e-ISSN: 0975-9506, p-ISSN: 2961-6093

Available online on www.ijpqa.com doi: 10.25258/ijpqa.16.5.9

International Journal of Pharmaceutical Quality Assurance 2025; 16(5); 59-65

Original Research Article

Role of Epidural Nalbuphine as Adjuvant In Perioperative Pain Management in Lower Limb Surgeries

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Received: 10-03-2025 / Revised: 09-04-2025 / Accepted: 10-05-2025
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Conflict of interest: Nil

Abstract:

Introduction: The Opioids are frequently used as adjuncts to local anesthetics in epidural anesthesia. Although the systemic use of narcotic analgesics does provide acceptable analgesia, but when these drugs are used through epidural route, they provide superior quality of analgesia without systemic side effects. Nalbuphine is one such opioid which has been used extensively via systematic route but not through epidural pathway.

Aims: We aim to study the efficacy and duration of postoperative analgesia and safety of Bupivacaine with nalbuphine via epidural route for lower limb surgeries.

Settings and Design: A prospective, randomized and double-blind study was conducted involving 80 patients for elective lower limb surgeries carried under epidural anesthesia.

Methods and Material: Epidural anesthesia at L1-2 space was given with 15 ml bupivacaine(0.5%) in control group and 15ml of bupivacaine(0.5%) with nalbuphine (10mg in 1ml) in the test group.

The time to reach the sensory and motor blockade as well as duration of same along with quality and duration of analgesia was assessed along with any side effects such as respiratory depression, sedation or vomiting etc.

Results: The Mean time of onset of sensory blockade with Nalbuphine as adjuvant observed in present study is found to be 5.4 ±1.12 minutes while that without adjuvant was 15.95± 2.64 minutes($p<0.005$). The mean duration of analgesia in group receiving nalbuphine was 287.37± 23.72 minutes which was significantly longer (P value = 0.001) when compared to control group which had mean duration of sensory blockade of 162.95 ± 37.89 minutes. Similarly, the mean time to achieve complete motor blockade was significantly (p value<0.0001) earlier (12.35 ± 1.24 minutes) in Nalbuphine group compared to control group (23.04 ±2.80 minutes) and the duration of motor block was significantly longer as well in the group receiving epidural nalbuphine (168.85 ± 16.76 in nalbuphine group vs 120.25 ± 20.51minutes in control group with p value <0.0001). The hemodynamic parameters were comparable in both the groups and no significant respiratory depression or any other side effect was noted.

Conclusions: The addition of nalbuphine with bupivacaine epidurally was effective for postoperative analgesia in terms of quality and duration of analgesia without any systemic side effects or hemodynamic instability.

Keywords: epidural anesthesia, nalbuphine, postoperative analgesia

Introduction

Spinal anesthesia is a simple method requiring small dose of local anesthetic agent to establish dense immediate and reliable motor and sensory blockade [1] but hypotension and difficulty in controlling the level of analgesia are major disadvantages of spinal block.[2] However, epidural block technique gives better control of the level of analgesia, lesser hemodynamic changes and can be used for postoperative pain relief by using different drugs such as opioids or local anesthetic agents.

The epidural technique aims to prolong the duration of analgesia during intraoperative period and extending it to the postoperative period.[3] Narcotic analgesics are frequently used as adjuncts to local anesthetics in epidural anesthesia. Although the systemic use of narcotic analgesics does provide acceptable analgesia, but when these drugs are used through epidural route, they provide superior quality of analgesia, uninterrupted pain relief, early mobilization, earlier restoration of bowel and bladder function and reduced risk of postoperative respiratory and thromboembolic complications.

Therefore, efforts centered on these techniques not only challenge traditional thinking but also improve the overall outcome of the patient [4].

Nalbuphine, is a synthetic μ receptor antagonist and κ receptor agonist opioid. It has the potential to maintain or even enhance μ opioid based analgesia while simultaneously mitigating the μ opioid side effects.[5] Nalbuphine was found to produce lesser respiratory depression, and has larger margin of safety with lesser incidence of nausea, vomiting, urinary retention, pruritus and significantly less inhibition of gastrointestinal activity than any of the clinically useful narcotic or agonist/antagonist analgesics tested in animals.[6]

The present study was undertaken to observe the efficacy and duration of postoperative analgesia and safety of Bupivacaine with nalbuphine via epidural route for lower limb orthopedic surgeries.

Subjects and Methods

A total of 80 patients under ASA grade I and II between ages 18-60 years, scheduled for elective lower limb surgeries were recruited in our study. Patients having higher ASA grade (more than II), hypersensitivity to nalbuphine, pregnant and lactating patients or patients with any contraindications for neuraxial anesthesia were excluded for the study.

A written informed consent was received from all the patients and trial was registered in clinical trials registry of india CTRI/2021/10/037198.

Under standard ASA monitoring, patients were administered epidural anesthesia by inserting epidural catheter using 18 G tuohy needles at L2-3 or L1-2 space with the help of loss of resistance technique.

A test dose of 2 ml of 2% lignocaine with 10 microgram of adrenaline was injected through the catheter and after ruling out intrathecal or intravascular spread, a total dose of 15 ml of 0.5% Bupivacaine with injection nalbuphine 10mg (1ml) was injected through the catheter. The control group received a total dose of 15 ml of 0.5% bupivacaine only.

The characteristics of epidural block were observed in terms of onset and offset of sensory (time to reach T10 level) and motor block (time to reach grade 3 motor block), hemodynamic parameters and respiratory parameters. A fall in systolic blood pressure by 20% from the baseline value was defined as hypotension and managed with IV fluid 2ml/kg bolus followed by inj. ephedrine in incremental doses.

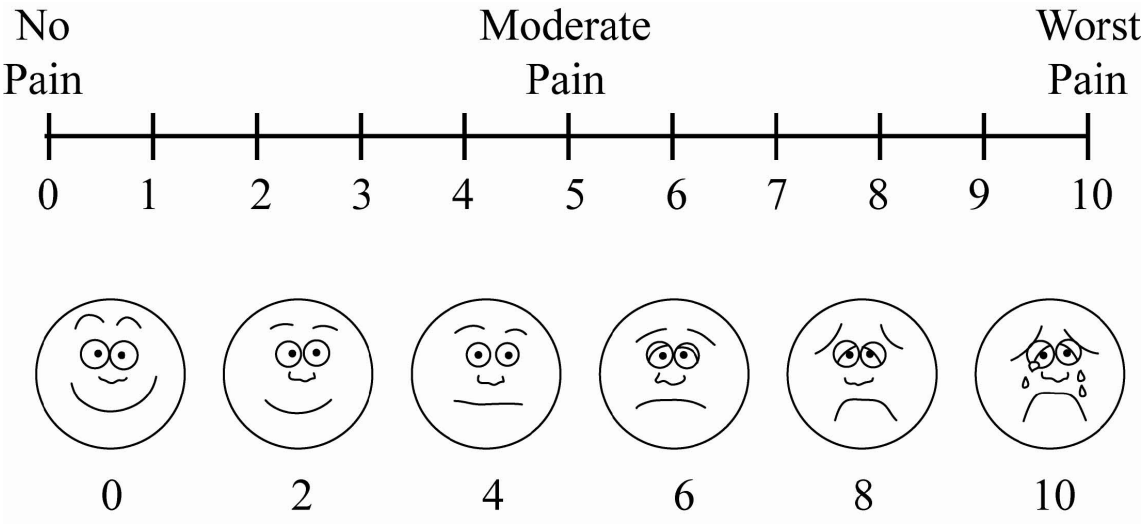
At end of surgery patients were observed in the recovery room. The level of consciousness was assessed every half hour and graded according to the **ramsay sedation score (figure 1).**

The Ramsay Sedation Scale (RSS) (modified)

Value	*Description (level of sedation)*	*Test to follow:*
1	Awake: Patient is anxious and agitated, or restless, or both.	Observe the patient.
2	Awake: Patient is co-operative, orientated, and tranquil.	Observe the patient. Does patient make eye contact and respond to commands?
3	Awake: Patient responds to commands only.	Talk to the patient. Does patient make eye contact and respond to commands?
4	Asleep: Patient reacts with a brisk response to a light glabellar tap or a loud auditory stimulus.	Physically stimulate the patient by shaking the shoulder while speaking loudly. Does patient respond within 10 sec?
5	Asleep: Patient reacts with a sluggish response to a light glabellar tap or a loud auditory stimulus.	Physically stimulate the patient by shaking the shoulder while speaking loudly. Does patient respond after 10 sec?
6	Asleep: Patient does not respond to pain.	Use painful stimuli. No response.

Modified after Ramsay M.A., Savege T.M., Simpson B.R., Goodwin R.: Controlled sedation with alphaxalone-alphadolone. BMJ 1974, 2:656- 659, and van Dishoeck A.M. *et al*. Reliable assessment of sedation level in routine clinical practice by adding an instruction to the Ramsay Scale. Eur J Cardiovasc Nurs. 2009 Jun;8(2):125-8.

Any side effect attributable to Nalbuphine was also recorded. **The visual Analogue scale** (0-10) was used to quantify the pain felt by patient every half hour in postoperative period **(figure 2).**



Patients having VAS Score more than 3 were given rescue analgesic (injection diclofenac 75mg stat) and duration of post operative analgesia was recorded.

The duration of analgesia was taken as the period from the time of giving epidural analgesia till the patient's first requirement of systemic analgesic medication.

Statistical Analysis: Continuous numeric data– onset and offset time of epidural block, hemodynamic parameters and respiratory parameters were analyzed by Mean, standard deviation and standard error of mean.

Nominal data on pain intensity and pain free period were analyzed by chi square test.

Sample size was calculated based on a previous study18 and its formula is given by

$$n = \frac{Z^2\sigma^2}{L^2}$$

Where,

Z=1.96 at 95% Confidence interval

σ =11.49 min duration of analgesia

L(Precision) =3.7

(Precision= Z X Standard error of mean)

standard error= SD/√n (previous study) so 11.49/√40

So, sample size~ 40 cases each.

Results and discussion

Both the groups were comparable in terms of demographic parameters like age and sex

Table 1: Demographic distribution in two groups

Sex	Group	
	Nalbuphine Group	**Bupivacaine Group**
F	7	8
	17.5%	20%
M	33	32
	82.5%	80%
Mean Age	35.8	34.8

Table 2: Showing timing of sensory and motor blocks along with their durations in both the groups.

Parameters studied	Group	
	Nalbuphine Group	**Bupivacaine Group**
Mean onset of sensory block	5.4 ± 1.12 minutes	15.95±2.64 minutes
Mean duration of sensory block	287.37±23.72 minutes	165.42±29.43 minutes
Mean onset of motor block	12.35 ±1.24 minutes	23.04±2.80 minutes
Mean duration of motor block	168.85±16.76 minutes	120.25±20.51minutes
Mean duration of rescue dose of analgesia	4.99±0.21 Hours	2.37±0.50 Hours

Mean time of onset of sensory blockade with Nalbuphine as adjuvant observed in present study is found to be 5.4 ±1.12 minutes while that without adjuvant was 15.95± 2.64 minutes ($p<0.005$). This shows that nalbuphine hastens the sensory blockade which correlated well with the previous studies. [7,8,9] Nalbuphine being highly lipophilic in nature10 are considered safe because of segmental localization[11]. High lipid solubility and high potency may explain the faster onset of pain relief in nalbuphine group.[12]

The potency and duration of analgesia vary considerably for different opioids and are influenced by several factors, including lipophilicity of the drug, its receptor affinity, its intrinsic agonist activity, and its removal via circulation in the spinal cord[11].

In present study mean duration of analgesia in group receiving nalbuphine was 287.37± 23.72 minutes which was significantly longer (P value = 0.001) when compared to control group which had mean duration of sensory blockade of 162.95 ± 37.89 minutes which correlated well with the previous studies[13,14,15]. Mohamed F Mohamed, et al[13] in their study among pediatric population undergoing lower abdominal surgeries administered Nalbuphine 0.1mg/kg with Bupivacaine 0.25% (1ml/kg) as single shot caudal epidural block found that there is prolonged duration of analgesia of 10.1 ± 1.5 hours with nalbupine as adjuvant, which is very significantly longer than our group. This was probably due to higher dose of bupivacaine used in their study which would have led to higher level of sensory blockade. The level of blockade was not mentioned in this study as general anesthesia was administered to the pediatric population which would additionally have a confounding effect prolonging the analgesia and sedation time.

The longer duration of action and analgesic efficacy of epidural nalbuphine can be explained by its high affinity for spinal receptors. Thus, smaller doses of nalbuphine produce a high concentration of the drug at spinal receptors. The higher lipid solubility of Nalbuphine in presence of epidural fat favors its slow diffusion in to spinal cord.

The diffusion from the spinal cord in to the blood stream is slow and does not approach the bulbar centers. Thus, because of this property intense, uninterrupted and prolonged analgesia was obtained[10,11].

Similarly, the mean time to achieve complete motor blockade was significantly (p value<0.0001) earlier (12.35 ± 1.24 minutes) in Nalbuphine group compared to control group (23.04 ±2.80 minutes) and the duration of motor block was significantly longer as well in the group receiving epidural nalbuphine (168.85 ± 16.76 in nalbuphine group vs 120.25 ± 20.51minutes in control group with p value <0.0001). Thus, it is important to note that nalbuphine not only hastens and prolongs analgesic effect but also has an adjuvant effect on motor blockade of bupivacaine. This correlated well with few studies done in past[9,16] however, the mechanism behind prolongation of motor block still needs to be studied as prolong immobilization may not be suitable in terms of early post operative recovery.

Mean of time to demand rescue dose of analgesic in present study was found to be 4.99 ± 0.21 hours (299 minutes) which was statistically significant (p value<0.05) when compared with control group which had a mean time of only for 2.7 ± 0.50 hours (162 minutes). The results not only correlated well with previous studies[14-18] but also correlated well with the duration of sensory blockade as described above, moreover the rescue dose was required much later suggesting that analgesic effect of nalbuphine persisted longer despite tapering of sensory blockade.

The heart rate and systolic blood pressure between the two groups was compared and it was seen that reduction in BP was similar in both the groups (figure 3 and 4).

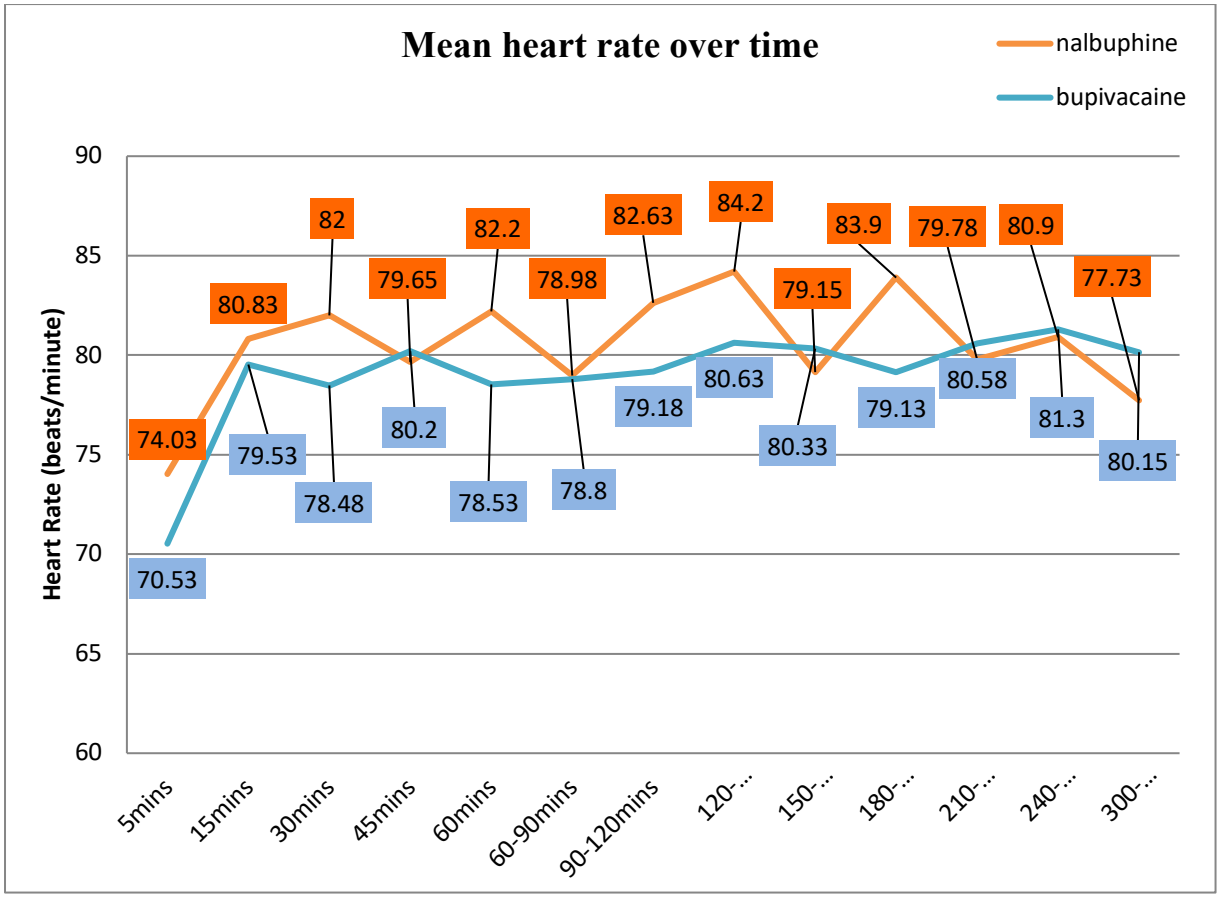


Figure 1: Mean heart rate over time

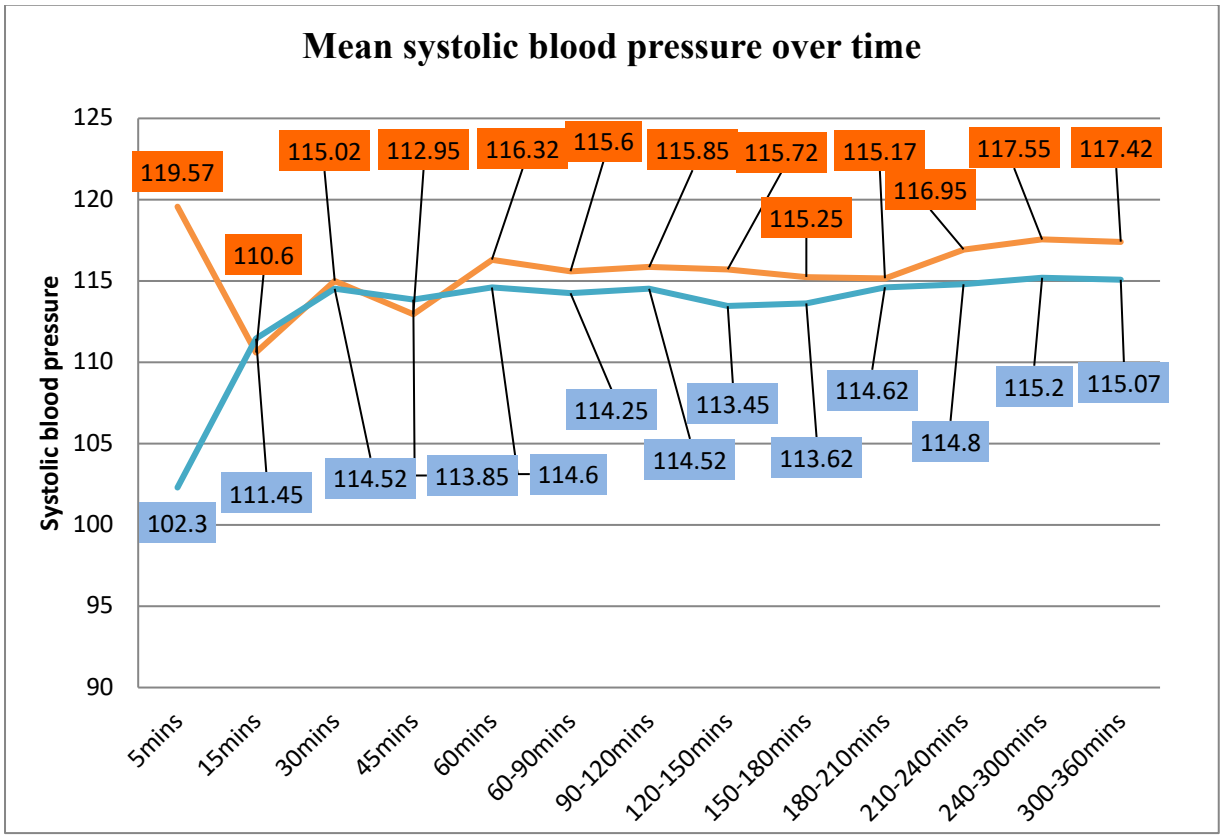


Figure 2: Mean systolic blood pressure over time

This remained within 10% of the pre operative value at all times. However, the fall in blood pressure was more at 5 minutes interval in control group compared to the group receiving nalbuphine suggesting better hemodynamic with the addition of nalbuphine. The mean heart rate for nalbuphine treated patients was found to be 78.1 beats per minute. In a study Lee and associates[19] compared nalbuphine and morphine in patients with acute myocardial infarction, nalbuphine did not produce any untoward clinical or hemodynamic effects in such patients, as did morphine. Nalbuphine decreased heart rate but maintained aortic pressure, thereby maintaining the balance between myocardial oxygen supply and demand[19].

The analysis of VAS scoring in present study showed that in first four hours patients receiving Nalbuphine had less score values indicating maximum pain relief while that in control group was increased after 2 hours requiring rescue analgesics. This was also observed in study by Parker et. al [20] where the majority of the patients preferred to use PCEA in dose of 0.8mg/kg Nalbuphine as this dose effectively managed their postoperative pain.

On assessing the sedation level of patients who were administered Nalbuphine via epidural route; mean sedation score after two hours of present study were similar to the control group between 2 -3 (figure 5).

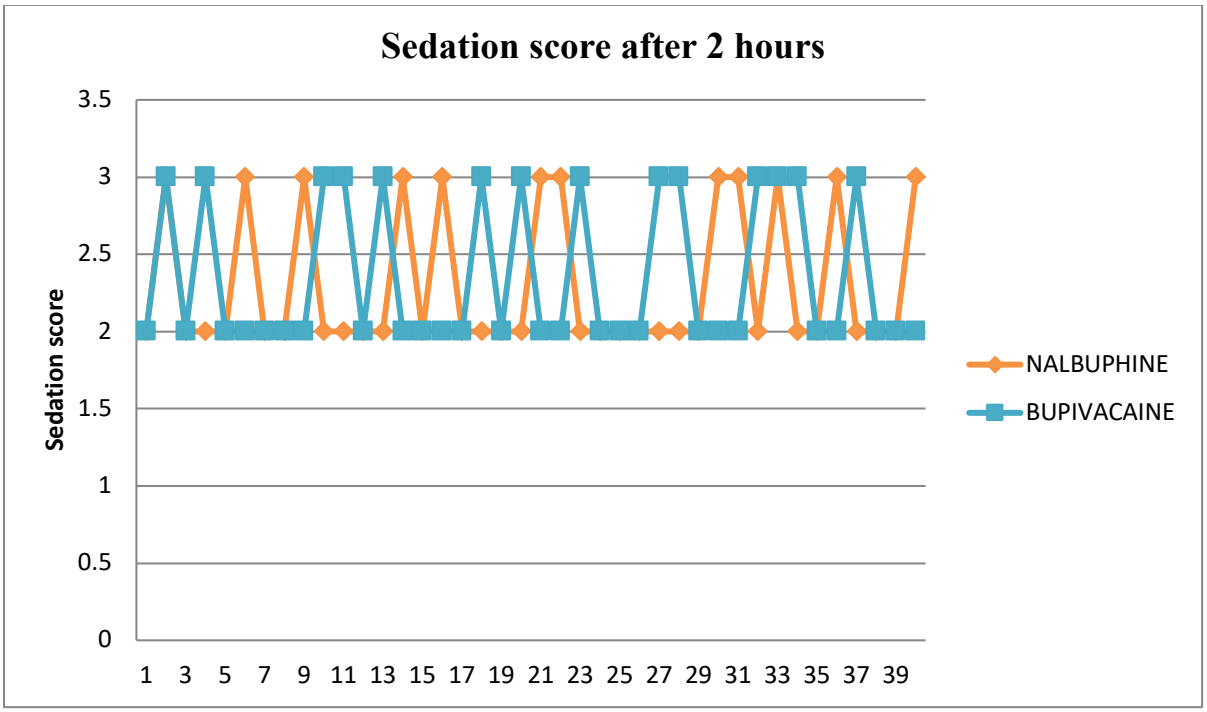


Figure 3: Sedation score after 2 hours

Similarly, the respiratory rate was comparable in both the groups throughout the study period suggesting no signs of respiratory depression with use of nalbuphine. This was supported by previous studies as well which suggest that Nalbuphine has a ceiling effect on both the degree and duration of respiratory depression. [18,21,22] No other side effects were noted with the use of nalbuphine in our study.

Limitations: The patient profile in our study mainly consisted of patients without any cardiac comorbidities. The effect of nalbuphine in patients with known cardiac disease needs to be further studied as well to ascertain its hemodynamic stability further. Our study also revealed that the motor blockade was additionally prolonged by addition of nalbuphine. This effect may be counterproductive in early mobilization of patients. Hence, its combination with ropivacaine in place of bupivacaine offers further research options.

Conclusion We conclude that addition of epidural Nalbuphine as adjuvant with Bupivacaine (0.5%) provides excellent operative conditions and satisfactory postoperative analgesia of prolonged duration without any respiratory depression or cardiovascular instability.

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