxone group; P = 0.012) with a significant decrease at these intervals between the low dose naloxone group compared with the control group and between the high dose naloxone group (P<0.05; Table 2). The trend of changes in pressure algometry of the three measured areas is shown in Fig. 2.

The mean visual analogue scale one hour after the surgery was 5.27±1.12 in general, 5.41±1.10 in the low-dose naloxone group, 5.12±1.03 in the high-dose naloxone group, and 5.29±1.26 in the control group (P = 0.674). The mean visual analogue scale eight hours after the surgery was 2.73±0.58 in general, 2.62±0.57 in the low-dose naloxone group, 2.79±0.58 in the high-dose naloxone group, and 2.79±0.58 in the control group (P = 0.525). Postoperative nausea and vomiting were present in 13 patients (18.1%); four patients in the low-dose naloxone group (16.7%), five patients in the high-dose naloxone group (20.8%), and four patients in the control group (16.7%; P = 1.00).

The mean Ramsay score of the patients was not different 1 hour after the surgery (1.79±0.41 in the control group, vs. 1.75±0.44 in the low-dose naloxone group, and 1.70±0.46 in the high-dose naloxone group; P = 0.808) and the mean Ramsay score was 2.00±0.00 in all groups eight hours after the surgery (Table 3). The mean pethidine dose received by the patients at the recovery room (16.04±8.33 in the control group, vs. 18.13±7.63 in the low-dose naloxone group and 16.67±6.01 in the high-dose naloxone group; P = 0.608) and in general (26.04±12.24 in the control group, vs. 26.25±11.44 in the low-dose naloxone group and 26.04±10.8 in the high-dose naloxone group; P = 0.997) were not different among the groups (Table 3).

Table 2
The comparison of mean difference of pressure algometry of the right and left forearm and abdomen among the study groups.

	Dependent Variable (pressure algometry right-hand N/cm^2)	(J) Group	Mean Difference (I-J)	P value
Right forearm	1 hour after surgery	Low-dose naloxone vs. control	−11.54	<0.001
		High-dose naloxone vs. control	−7.50	0.015
	2 h after surgery	Low-dose naloxone vs. control	−12.41	<0.001
		High-dose naloxone vs. control	−7.83	0.009
Left forearm	1 hour after surgery	High-dose naloxone vs. control	−11.91	<0.001
		High-dose naloxone vs. control	−8.75	0.007
	2 h after surgery	Low-dose naloxone vs. control	−10.37	0.001
		High-dose naloxone vs. control	−8.66	0.005
Abdomen	1 hour after surgery	Low-dose naloxone vs. control	−9.50	<0.001
		High-dose naloxone vs. control	−6.66	0.007
	2 h after surgery	Low-dose naloxone vs. control	−7.66	0.001
		High-dose naloxone vs. control	−5.54	0.012
	8 h after surgery	Low-dose naloxone vs. control	−7.62	0.004
		High-dose naloxone vs. control	−10.13	0.04

Discussion

This study presented the results of comparing opioid-induced hyperalgesia, postoperative pain, among three groups with similar demographics, two interventional groups, receiving low-dose and high-dose naloxone (0.02 and 0.05 μg/kg/min, respectively) and one placebo group (control). Opioid-induced hyperalgesia is suggested an important adverse effect of remifentanil, mainly observed at doses >0.2 μg/kg/min.[10] Remifentanil with a dose 0.4 micrograms/kg/min for the evaluation of hyperalgesia shows better results and in surgery, this dose is also common and has no specific side effects compared to lower doses. As a paradoxical response, induced by nociceptive sensitizations, opioid-induced hyperalgesia can increase the patients' postoperative pain, which contradicts the initial indication of remifentanil.[3] Furthermore, it has been reported that opioid-induced hyperalgesia results in delayed postsurgical recovery and increases the duration of hospitalization, plus patients' discomfort and increased use of analgesics and therefore requires treatment.[7]

According to the evidence, naloxone binds to the scaffolding protein pentapeptide in filament A and prevents the G protein mating, which is mediated by the mu opioid receptor.[11] This mechanism can justify the prevented opioid tolerance because it desensitizes the antinociceptive opioid system.[12] Therefore, in the present study, the preventive effect of naloxone was investigated; opioid-induced hyperalgesia was measured

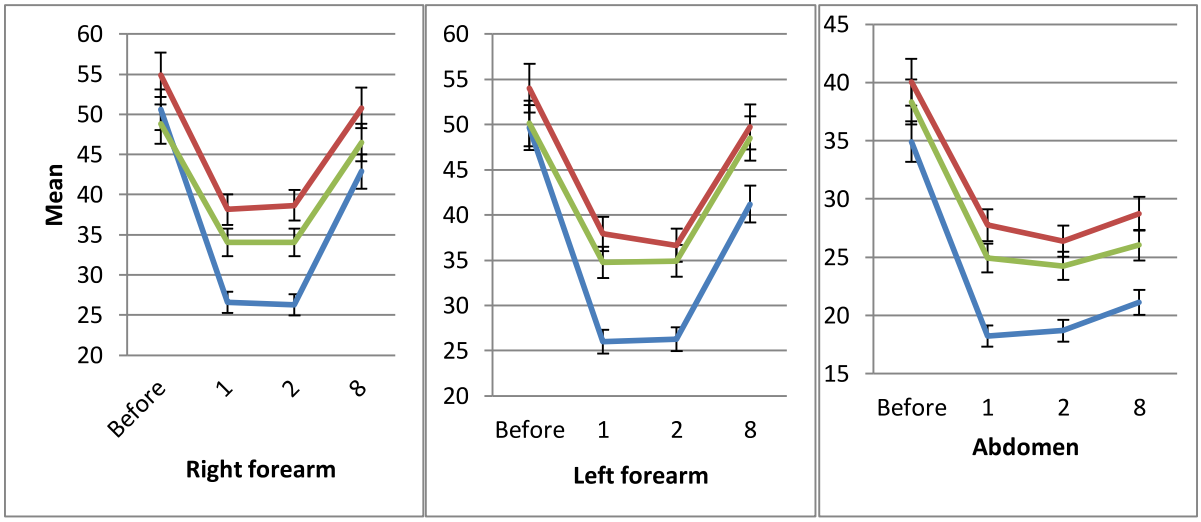

Fig. 2. The trend of changes in the pressure algorithm of the right forearm, left forearm, and abdomen.

Table 3
The comparison of postoperative Ramsay score and pethidine use among the three study groups.

Variable	Total	Control group	Low-dose naloxone	High-dose naloxone	P value
Ramsay score after 1 h	1.75±0.46	1.79±0.41	1.75±0.44	1.70±0.46	0.808
Ramsay score after 8 h	2.00±0.00	2.00±0.00	2.00±0.00	2.00±0.00	–
Pethidine use at recovery room (mg), mean±SD	16.94±7.34	16.04±8.33	18.13±7.63	16.67±6.01	0.608
Pethidine use in general (mg), mean±SD	26.11±11.35	26.04±12.24	26.25±11.44	26.04±10.8	0.997

using pressure algometry of the right forearm, left forearm, and abdomen, a quantitative sensory test of pressure pain threshold, used for assessing opioid-induced hyperalgesia,[13] and the results showed that the baseline pressure algometry mean values were not different among the three study groups, but the intervention groups had significantly lower pressure algometry values after surgery, compared with the control group, although the effect vanished eight hours after the surgery in the forearms. These results indicated that both low-dose and high-dose naloxone could reduce opioid-induced hyperalgesia, induced by 0.4 μg/kg/min remifentanil during the hysterectomy. The best pressure algometry results were observed with low-dose naloxone but it was not significant.

In an another study by Makarem et al. conducted on women undergoing laparotomic hysterectomy, the results of administrating 0.3 μg/kg/min remifentanil with and without low-dose naloxone (0.25 μg/kg/h) and the control group (receiving 50 mL saline infusion) were compared; the results showed a higher incidence of opioid-induced hyperalgesia in remifentanil group without naloxone, compared with the naloxone and control groups, 0.5, 2, 6, 12, and 24 h after surgery,[14] which comply with the results of the present study; although the measured intervals differed. Koo et al. evaluated pain threshold on the forearm and perioperative areas 24 and 48 h after thyroid surgery and showed higher pain thresholds in the group receiving low-dose naloxone (0.05 μg/kg/h) plus high-dose remifentanil (4 ng/ml), compared with placebo,[15] which confirmed the results of the present study; although the administered doses and type of surgery differed. In a rat model, administration of 4 μg/kg/min remifentanil resulted in mechanical nociceptive thresholds (evaluated using von Frey) two and four days after administration, effectively blocked by 0.17 ng/kg/min (ultra-low dose) naloxone.[16] These results are similar to our results, suggesting the efficacy of low-dose naloxone, however, our study was a randomized clinical trial. Presumably, the effect of low doses of naloxone is attributed to the nanomolar and picomolar affinity of μ-opioid receptor to "filamin A" that prevents G-protein coupling, resulting in enhanced effects for naloxone.[17, 18]

Another important variable measured in the present study was postoperative pain, and the results showed that the patients of the three study groups had no difference in mean pethidine requirement at recovery and in general, and no difference in mean visual analogue scale score and Ramsay score 1 hour and 8 h after the surgery, suggesting that naloxone did not reverse or enhance the analgesic effect of remifentanil. In the rat model, ultra-low dose naloxone had no additional antinociceptive effects,[16] which confirms our findings. In another rat model, it was shown that co-infusion of ultra-low dose naloxone (15pg/h) with morphine infusion (15microg/h) for 5 days resulted in the preservation of the antinociceptive effect, attenuated tolerance, reversed the expression of glutamate transporters, and inhibited the NMDR expression and phosphorylation, as well as glial cell activation in rats.[19] Similarly, Koo et al. showed that, postoperative pain and analgesic consumption were not different among study groups,[15] which confirm our results, nevertheless the administered dose and type of surgery differed. It has been suggested that naloxone has an anti-analgesic effect and the analgesic effect of remifentanil also disappears by its withdrawal, both acting through the μ-opioid receptor, resulting in postoperative pain of such patients.[20, 21] A systematic review of studies has also shown that low-dose naloxone cannot reduce morphine requirement or visual analogue scale pain scores after surgery,[22] which is in line with the results of our study. On the contrary, some others have reported that naloxone, administered after opioids, results in descending facilitation of pain, enhanced release of endogenous opioids, and up-regulation of opioid receptors, which can result in reduced postoperative pain.[23] In the randomized clinical trial performed by Makarem et al., the authors showed that administration of 0.25 μg/kg/h naloxone could significantly reduce the postoperative pain, measured by visual analogue scale, as well as morphine use at recovery and in general,[14] which is inconsistent with our results . Also, in another study on 72 patients undergoing colorectal surgery, the results showed that the addition of low-dose naloxone (0.25 μg/kg/h) to high-dose remifentanil (0.30 μg/kg/min) resulted in reduced morphine requirement and faster recovery.[24] Others have also shown that high-dose naloxone (3.25

mg/kg), infused in three steps, could sufficiently block the endogenous opioid system after groin repair surgery.[25] Also, Ramsay score was measured in the present study, and the results showed no difference among the study groups, one hour or eight hours after the surgery. These results show similar sedation one hour and eight hours after surgery in different study groups. As far as we are concerned, studies investigating the effect of naloxone on remifentanil-induced hyperalgesia have not measured this score to be comparable to the results of the present study. Nevertheless, other studies that evaluated other methods for reducing of remifentanil-induced hyperalgesia have evaluated this score.[26, 27]

Another postoperative complication evaluated in the present study was the frequency of postoperative nausea and vomiting that was similar among the three groups. The results of the systematic review by Barrons et al. are consistent with the results of the present study, indicating that low- or high-dose naloxone could not prevent the incidence of postoperative nausea and vomiting.[22] However, the overall frequency of postoperative nausea and vomiting was low in our study (18.1%), as Makarem and others reported postoperative nausea and vomiting in 28%, 32%, and 32% of patients receiving remifentanil-naloxone, remifentanil, and placebo,[14] which seems higher than that of the present study, although the surgical types were similar (hysterectomy). The results of the present study suggested that low- and high-dose naloxone resulted in the reduction of opioid-induced hyperalgesia induced by remifentanil in women undergoing hysterectomy and is therefore suggested as an efficient preventive measure for the reduction of this postoperative complication. Of note, both doses of naloxone had similar efficacy and adverse effects, which suggests the priority of using low doses of naloxone for the aim of reduction of remifentanil-induced hyperalgesia after hysterectomy.

Limitation

One of the limitations of the present study was that the procedures were performed by different surgeons, and the difference in the surgeon's experience and surgical details could affect the results of the study. Also, we only use one experimental test for analgesia (skin pressure) whereas hyperalgesia may occur quite differently with different experimental modes. Moreover, we do not know the duration of hyperalgesia as there was no testing between 2 and 8 hrs. The duration could be time from 2.5 - 7.5 h, which will be of interest to know more about.

Declaration of Competing Interest

The authors declare that they have no conflict of interest to declare.

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Consent to participate

The patients signed the informed consent for participating in the study.

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