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Influence of Low Dose Intrathecal Naloxone on Bupivacaine - Fentanyl Spinal Anaesthesia for Lower Limb Orthopedic Surgery in Elderly Patients

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ABSTRACT

Background: Fentanyl as an adjuvant in spinal anesthesia is known to potentate postoperative analgesia. However, its adverse effects decrease patient satisfaction.

Objectives: This study evaluated the effect of adding low-dose intrathecal naloxone to bupivacaine-fentanyl spinal anesthesia on the incidence of pruritus.

Patients and Method: In total, 92 patients who underwent lower limb orthopedic surgery under spinal anesthesia were randomly allocated into two equal groups. In the bupivacaine-fentanyl (BF) group, patients received spinal anesthesia with 12.5 mg hyperbaric bupivacaine 0.5% plus 25 µg fentanyl, whereas in the bupivacaine-fentanyl-naloxone (BFN) group, 12.5 mg hyperbaric bupivacaine 0.5% plus 25 µg fentanyl and 20 µg naloxone was administered. Postoperative Mini-mental state examination (MMSE), arterial blood gas analysis, analgesia, and sedation were recorded postoperatively.

Results: The incidence of postoperative pruritus and other fentanyl-induced side effects was significantly lower in the BFN group than in the BF group in the first 4 hours postoperatively. The onset of sensory and motor blockade was not statistically significant between the two groups. In the BFN group, the duration of sensory blockade, motor blockade, postoperative analgesia, and the total postoperative analgesic requirements with no significant difference in MMSE scores between the two groups.

Conclusions: The addition of low-dose naloxone to intrathecal BF in lower limb orthopedic surgeries in older adults is associated with fewer incidences of fentanyl-induced side effects and more analgesic efficacy with no influence on cognitive function.

Keywords: elderly, intrathecal, fentanyl, naloxone, pruritus.

INTRODUCTION

The most popular anesthetic method for lower limb surgeries is spinal anesthesia[(1)]. It is well renowned for offering a quick start and powerful sensory and motor block. As blood loss, thromboembolic event risk, ileus length, and postoperative morbidity are all reduced, surgical results are improved[(2)].

With sustained postoperative analgesia and limited potential side effects on sympathetic pathways, low-dose local anesthetic coupled with opioids in spinal anesthesia provides significantly superior hemodynamic stability and a more potent synergistic nociceptive analgesic effect[(3)]. Local anesthetic solutions that are injected intrathecally can have different opioids added to them[(4)]. The clinical profile of lipophilic opioids is more favorable because of their quick onset, short duration of action, and little risk of delayed respiratory depression. The most widely used lipophilic spinal opioid is fentanyl[(5)]. Pruritus, nausea, and vomiting are among the side effects of intrathecal fentanyl administration that might lower patient satisfaction with anesthesia, delay post-anesthesia care unit release, and raise costs [(6-7)].

Older folks need orthopedic operations because they are more prone to fractures. Unfortunately, a high incidence of pruritus ranging from 30% to 60% has been linked to the use of intrathecal fentanyl in orthopedic surgery [(8)]. According to a recent study, intrathecal opioids combined with low-dose intrathecal naloxone effectively manage postoperative pain while also controlling pruritus, nausea, and vomiting[(9)].

We hypothesized that using intrathecal naloxone as an adjuvant to opioids during spinal anesthesia in older persons could lessen the adverse effects of the opioids, maintain or perhaps improve postoperative analgesia, and possibly even lower the risk of postoperative cognitive dysfunction (POCD).

Therefore, this study was conducted to evaluate the effect of adding low-dose intrathecal naloxone to bupivacaine-fentanyl spinal anesthesia in older adults scheduled for unilateral lower limb orthopedic procedures. The primary outcome was the incidence of fentanyl-induced pruritus within 4 hours postoperatively. The secondary outcomes were the influence of low-dose intrathecal naloxone on the time until the first postoperative analgesic dose, the incidence of other fentanyl-induced side effects, and the change in postoperative cognitive function within 4 hours postoperatively.

PATIENTS AND METHODS

This prospective, randomized, double-blinded comparative study was carried out from December 2020 to April 2021 at Mansoura University Hospitals after obtaining approval from the Mansoura Faculty of Medicine Institutional Research Board (code number MS/19.09.830). This study was registered at ClinicalTrials.gov with a trial ID NCT04673812.

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Patients of both genders; age >60 years; classified as American Society of Anesthesiologists (ASA) score I, II, or III; and scheduled for elective unilateral lower limb orthopedic surgery under spinal anesthesia were included in this study. Exclusion criteria were as follows: patient's refusal to participate in the study; any contraindication to spinal anesthesia including cardiovascular disorders with low fixed cardiac output state, sepsis, infection at the puncture site for intrathecal injection, history of allergy to the anesthetic drugs, coagulopathy, or increased intracranial pressure; and a traumatized hemodynamically unstable or multi-trauma patient. Also, patients with body mass index (BMI) ≥ 35 kg/m^2, neuromuscular diseases, severe spinal deformity, patients taking opioid analgesics or opioid abuse, those with any active dermatological disorder causing pruritus, and patients with a preoperative mini-mental state examination (MMSE) scoring < 24 were also excluded.

Preoperative preparation:

All patients were assessed with a detailed history, thorough physical examination, and baseline laboratory investigations, and electrocardiographs were reviewed. Comorbidities, demographic data, and ASA scores were recorded. All patients had a urinary catheter pre-operatively or had one place after the induction of spinal anesthesia.

Preoperative cognitive function was evaluated using the MMSE test. An Arabic version of the MMSE, which was developed by St. Louis University, was used for this purpose[(10)]. Any patient with MMSE scoring < 24 was excluded[(11)].

An 11-point verbal numerical rating scale (VNRS) for pain assessment was explained to the patients (where 0 = no pain and 10 = worst pain imaginable). A 4-category verbal rating scale (VRS-4) (0 to 3 scale) for the assessment of intrathecal fentanyl-induced side effects including pruritus, nausea, and shivering was used, with 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms.

The patients fasted for 6 hours for solid foods and 2 hours for clear fluids before the procedure. No pre-medications were given to the patients.

Intraoperative management:

A peripheral intravenous line was secured. Warmed Ringer's acetate 7 mL/kg was infused 30 minutes before the induction of spinal anesthesia. A prophylactic intravenous antibiotic after a negative sensitivity test was administered.

In the operative theater, standard monitoring was applied. An arterial blood sample was drawn for arterial blood gas (ABG) analysis.

Patients were randomly allocated into two groups using a computer-generated random number table. The allocation was concealed in sequentially numbered, sealed, opaque envelopes that were opened only after obtaining consent and recording all the baseline data.

In the bupivacaine-fentanyl group (BF group) (n = 46), patients received spinal anesthesia with 12.5 mg hyperbaric bupivacaine 0.5% (2.5 mL) plus 25 µg fentanyl (0.5 mL) and (0.5 mL) normal saline added in the same syringe in a total volume of 3.5 mL.

In the bupivacaine-fentanyl-naloxone group (BFN group) (n = 46), patients received spinal anesthesia with 12.5 mg hyperbaric bupivacaine 0.5% (2.5 mL) plus 25 µg fentanyl (0.5 mL) and 20 µg naloxone (prepared in 0.5 mL normal saline) added in the same syringe in a total volume of 3.5 mL.

The injectate used in each group was prepared in identical syringes by an anesthetist who was not involved in the data collection or the perioperative assessment.

Intraoperative management:

Spinal anesthesia was obtained in the sitting position under aseptic technique. A lumbar puncture at the L3–4 or L4–5 interspaces was performed using a 25-gage Quincke spinal needle after infiltrating the skin with 2 mL of 2% lidocaine. After a successful dural puncture and ensuring free flow of cerebrospinal fluid, injectate according to the group was administered slowly over 20 seconds without barbotage. Patients were placed supine, and 2–3 L/min oxygen was administered via nasal cannula.

The evolution and regression of the sensory and motor block were evaluated.

The sensation was assessed by blunt pinprick in the mid-clavicular line with grade 0 sharp pain felt, grade I dull sensation felt, and grade II anesthesia no sensation felt[(12)]. Motor blockade was assessed according to the modified Bromage scale[13], where 0 was able to move the hip, knee, ankle, and toes; 1 was unable to move the hip, but able to move the knee, ankle, and toes; 2 was unable to move the hip or knee, but able to move the ankle and toes; 3 was unable to move the hip, knee, or ankle, but able to move the toes; and 4 was unable to move hip, knee, ankle, or toes.

The sensory block was tested in the limb undergoing the operation to confirm the success of spinal anesthesia. Motor function was tested in the opposite limb. The assessment was done immediately after the spinal injection and at 1-minute intervals during the first 5 minutes and then every 2 minutes for 10 minutes. The spinal anesthesia was termed successful and adequate when a grade II sensory block above the level of T10 and a modified Bromage score ≥ 3 for the motor block were confirmed, and then the procedure was permitted. If the spinal anesthesia was inadequate 20 minutes after intrathecal injection, the patient was supplemented with general anesthesia and excluded from this study.

In addition to the continuous intraoperative hemodynamic monitoring, intraoperative sensory and motor blocks were evaluated every 15 minutes until the end of the procedure. Adverse effects including hypotension and bradycardia were reported and managed.

Postoperative assessment:

After the procedure, the patient was transferred to the post-anesthesia care unit where hemodynamic parameters were followed every 30 minutes for 2 hours. After stability, patients were transferred to the ward. Postoperative cognitive function was assessed 2 h postoperatively using the MMSE, and a blood sample for ABG analysis was drawn.

Fentanyl-induced side effects (pruritus, nausea, and shivering) were assessed using the VRS-4; the incidence of vomiting was assessed within the first 4 hours postoperatively and was reported and managed according to its severity. Mild to moderate pruritus was treated with IV pheniramine maleate up to 45.5 mg [(14)]. If no response at 2 hours, 10 mg IV propofol was given; if no response after another 2 hours, 4 to 10 µg IV naloxone was administrated and could be repeated in refractory cases[(15, 16)]. Nausea and vomiting were treated with ondansetron 4 mg IV[(17)]. Persistent nausea and vomiting were treated by an intravenous combination of 8 mg dexamethasone and 4 mg ondansetron[(18)]. Warming was the first-line treatment for shivering. Pethidine 20 mg IV was added for persistent shivering[19].

Postoperative sedation was assessed using the Ramsay Sedation Scale and pain intensity measured by the VNRS was assessed at 1, 2, 4, 6, 8, 12, 18, and 24 hours postoperatively.

If VNRS was reported > 3, postoperative analgesia was provided using a fixed regimen of IV paracetamol 1 gm/8h. If the pain was not controlled 30 minutes after paracetamol administration, 30 mg IV ketorolac was given and repeated as needed after 8 hours. The total dose of ketorolac at 24 hours postoperatively was calculated. Intravenous fentanyl was given as a third-line analgesic at a dose of 0.5 µg/kg if VNRS was still > 3 after 30 minutes of IV ketorolac administration. Fentanyl could be repeated after 4 hours if needed. The total amount of fentanyl used for the first 24 hours postoperatively was calculated, and the time from intrathecal injection to the first rescue analgesic (paracetamol) was also recorded.

The recovery of sensory and motor blockade was evaluated in the non-operated limb every 30 minutes postoperatively. The duration of sensory block, time from injection of spinal anesthesia till the recovery of sensation at the level of S1 (the return of pinprick sensation on the lateral aspect of the foot), was assessed. The duration of the motor block was also recorded as the time from injection of spinal anesthesia till complete motor block regression using the modified Bromage scale.

Ethical consent:

Written informed consent was obtained from all participating subjects. Adhered to the Declaration of Helsinki 2013 statement of ethical principles and is presented following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement. Before subject enrollment, the study protocol was approved by the institutional review board (Code number: MS/19.09.830) and was registered at ClinicalTrials.gov (NCT04673812).

Sample size calculation:

A G*Power sample size calculation was done to estimate the study sample size that could detect an assumed 50% difference in the incidence of pruritus between the two groups of this study. Based on previous studies, the incidence of pruritus following a 25 µg intrathecal fentanyl dose ranged from 68% to 70%[20, 21]. In total, 84 patients were required to achieve a study power of 90% with a one-tailed type I (α) error of 0.05. Allowing for a 10% dropout, 46 cases were included in each group.

Statistical analysis

The Statistical Package for the Social Sciences software program (SPSS), version 22 (IBM, SPSS Inc., Chicago, IL, USA) was used for all the statistical comparisons. Data were tested for normality using Shapiro–Wilk test. Continuous quantitative data were expressed as mean ± standard deviation or median (range) and were analyzed using an unpaired t-test and Wilcoxon rank test as appropriate. Nominal qualitative data were expressed in frequency and proportion (percentage) and were analyzed using the Chi-square test. Repeated measures were analyzed using a two-way analysis of variance (ANOVA). The ANOVA analysis was followed by Tukey's post hoc test. A p-value of < 0.05 was considered statistically significant.

RESULTS

This study assessed 134 patients for eligibility wherein 42 patients failed to meet the inclusion criteria. Thereafter, the remaining 92 patients aged ≥60 years who presented for unilateral lower limb orthopedic surgery were randomized to receive spinal anesthesia using either bupivacaine-fentanyl (BF group) or bupivacaine-fentanyl-naloxone (BFN group). No patients reported failure of the spinal block in either group **(Fig. 1).**

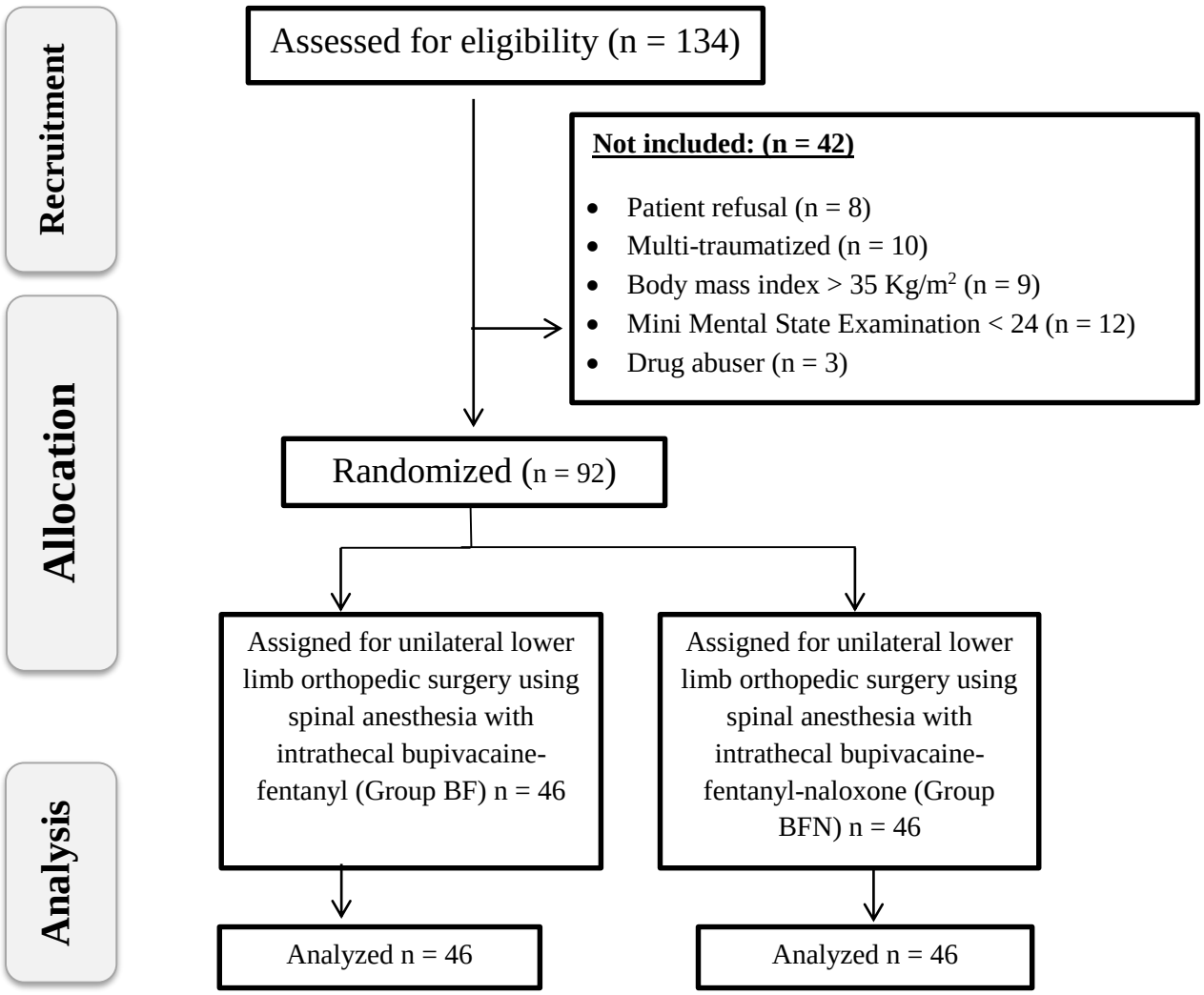

Fig. (1) Study flowchart.

No significant statistical difference was noted between the two groups regarding age, gender, BMI, ASA classification, comorbidities, type of procedure, or duration of the operation **(Table 1).**

Table (1): Demographic characteristics (American Society of Anesthesiologists (ASA) classification, associated comorbidities, and the operative duration in the studied groups)

Variables		Group BF (n = 46)	Group BFN (n = 46)	P-value
Age (years)		70.0 ± 6.7	67.8 ± 5.2	0.084
Body mass index (kg/m^2)		28.9 ± 2.4	28.7 ± 2.9	0.678
Gender	**Male**	43.5% (20)	63.0% (29)	0.060
	Female	56.5% (26)	37.0% (17)	
American Society of Anesthesiologists (ASA)	**I**	60.9% (28)	63.0% (29)	
	II	34.8% (16)	28.3% (13)	0.608
	III	4.3% (2)	8.7% (4)	
Associated comorbidities	**Diabetes mellitus**	17.4% (8)	26.1% (12)	0.312
	Hypertension	26.1% (12)	21.7% (10)	0.625
	Ischemic heart disease	6.5% (3)	10.9% (5)	0.459
Type of surgery	**DHS**	15.2% (7)	10.9% (5)	0.831
	THA	17.4% (8)	21.7% (10)	
	Hip hemiarthroplasty	10.9% (5)	6.5% (3)	
	Interlocking nail femur	8.7% (4)	15.2% (7)	
	DCS	4.3% (2)	10.9% (5)	
	TKA	21.7% (10)	15.2% (7)	
	Interlocking nail tibia	6.5% (3)	8.7% (4)	
	Fixation of proximal tibial plateau	4.3% (2)	2.2% (1)	
	Pott's fracture of the ankle	10.9% (5)	8.7% (4)	
Operative duration (minutes)		173.0 ± 37.4	162.7 ± 45.5	0.238

BF=bupivacaine-fentanyl, BFN=bupivacaine-fentanyl-naloxone, DHS=dynamic hip screw, THA=total hip arthroplasty, DCS=dynamic condylar screw, TKA=total knee arthroplasty

The time to the onset of sensory and motor blockade was not statistically significant between the two groups. The mean duration of sensory blockade (time from intrathecal injection till the recovery of S1 sensation) and the mean duration of motor blockade (time from injection till complete motor recovery Bromage = 0) were significantly longer in the BFN group (491.52 ± 43.26 min and 340.87 ± 39.95 min, respectively) than they were in the BF group (391.41 ± 31.59 min and 245.76 ± 25.51 min, respectively) **(Table 2).**

The duration of postoperative analgesia in the first 24 h was significantly prolonged in the BFN group with a mean (standard deviation) of (431.74 ± 63.72) min compared to the BF group of (329.57 ± 39.81) min. The total analgesic requirements of ketorolac (39.1 ± 9.3 mg) and fentanyl (22.6 ± 35.55 µg) were also determined to be significantly less in the BFN group than in the BF group (54.13 ± 16.27 mg and 74.23 ± 43.12 µg, respectively) in the first 24 hours postoperatively **(Table 2).**

Table (2): Characteristics of the spinal blockade and the postoperative analgesic requirement in the studied groups

	Group BF (n = 46)	Group BFN (n = 46)	P-value
Time from injection to T10 sensory level blockade (min.)	5.9 ± 0.9	6.1 ± 0.7	0.343
Time from injection to complete motor blockade Bromage 4 (min.)	8.9 ± 1.0	9.0 ± 1.0	0.489
Highest sensory level	T8 (T_{4-10})	T8 (T_{4-10})	0. 544
Duration of sensory block (min.)	391.4 ± 31.5	491.5 ± 43.2	< 0.001*
Duration of motor block (min.)	245.7 ± 25.5	340.8 ± 36.9	< 0.001*
Time of the first request of postoperative analgesia (min.)	329.5 ± 39.8	431.7 ± 63.7	< 0.001*
Total postoperative Ketorolac consumption (mg)	54.1 ± 13.2	39.1 ± 9.3	< 0.001*
Total postoperative Fentanyl consumption (µg)	74.2 ± 16.3	22.6 ± 5.1	< 0.001*

BF=bupivacaine-fentanyl, BFN=bupivacaine-fentanyl-naloxone, *P-value is significant when < 0.05

Table 3 shows the incidence of postoperative intrathecal fentanyl-induced adverse effects. In the first 4 hours postoperatively, the incidence of pruritus was significantly lower in the BFN group (54.3%) than in the BF group (100%), as well as the incidence of severe pruritus (0% vs 43.47% respectively). The incidence of nausea was also significantly lower in the BFN group than in the BF group (26.1% vs 54.3%) within the first 4 hours postoperatively. Again, the incidence of severe nausea was significantly lower in the BFN group than in the BF group (0% and 23.9%, respectively). The incidence of vomiting in the first 4 hours postoperatively was significantly lower in the BFN group than in the BF group (2.17% vs 32.6%). Postoperative shivering was mostly mild, and the incidence did not show a statistically significant difference between the two groups.

Table (3): Incidence of postoperative intrathecal fentanyl-induced adverse effects:

Postoperative adverse effects	Group BF (n = 46)	Group BFN (n = 46)	P-value
Incidence of pruritus within the first 4 hours	46 (100%)	24 (54.3%)	< 0.001*
Incidence of severe pruritus within the first 4 hours	20 (43.4%)	0 (0.0%)	< 0.001*
Incidence of nausea within the first 4 hours	25 (54.3%)	12 (26.1%)	0.006*
Incidence of severe nausea within the first 4 hours	11 (23.9%)	0 (0.0%)	< 0.001*
Incidence of vomiting within the first 4 hours	15 (32.6%)	1 (2.1%)	0.001*
Incidence of shivering within the first 4 hours	13 (28.2%)	11 (23.9%)	0.584
Incidence of severe shivering within the first 4 hours	2 (4.3%)	1 (2.2%)	0.557

BF = bupivacaine-fentanyl, BFN = bupivacaine-fentanyl-naloxone, Data are expressed as mean and standard deviation
*P-value is significant when < 0.05

Hemodynamic stability was monitored during the study period. The preoperative and the 2-hour postoperative ABG values showed no statistically significant difference between the groups, and both the preoperative and postoperative variables were within the normal physiological values **(Table 4).**

Table (4): Pre- and postoperative arterial blood gases (ABG) parameters in the studied groups

		Group BF (n = 46)	Group BFN (n = 46)	P-value
Basal preoperative	**PH**	7.3 ± 0.0	7.3 ± 0.0	0.461
	$PaCO_2$	36.0 ± 3.1	35.5 ± 3.7	0.468
	PaO_2	88.4 ± 4.4	88.3 ± 5.2	0.916
	HCO_3	25.0 ± 2.0	24.2 ± 2.2	0.072
Two hours Postoperative	**PH**	7.3 ± 0.0	7.3 ± 0.0	0.936
	$PaCO_2$	36.3 ± 2.3	36.4 ± 2.5	0.932
	PaO_2	87.9 ± 5.2	88.6 ± 5.3	0.541
	HCO_3	22.0 ± 2.2	22.6 ± 2.0	0.155

BF=bupivacaine-fentanyl, BFN=bupivacaine-fentanyl-naloxone, PaO_2=arterial partial pressure of oxygen, $PaCO_2$=arterial partial pressure of carbon dioxide, HCO_3=bicarbonate
95% CI: 95% confidence interval of the mean difference between both groups.
*P-value is significant when < 0.05

There was a statistically significant reduction of the VNRS scoring of postoperative pain intensity in the BFN group at 1, 2, 4, 6, 8, 12, 18, and 24 h postoperatively compared to the BF group **(Fig. 2).**

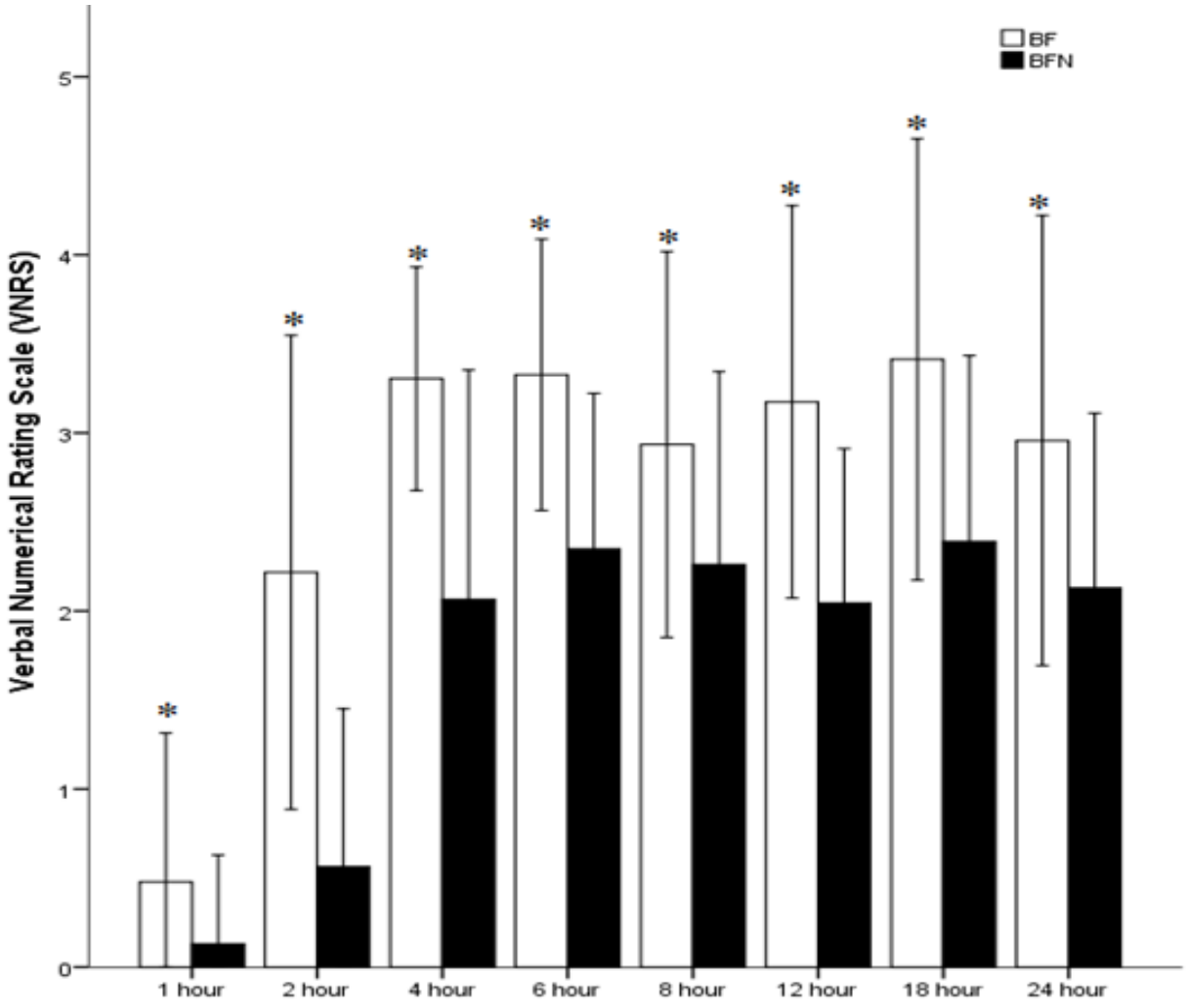

Fig. (2): Post-operative verbal numerical rating scale (VNRS) of post-operative pain (Scale: 0= no pain to 10=worst pain imaginable) (values are mean ± standard deviation). BF= Bupivacaine-Fentanyl, BFN= Bupivacaine-Fentanyl-Naloxone. *P-value is significant when < 0.05.

Concerning the Ramsay Sedation Scale scoring, there was a statistically significant difference between the two groups at 1, 2, 4, 6, and 8 h postoperatively where the patients showed a greater degree of sedation in the BFN group than it was in the BF group **(Fig. 3).**

Regarding patient cognitive function, no significant difference was noted in terms of the MMSE scores between the BF and BFN groups preoperatively (28.00 ± 1.47 vs 27.89 ± 1.41, respectively, with P = 0.720) or in the 2-hour postoperative assessment scores (27.89 ± 1.66 vs 27.57 ± 1.54, respectively, with P = 0.332).

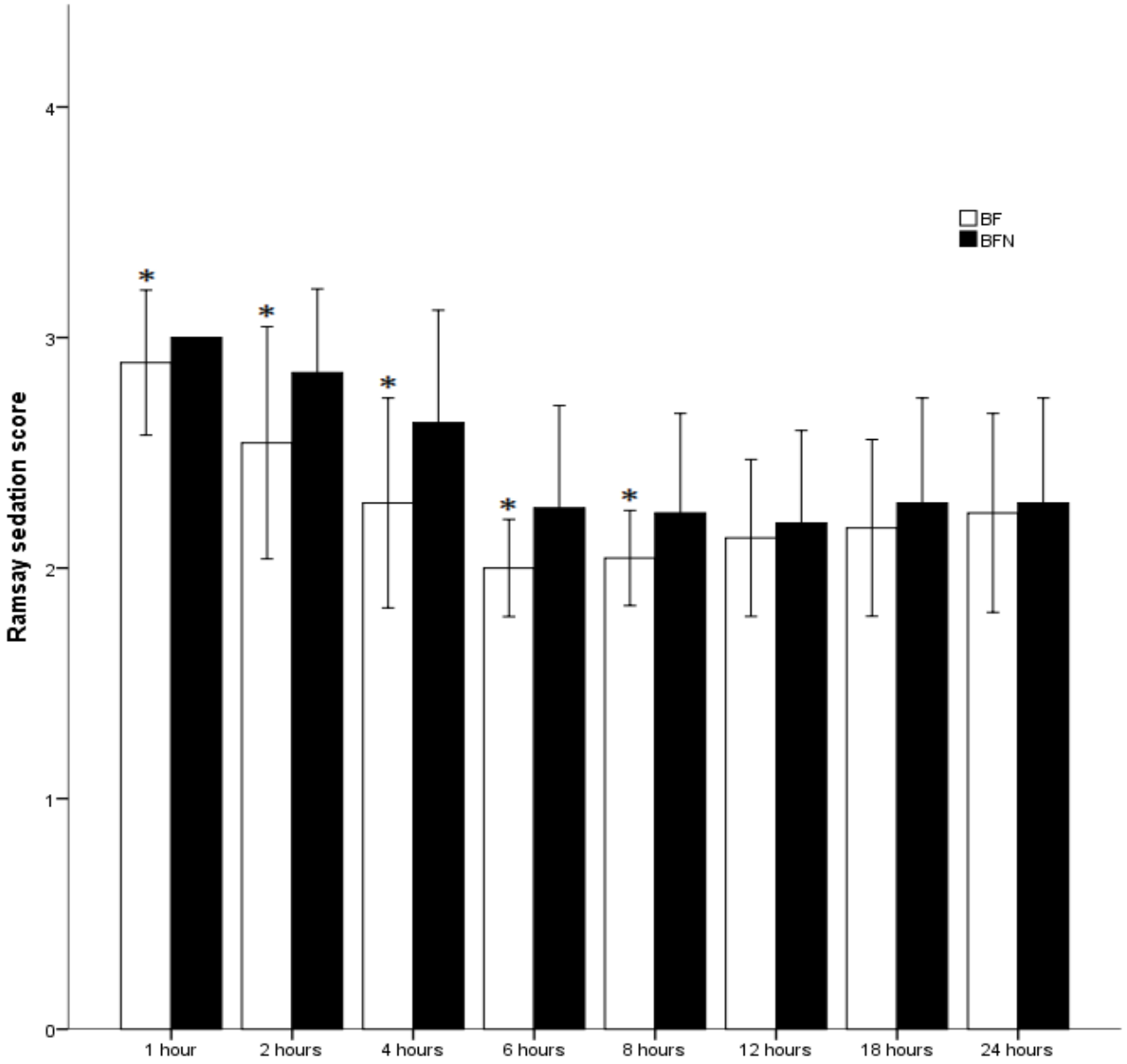

Fig. (3): Post-operative Ramsay sedation score (values are mean ± standard deviation). BF=Bupivacaine-Fentanyl, BFN=Bupivacaine-Fentanyl-Naloxone. *P-value is significant when < 0.05.

DISCUSSION

The addition of low-dose intrathecal naloxone to bupivacaine-fentanyl spinal anesthesia for older adult lower limb orthopedic surgeries in this study was able to significantly reduce the incidence of adverse effects including pruritus, nausea, and vomiting. It significantly improved the quality of analgesia with a lower VNRS, lengthened the time to the first request for analgesia, and decreased postoperative analgesic use without an alteration in patients' cognitive functions. Additional significant improvements in the characteristics of the spinal blockade in conjunction with hemodynamic stability were also reported.

The μ receptor is primarily responsible for pain modulation and some side effects. The μ-1 receptor is responsible for analgesia. The adverse effects of intrathecal opioid pruritus, nausea, vomiting and shivering are mediated by the μ-2 opioid receptor[22, 23, 24].

Intrathecal fentanyl caused adverse effects of shorter duration. Pruritus, nausea, and vomiting usually occur within 4 hours of injection[25, 26]. This could be because fentanyl is a lipophilic opioid, which makes it easier to be absorbed rapidly by the spinal cord; therefore, a small amount of it moves upward in the cerebrospinal fluid [26].

The occurrence and severity of pruritus and other side effects appear to be reduced when the least effective dose of fentanyl is used, along with local anesthetics [8].

Investigations are still being conducted on the pathophysiology of intrathecal lipophilic opioid-mediated pruritus. Prostaglandins, the spinal serotonergic system, the medullary dorsal horn, the existence of an "itch center" in the central nervous system, and antagonistic effects of inhibitory neurotransmitters are among the hypotheses[23, 27]. According to a different idea, morphine or fentanyl can activate opioid receptors that are found in the spinal cord and supraspinally [25].

A pure opioid antagonist is naloxone. It binds to μ-opioid receptors quite strongly. The inhibitory Gi/o receptor complexes required for analgesia are unaffected by naloxone, which exclusively inhibits excitatory Gs protein receptor complexes. The scaffolding protein (filamin A), which connects Gs to the opioid receptor and consequently reduces the excitatory response, is interfered with by naloxone [28].

The studies have shown that intrathecal opioids and low-dose intrathecal naloxone can successfully treat nausea and pruritus while also perhaps providing excellent postoperative pain management [9, 29].

The results of this study demonstrate a significant reduction in the incidence of pruritus during the first 4 hours postoperatively in the BFN group compared to the BF group (54.3% vs 100%, respectively, p-value < 0.001). A concomitant reduction in the incidence of severe pruritus was also noted (0% vs 43.47% P-value < 0.001). This can be attributed to the antagonistic effect of naloxone on μ-opioid receptors[9].

Nausea and vomiting induced by intrathecal fentanyl are likely the results of cephalad migration of the drug in cerebrospinal fluid and subsequent interaction with opioid receptors in the brainstem. Sensitization of the vestibular system to motion and decreased gastric emptying may also play a role[26].

The results of this study showed a significant reduction in the incidence of nausea in the BFN group compared to the BF group (26.1% vs 54.3% P <0.006) and in the incidence of severe nausea (0% vs 23.9% P < 0.001). Significant reduction in the incidence of vomiting (2.17% vs 32.60% P < 0.001) was also found, which may be due to the antagonistic effect of naloxone on μ-receptors[9].

A relatively high incidence of adverse effects was determined in this study. Mu-opioid receptor upregulation is proposed as the primary cause of increased sensitivity of older adults to opioids leading to an increased incidence of adverse effects[30]. Preoperative patient education about the possibility of adverse effects and the plan to ask direct questions about the occurrence of pruritus and other adverse effects may be contributing factors that raised the incidence of pruritus and other adverse effects in this study. Previous studies reported planning to ask about pruritus increased its incidence[31, 32].

Opioids have conventionally been believed to exert their analgesic effects through coupling with Gi/o-receptor-coupled complexes through agonist binding[33]. By blocking only excitatory Gs protein receptor complexes and keeping the inhibitory complexed receptors available for pain management, small dosages of naloxone may reduce opioid-induced side effects and enhance pain control[28, 34].

There is a paucity of studies that evaluate the effect of adding naloxone to fentanyl in spinal anesthesia. The investigators cannot find published data on the influence of a combination of intrathecal fentanyl and naloxone on the quality of postoperative analgesia and associated opioid-induced adverse effects including pruritus, nausea, and vomiting. Low naloxone doses were added to local anesthetic-opioid combination in several regional anesthesia block techniques including epidural and supraclavicular and were found to be successful in providing a better quality of postoperative analgesia and reducing the associated opioid-induced adverse effects including pruritus, nausea, and vomiting when compared to bupivacaine-fentanyl alone[35].

This study demonstrated that the addition of low-dose intrathecal naloxone to bupivacaine-fentanyl spinal anesthesia has significantly improved the quality of analgesia with a lower VNRS over the first postoperative 24 hours, a long time until the first request for analgesia and a decreased postoperative analgesic requirement which reflects the ability of naloxone added to bupivacaine-fentanyl intrathecally to improve the quality of postoperative analgesia.

In this study, the mini-mental state examination (MMSE) scores were above 24, which reflected an absence of any acute cognitive decline in the groups. This might be attributed to the optimization of the patient's

perioperative condition including maintaining perioperative hemodynamic stability, good preoperative hydration, maintaining normal blood gas levels, achieving acceptable sedation levels, and adequate pain control as reported in this study. These factors were important to maintain cognitive function, especially in the older adult patient group undergoing lower limb orthopedic surgeries under spinal anesthesia.

Limitations of this study include that data about the incidence of intraoperative pruritus and other adverse effects were not available, and the postoperative assessment of pruritus and other adverse effects was recorded for only 4 hours postoperatively.

CONCLUSION

Adjuvant low-dose intrathecal naloxone added to spinal bupivacaine-fentanyl in older adult lower limb orthopedic surgeries significantly reduces the incidence of adverse effects including pruritus, nausea, and vomiting and may improve the quality of postoperative analgesia. It significantly prolonged the time to the first request for analgesia and decreased the postoperative analgesic requirement without a negative impact on cognitive function.

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