Ultra-low dose of intratecal naloxone to minimize morphine - induced adverse effects

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Background
Intrathecal morphine is not devoid of adverse effects such as nausea, vomiting, and pruritus. Our goal was to study the efficacy of intrathecal ultra-low-dose naloxone in decreasing postoperative morphine-induced adverse effects.

Patients and methods
A prospective randomized double-blind controlled clinical trial was conducted that involved 100 adult patients undergoing minor anal surgeries under spinal anesthesia. Patients were equally randomized into two groups: group B received 5 mg of 0.5% hyperbaric bupivacaine with 0.2 mg morphine and normal saline as placebo in 2-ml volume, and group L received the same dose of bupivacaine with 0.2 mg morphine, and 5 ng/kg naloxone in the same volume. Postoperative nausea and vomiting (PONV) incidence was assessed during the first postoperative day. Both PONV and itching severity through visual analog scale for each were assessed every 2 h along the first postoperative day.

Results
There were significant differences between groups regarding the incidence of PONV (P = 0.031). Scales of PONV were significantly higher in group B in the early 10 postoperative hours, and at the 16th-hour score. Pruritus scale was significantly higher in group B than group L at the second and fourth postoperative hours.

Conclusion
The use of 5 ng/kg intrathecal naloxone along with morphine can reduce the incidence and severity of postoperative intrathecal morphine-induced nausea, vomiting, and itching.

Keywords:
acute pain, morphine, naloxone, postoperative nausea and vomiting, pruritus, spinal anesthesia

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Introduction

A prior large prospective cohort study revealed that even minor operative procedures could be associated with considerable pain, with visual analog scale (VAS) higher than six in the first 24 postoperative hours [1]. Bupivacaine which is commonly used in spinal anesthesia has a limited duration of analgesia (75–150 min); therefore, other adjuvants should be used to prolong and improve the quality of analgesia [2]. Morphine is considered as a beneficial adjuvant to intrathecal local anesthetics, with a relatively wide dose range of its intrathecal injection, and a study mentioned that up to a mean dose of 14 μg/kg could be sufficient to offer safe effective and sustained analgesia [2–4]. Unfortunately, intrathecal morphine is not devoid of problems, for example, pruritus (53%), nausea and vomiting (43%), and urinary retention (43%) [5,6].

Naloxone is a pure opioid-competitive antagonist, which has an extremely high affinity for μ-opioid receptors [7]. Its co-administration with morphine can decrease morphine adverse effects, for example, pruritus, nausea, emesis, constipation, urinary retention, respiratory depression, and undesirable sedation [8]. We have selected its intrathecal administration based upon previous reports to test its efficacy in prevention of some adverse effects of intrathecal morphine [9,10].

The primary goal is to investigate the efficacy of intrathecal ultra-low-dose of naloxone to attenuate what is called morphine-induced nausea and vomiting. The secondary goals include the naloxone efficacy to reduce morphine-induced pruritus, and its implications upon suspected respiratory depression and morphine antinociceptive benefits.

Patients and methods

This is a prospective randomized double-blind study that was performed in Assiut University Hospital, Egypt. After approval by the local ethics committee (IRB

no: 17100978), the study was registered in the clinical trials (NCT03230474). It adhered to all applicable laws and regulations, as well as the Declaration of Helsinki, and was conducted in accordance with the CONSORT checklist. An informed consent was obtained from each patient.

A total of 100 adult patients undergoing minor anal surgeries under spinal anesthesia with the American Society of Anesthesia physical status I–II were consented to take part in this study. Exclusion criteria included any contraindication to regional anesthesia (allergy to local anesthetics, coagulopathy, infection nearby the injection site); history of significant hepatic, renal, neurologic, or cardiac problems; problems in communication with the investigator; or chronic opioid therapy.

Participants were randomly and equally assigned into one of the two groups: group B received an intrathecal injection of 5 mg of hyperbaric bupivacaine 0.5% with 0.2 mg morphine in 0.5 ml volume, plus 0.5 ml normal saline as placebo (total volume 2 ml), and group L received 5 mg of hyperbaric bupivacaine 0.5% with 0.2 mg morphine in 0.5 ml volume, plus 5 ng/kg naloxone in 0.5 ml (total volume 2 ml). Randomization was done though the web-based randomizer (https://www.randomizer.org/).

All patients were investigated a day before surgery and were trained to use VAS scale for postoperative pain assessment, and itching. They fasted for 6–8 h before the procedure and received no premedication. The procedure was done under basic anesthesia monitoring (five-lead ECG, pulse oximetry, and noninvasive blood pressure). After securing an intravenous (20 G) cannula in the dorsum of the left hand, 10 ml/kg Ringer's lactate solution was infused as a preload. With the patient in sitting position, and under complete aseptic conditions, the subarachnoid injection was done at L3–4 or L4–5 interspinous space via 25-G Quincke spinal needle. Successful placement of the spinal needle in subarachnoid space was confirmed by aspiration of cerebrospinal fluid, and the study drug mixture was injected over 10 s, and then the patient was left in sitting position for ten minutes to obtain saddle block. The patient was then asked about any motor block or weakness, if not, then the patient was allowed to set himself in the lithotomy position. The sensory blockade was gently tested by surgical toothless clamp radially starting from the anal orifice in different diagonal directions. The motor blockade was assessed through modified Bromage scale (grade 0: free movement of legs and feet, grade 1: just able to flex knees with free movement of feet, grade 2: able to flex ankle only, and grade 3: full motor block) [11]. A urinary catheter was inserted and left over the next 24 h postoperatively. A fall of systolic blood pressure less than 90 mmHg or more than 20% of baseline value was defined as hypotension and treated with increments of i.v. 3–5 mg ephedrine. Bradycardia was defined as a fall in heart rate (HR) less than 60 beats/min and treated with i.v. 0.3 mg atropine. By the end of surgery, the patient was transferred to the postanesthesia care unit until the modified Aldrete score was more than or equal to 9 [12], and then discharged to the ward. The postoperative follow-up physician and the patients were kept blinded to the grouping process.

Data collection

Postoperative nausea and vomiting (PONV) were recorded along with itching and pain VAS scales every 2 h in the first postoperative day. PONV severity was evaluated face to face using a numerical scale based upon the Edmonton Symptom Assessment System, with a numerical rating scale as follows: 0–2 (mild), 3–6 (moderate), and 7–10 (intense) [13]. Pruritus was assessed by VAS scale as follows: the patient selected the scale that best represented the severity of his or her itching (no = itching and 10 = worst possible itching). The time passed from the successful sensory block (S4 block) until regression of such block, modified Bromage scale after block, and time for its regression were recorded. Vital data, including HR, mean arterial blood pressure (MAP), oxygen saturation (SpO2), and respiratory rate (RR), were recorded before the procedure, and then after the subarachnoid anesthesia at the 5th, 10th, 15th, and 30th minutes. The same data were collected during the postoperative period in the 2nd, 4th, 6th, 12th, 18th, and 24th hour. Respiratory depression was monitored through RR, SpO2, and level of consciousness.

Statistical analysis

A calculated sample size of 46 participants would have an 80% power to detect a difference of 20% in the incidence of PONV (primary outcome variable) with type I error of α=0.05 using a confidence interval of 95%, and an effect size value of 0.5. A total of 50 patients were enrolled in each group to compensate for any dropouts during the study. Data were expressed as mean ± SD, mean ± SE, median and range, or numbers and ratios as appropriate. Categorical variables were compared through χ^2 test. Continuous variables were compared through unpaired *t* test. Nominal and non-normally distributed variables were compared using the Mann–Whitney test. Repeated measures analysis of variance was used for comparisons within the same group over the different time points. For all tests, *P* value less than 0.05 was considered statistically significant. Statistical analysis was done using the computer program

Statistical Package for Social Sciences, Version 22, 2015 (Armonk, NY: IBM, USA).

Results

A total of 100 patients were enrolled and completed this study, as shown in the CONSORT protocol of clinical trials (Fig. 1).

Both groups were comparable regarding age, sex, weight, height, and surgery (type and duration), as shown in Table 1, with insignificant differences in between.

The PONV incidence was significantly higher in group B (Table 2).

The PONV scales were significantly lower in group L than group B during the early 10 postoperative hours and the 16th hour (Fig. 2).

Comparison between each PONV scale reading and its corresponding previous one showed significant differences during the first 12 h in the control group B and the 20 h in the study group L. Itching scales were significantly lower in group L than group B at the second and fourth postoperative hours (Fig. 3).

Comparison between itching scale reading and its corresponding previous one showed significant differences during the whole study period in both groups. There were significant differences between both groups regarding the percentages of patients who had pruritus and mixed PONV with pruritus, as shown in Table 2. No other complications have been recorded

Table 1 Demographic and operative data

Variables	Group B (*n*=50)	Group L (*n*=50)	*P*
Age (years)	33±8	32±8	0.7
Sex (male/female)	26/24	28/22	0.2
Height (cm)	166.7±8	168±6	0.43
Weight (kg)	74±11	74±9	0.47
Surgery			
Hemorrhoidectomy	40	35	0.25
Fistulectomy	10	15	

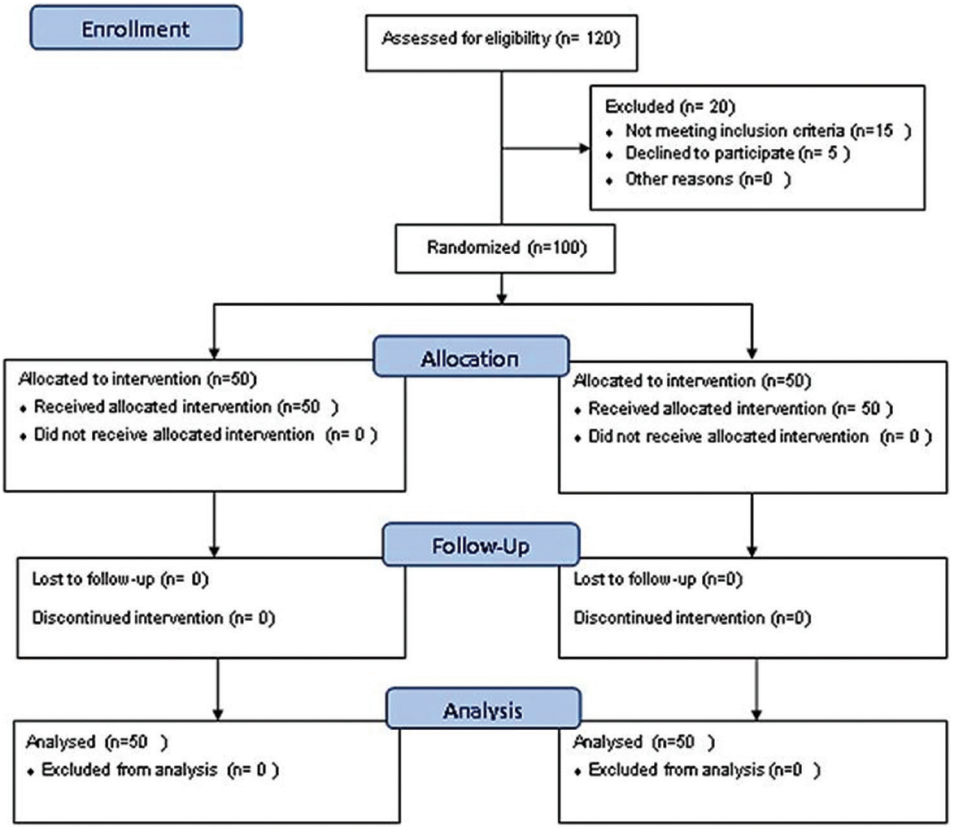
Data are expressed as mean±SD, ratio, or numbers. *P*<0.05 is considered statistically significant.

Table 2 Complications and complaints

Variables	Group B (*n*=50)	Group L (*n*=50)	*P*
PONV	19 (38)	8 (16)	0.031
Pruritus	16 (32)	4 (8)	0.002
Respiratory depression	0	0	-
Rescue analgesia	0	0	-

Data are presented as *n* (%). PONV, postoperative nausea and or vomiting. *P*<0.05 is considered as statistically significant.

Figure 1



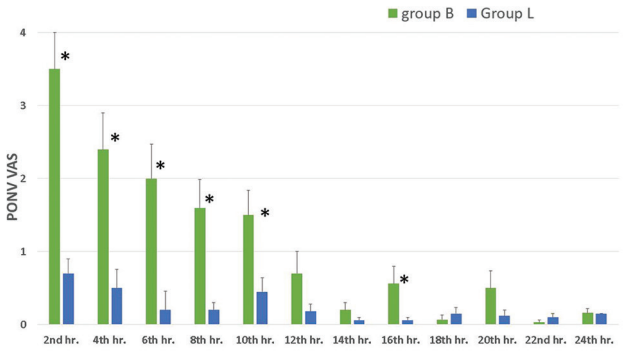
CONSORT flow diagram of participants

during the study period. No rescue analgesia was required by any of the participants, with VAS values equal to zero during the whole follow-up period in both groups (Table 2).

Characteristics of the intrathecal block and surgery are shown in Table 3.

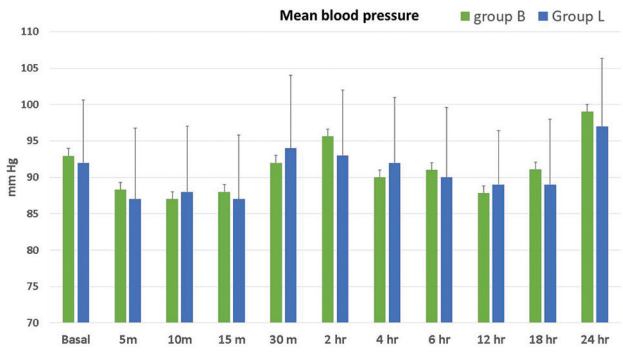
There were nonsignificant differences between the study groups regarding MAP, HR, SpO2, and RR (Fig. 4–7).

Figure 2



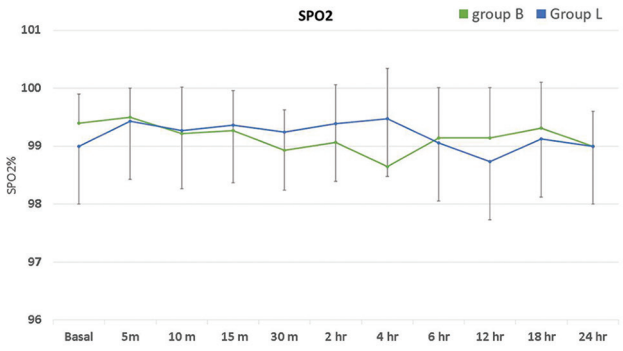
Postoperative nausea and vomiting scale during the postoperative 24 h.

Figure 4



Changes in MAP. MAP, mean arterial blood pressure.

Figure 6



Changes in SpO2. SpO2, oxygen saturation.

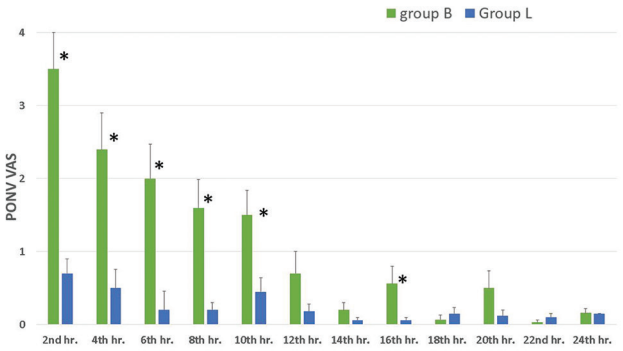
Discussion

Intrathecal morphine is not devoid of adverse effects such as itching, nausea, vomiting, respiratory depression, urinary retention, and constipation [14,15].

Up to our knowledge, there are some reports addressing the intrathecal administration of naloxone [9,10,15]. The maximum total dose of naloxone we injected was 415 ng, which was close to the dose mentioned by the study by Block *et al.* [9].

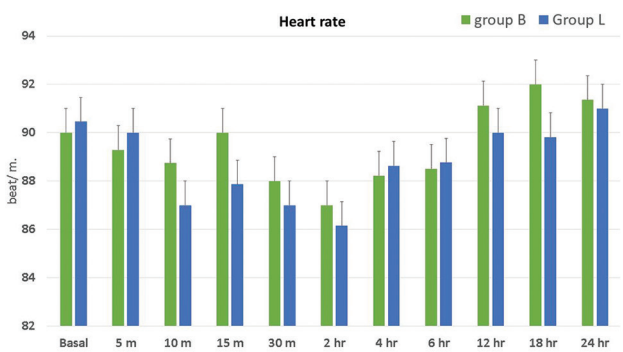
Regarding itching and PONV, our study showed a noticeable significant decrease in the incidence

Figure 3



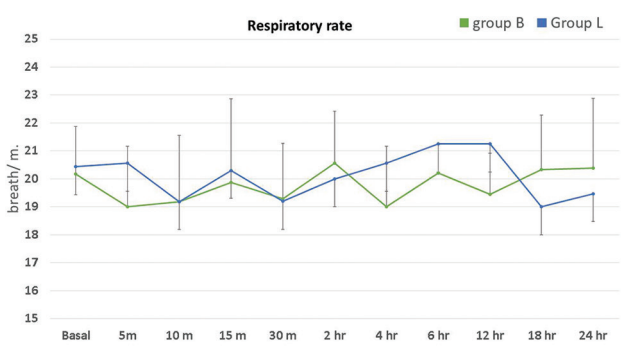
Itching scale during the postoperative 24 h.

Figure 5



Changes in HR. HR, heart rate.

Figure 7



Changes in RR. RR, respiratory rate.

Table 3 Block characteristics

Variables	Group B (*n*=50)	Group L (*n*=50)	*P*
Sensory block			
Immediately before surgery	S4 (S3-S4)	S4 (S3-S4)	-
At the end of surgery	S4 (S3-S4)	S4 (S3-S4)	-
Progression of S4 (min)	78±8.5	79±7.3	0.32
Modified Bromage scale			
Immediately before surgery	0	0	-
At the end of surgery	0	0	-
Motor regression	NA	-	

Data are expressed as median (range), or mean±SD. *P*<0.05 is considered as statistically significant.

and severity of such complications in the group that received naloxone. We think that intrathecal ultra-low dose of naloxone is more efficient than a higher dose of intravenous naloxone for prevention of undesirable morphine effects. We built our hypothesis upon some studies which documented that intravenous naloxone may lack the benefit of emesis reduction [16,17]. Our findings are in agreement with Murphy *et al.*[17] in their meta-analysis, which involved patients who received morphine for postoperative analgesia. A group of 424 patients received i.v. naloxone versus placebo in another control group of 376 patients. They mentioned that the administration of i.v. naloxone has significantly reduced the incidence of pruritus and nausea, with *P* values of 0.006, and 0.009, respectively. However, i.v. naloxone did not decrease the incidence of emesis. The same results were obtained by the meta-analysis of Barrons and Woods [16], which involved 946 patients.

On the contrary, a meta-analysis involved 1138 patients done by He *et al.*[18] showed that naloxone can significantly reduce the incidence of opioid-induced pruritus (risk ratio=0.252, 95% confidence intervalI=0.137–0.464), nausea (risk ratio=0.323, 95% confidence interval=0.245–0.428), and vomiting (risk ratio=0.338, 95% confidence interval=0.192–0.593); at the same time, naloxone did not relieve pain and somnolence, and our results are in agreement with this study regarding PONV and pruritus. We are also in agreement with Firouzian *et al.*'s[15] double-blind randomized controlled study, which involved 80 patients. Postoperative pain amelioration was attained by patient-controlled morphine analgesia. One group received intravenous naloxone (0.25 μg/kg/h) and demonstrated a reduced incidence of nausea and pruritus. West *et al.*[19] documented a significant decrease of the incidence and severity of morphine-induced pruritus in 92 patients through the use of 12 μg naloxone per 1 mg morphine, but when infused separately. Ganesh and Maxwell[20] assumed that the most consistent in terms of decreasing opioid-induced itching is what is called micro-opioid receptor antagonists; however, the dose and method of administration is still under debate.

Regarding the dose of morphine which we have used (0.2 mg), our results are in disagreement with Gehling and Tryba[21] who mentioned that the low dose of intrathecal morphine (<0.3 mg) had decreased the incidence of nausea (risk ratio = 1.4, 95% confidence interval = 1.1–1.7), vomiting (risk ratio = 3.1, 95% confidence interval = 1.5–6.4), and pruritus (risk ratio = 1.8, 95% confidence interval = 1.4–2.2).

Our patients have not required any rescue analgesia in both groups and the pain VAS scale equaled zero during the first postoperative day. We have noted that the addition of such an ultra-low dose of naloxone to morphine has not interfered with its antinociceptive effect. We are in agreement with some studies which showed that naloxone administration had reduced postoperative morphine consumption and augmented the analgesic efficacy of morphine [15,20,22,23]. Moreover, Hamann *et al.*[10] reported that a small dose of naloxone intrathecally can augment neuraxial morphine-induced analgesia. This is in contrast to Barrons and Woods[16] who mentioned that the naloxone dose used for PONV prevention may not offer a reduction of morphine consumption nor the pain scores.

In our trial, hemodynamics (MAP and HR) showed insignificant differences and changes between both groups. It is well established that intrathecal morphine could offer better sustained hemodynamic stabilization, alleviating stress response with optimal analgesia, and this was evident in a recent study done upon patients who underwent major heart surgeries [24].

Respiratory depression which is the most feared complication of intrathecal morphine has not been encountered in our study. This may be assumed to the age of our participants (middle age) and the nature of surgery (minor short time procedures). We think that the relatively low dose of morphine (200 μg) used in our study is another cause. Shapiro *et al.*[25] have mentioned that many factors could influence the occurrence of respiratory depression with the use of neuraxial morphine administration, for example, age, sex, history of opioid administration, and the operative site. The optimal 'single shot' intrathecal dose could be 75–150 μg; this what was mentioned by Sultan *et al.* [26], who also noted that the use of opioid antagonists such as naloxone to prevent morphine-induced respiratory depression has many limitations. Gehling and Tryba[21] meta-analysis studied two groups of patients; some received neuraxial morphine dose of less than 0.3 mg, and others a little bit higher dose than 0.3 mg, and mentioned that intrathecal morphine in such

doses did not carry the risk of respiratory depression. No respiratory depression occurred also in the study performed by Cohen *et al.*[27] on a pediatric group of patients, who received a dose of 7.5 μg/kg intrathecal morphine for postoperative pain relief. However, it was reported that delayed morphine-induced respiratory depression could occur after 6 : 12 h; therefore, we followed up both RR and SpO2 in our patients during the first postoperative day [28]. The optimal frequency of intermittent RR monitoring is still unknown as mentioned by Shapiro *et al.* [25], and the study was done by Ready *et al.* [29], recommended monitoring of carbon dioxide rather than RR, because hypercapnia may occur despite normal RR over 18–24 h in case of the use of neuraxial morphine [28,29]. Samii *et al.*[30] mentioned that conscious disturbance is the most reliable sign of respiratory depression, in addition to pulse oximetry, which may be valuable in such group of patients.

The studies that have used naloxone through this route did not mention adverse effects related to it [9,10,15].

Further studies upon a larger sample size of participants could be done to inspect the safety of intrathecal naloxone as well as the optimal dose. We can conclude that the use of an ultra-low dose of intrathecal naloxone in combination with morphine can decrease the incidence and severity of morphine-induced nausea, vomiting, and pruritus.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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