

A comparative study of the analgesic efficacy of intrathecal nalbuphine in three different doses (1.0mg/ 1.5mg/ 2.0mg) as an adjuvant to 0.5% hyperbaric bupivacaine in spinal anaesthesia for lower abdominal and lower limb surgeries

Vishalakshi Patil¹, Lohit Kondikar^{2*}, Balaraju T C³, Chaitanya Ghanta⁴, A. Sanjana Reddy⁵

¹Associate professor, ²Assistant professor, ³Professor and HOD, ⁴IIIrd year Resident, ⁵IInd year Resident, Navodaya Medical College, Hospital and Research centre, Mantralayam road, Navodaya Nagar, Raichur – 584103, Karnataka, INDIA.

Email: anaesthesia.nmc@gmail.com, drlohitbk@gmail.com

Abstract

Background: Nalbuphine is a synthetic opioid, with kappa agonist or partial μ antagonist action. when added as adjuvant to intrathecal Bupivacaine acts on kappa receptors in the dorsal horn of the spinal cord producing analgesia. **Aim:** To evaluate the Onset and duration of sensory blockade and motor blockade, duration of post-operative analgesia, and adverse effects of different doses of Nalbuphine with Bupivacaine for spinal anaesthesia. **Materials and Methods:** Prospective Randomized controlled study done on 100 patients undergoing lower abdominal and lower limb surgeries under subarachnoid block. We randomly allocated four Groups A, B, C, and D, where Groups B, C, and D to receive 1.0, 1.5, and 2.0 mg Nalbuphine made up to 0.5ml with normal saline added to 3.0ml of 0.5% hyperbaric bupivacaine respectively, and Group A receive 0.5 ml of normal saline added to 3.0ml of 0.5% hyperbaric bupivacaine (3.5ml). Assessment of motor and sensory blockade was done by Bromage scale and pin prick method. Pulse rate, NIBP, Respiratory rate, SpO₂, and VAS score were monitored intraoperatively and 24hrs post-operative period. **Results:** The mean onset time of sensory block of Group C and D was significantly early as compared to the onset of sensory block as compared to Group A and B. Duration of two-segment regression of sensory block, duration of motor blockade, and duration of analgesia time were prolonged in Groups C (1.5mg) and D (2.0mg) and found to be significant. The incidence of adverse effects was frequently higher in Group D ($P < 0.05$) compared to other groups. **Conclusion:** Nalbuphine is effective adjuvant in spinal anaesthesia. Addition of 1.5mg of Nalbuphine to 0.5% hyperbaric Bupivacaine for subarachnoid block provides excellent analgesia with longer duration of action compared with 1.0 and 2.0mg without adverse effects.

Key Words: Bupivacaine, Nalbuphine, Subarachnoid block.

*Address for Correspondence:

Dr. Lohit Kondikar, Assistant professor, Navodaya Medical College, Hospital and Research centre, Mantralayam road, Navodaya Nagar, Raichur – 584103, Karnataka, INDIA.

Email: drlohitbk@gmail.com

Received Date: 12/03/2019 Revised Date: 27/05/2019 Accepted Date: 08/07/2019

DOI: <https://doi.org/10.26611/10151116>

Access this article online

Quick Response Code:



Website:

www.medpulse.in

Accessed Date:

14 July 2019

INTRODUCTION

Regional anaesthetic techniques of spinal anaesthesia offer many advantages over general anaesthesia including reduced stress response to surgery with postoperative analgesia. The surgical stress response peaks during the postoperative period and has major effects on almost all body systems. A pain-free and stress-free postoperative period definitely helps in early mobilization and recovery, thereby reducing morbidity and mortality. Most commonly used adjuvants are opioids, alpha-2 adrenergic

How to cite this article: Vishalakshi Patil, Lohit Kondikar, Balaraju T C, Chaitanya Ghanta, A Sanjana Reddy. A comparative study of the analgesic efficacy of intrathecal nalbuphine in three different doses (1.0mg/ 1.5mg/ 2.0mg) as an adjuvant to 0.5% hyperbaric bupivacaine in spinal anaesthesia for lower abdominal and lower limb surgeries. *MedPulse International Journal of Anesthesiology*. July 2019; 11(1): 30-34. <http://medpulse.in/Anesthesiology/index.php>

agonist, ketamine, midazolam, etc., but certain side effects such as pruritis, respiratory depression, nausea, vomiting, and urinary retention were observed with opioids^{1,2}. Nalbuphine is a μ receptor antagonist and κ receptor agonist^{3,4}. When Nalbuphine is added as an adjuvant to intrathecal Bupivacaine, it has potential to provide good intraoperative and post-operative analgesia with decreased incidence of μ receptor side effects like respiratory depression^{5,6}. Here we compared the effect of Nalbuphine addition at different dosages i.e., 1.0mg, 1.5mg and 2.0mg to 0.5% hyperbaric Bupivacaine intrathecally with 0.5% hyperbaric Bupivacaine alone for duration, quality of post-operative analgesia and any side effects.

MATERIALS AND METHODS

The study was approved by the local institutional ethics committee and written informed consent was obtained from all patients before participation. About 100 patients of American Society of Anaesthesiology (ASA) I and II, aged 18-60 years, both sexes posted for elective lower limb surgeries and lower abdominal surgeries under spinal anaesthesia included in the study.

Inclusion Criteria:

ASA physical status I and II. Patients of either sex. Patients aged between 18-60 years. Patient with written valid consent. Patient undergoing elective lower abdominal and lower limb surgeries.

Exclusion Criteria:

ASA III and IV grade. Lack of valid informed written consent. Infection at the subarachnoid block injection site. Patients with neurological and musculoskeletal disease. Patients with bleeding disorders. Patients on anticoagulants. Pregnancy. History of allergy to local anaesthetic. Patients on tranquilizers, hypnotics, sedatives, and other psychotropic drugs.

Patients were visited and detailed pre-anaesthetic examination done. Preparation of patients includes period of overnight fasting. Pre-medication done with oral tablet *alprazolam* 0.5mg and tablet *Ranitidine* 150mg given at night and morning on the day of surgery. The procedure of spinal anaesthesia was explained to the patients and informed written consent was obtained. The patients were educated about the use of visual analogue scale (VAS). Routine investigations like complete hemogram, blood sugar, electrocardiogram, chest X-ray were done. Ampoule containing preservative free Nalbuphine hydrochloride 10mg in 1 mL (NEON LABORATORIES

LTD.) was used. The dose of intrathecal Nalbuphine was measured using insulin syringe. In the Operating room, IV access was obtained on the forearm with 18 Gauge IV cannula and IV infusion started with Ringer Lactate or Normal saline. Monitors connected to the patients include three lead ECG in standard lead 2, non-invasive BP and pulse oximeter. Patient's basal parameters were recorded prior to spinal anaesthesia. Spinal anaesthesia was performed with the patient in the lateral decubitus position or sitting position using a 25-gauge Quincke needle at the L3-L4 or L4-L5 interspaces. Following free flow of CSF, respective drug was injected into subarachnoid space as mentioned in Table 1 and were positioned supine immediately. After the spinal block, intra-operatively and post-operatively vitals were observed and recorded at 5 min, 10 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, 6 hr, 12 hr, 24 hr.

The following Parameters were noted and used for Comparison between the Groups.

1. Time of Onset of Sensory Block (time of injection to loss pin prick sensation).
2. Time of Onset of Motor Block (time of injection to modified Bromage grade 3 block).
3. Duration of Sensory Block (Two segment regression time from the maximal level and regression to level L1).
4. Duration of Motor Block (time required for Grade 3 block to Grade 0 motor block in modified Bromage scale).
5. Duration of Effective Analgesia (i.e., time of onset of sensory block to the first rescue analgesia $VAS \geq 3$).
6. Side effects like Hypotension, Shivering, Nausea, Vomiting, Urinary retention, Respiratory depression and Itching were noted.

Pain was assessed by VAS (visual analogue scale). Here patient was given a scale marked from 0-10 and was asked to mark on the scale the degree of pain he /she experiencing from 0-no pain to 10 maximum pain, when $VAS \geq 3$, rescue analgesia given with inj. Diclofenac sodium and study ended.

STATISTICAL ANALYSIS

Statistical analysis of all the data was done by using One-way ANOVA, *Sample t-test* and Wilcoxon test. *P* value of 0.05 or less is considered significant for statistical analysis.

RESULTS

Patients were randomly allocated into four groups. Each group consists of 25 patients. They received either of drug solution as below (Table 1).

Table 1: Group Distribution.

Groups	Drugs
GROUP A	25 patients received 3mL (15mg) of 0.5% Hyperbaric Bupivacaine + Normal Saline (0.5mL) -- Total volume is 3.5mL.
GROUP B	25 patients received 3mL (15mg) of 0.5% Hyperbaric Bupivacaine + Nalbuphine 1.0mg (0.1mL diluted to 0.5mL with Normal saline) – Total volume 3.5mL.
GROUP C	25 patients received 3mL (15mg) of 0.5% Hyperbaric Bupivacaine + Nalbuphine 1.5mg (0.15mL diluted to 0.5mL with Normal saline) – Total volume 3.5mL.
GROUP D	25 patients received 3mL (15mg) of 0.5% Hyperbaric Bupivacaine + Nalbuphine 2.0mg (0.2mL diluted to 0.5mL with Normal saline) – Total volume 3.5mL.

The effects of intrathecal 0.5% hyperbaric Bupivacaine with Nalbuphine hydrochloride at three different doses (1.0, 1.5, and 2.0 mg) was studied and compared with 0.5% hyperbaric Bupivacaine alone in 100 patients belonging to ASA grade I and II who underwent lower limb surgeries and lower abdominal surgeries. The four Groups A, B, C and D did not differ significantly in demographic characteristics like Age, Sex, Weight and Height as shown in Table – 2. The results regarding the characteristics of Sensory block and Motor Block, Duration of Effective Analgesia were summarized in Table – 3. The mean time of onset of Sensory block and Motor block between the Groups are comparable with *P* – value <0.05 which are statistically significant (Table – 3). Two-segment regression time of Sensory blockade was progressively prolonged in Groups B, C, and D compared to Group A (Table – 3). Group D recorded with mean of 175.2 min compared with 166.5 min in Group C, in Group B 129.4 min and Group A 121 min. The duration of Motor blockade also prolonged progressively in Groups B, C, and D compared to Group A (Table - 3). Group D recorded with the longest duration of Motor blockade with a mean of 172.2 min compared to Group C 163.0 min, Group B 129.84 min, and Group A 117.0 min (Table - 3). The duration of Analgesia was prolonged progressively in Group B, C, D compared to Group A (Table – 3 and Figure – 1). Group C recorded with the longest duration of Analgesia with a mean of 328.2 min compared to Group D 325.2 min, Group B 267.9 min, and Group A 154.8 min (Table – 3 and Figure – 1). The side effects of Hypotension, Nausea, Vomiting, Shivering, Pruritis, Respiratory depression and Urinary retention are more common in Group D compared to other groups (Table – 4 and Figure – 2).

Table 2: Demographic Characteristics

	GROUP - A	GROUP - B	GROUP - C	GROUP - D	P - VALUE
AGE (years)	36.44 + 3.38	38.12 + 3.84	39.80 + 5.12	38.80 + 4.74	> 0.05
SEX	7 : 18	12 : 13	10 : 15	12 : 13	> 0.05
WEIGHT (Kg)	47.76 + 4.26	49.24 + 3.47	48.96 + 3.56	49.44 + 3.33	> 0.05
HEIGHT (cm)	157.8 + 2.42	159.4 + 2.75	157.9 + 6.24	160.3 + 5.65	> 0.05

Table 3: Summary of Results

	GROUP A	GROUP B	GROUP C	GROUP D	P - VALUE
Onset of sensory block (min)	2.98 ± 0.91	2.7 ± 0.62	2.06 ± 0.51	2.32 ± 0.64	< 0.0001
Onset of Motor block (min)	6.13 ± 0.98	6.3 ± 0.92	5.19 ± 0.63	5.08 ± 0.79	< 0.0001
Two segment regression time (min)	121 ± 9.46	129.4 ± 5.4	166.5 ± 7.2	175.2 ± 8.9	< 0.0001
Duration of Motor Block (min)	117 ± 7.05	129.8 ± 6.3	163.0 ± 7.1	172.2 ± 9.0	< 0.0001
Duration of Effective analgesia (time to 1 st rescue analgesic)	190 ± 12.9	294 ± 9.4	328.2 ± 9.3	325.2 ± 13.8	< 0.0001

Table 4: Side Effects

Groups	Hypotension	Nausea	Shivering	respiratory depression	Pruritis	Urinary retention
GROUP A	2	0	1	0	0	0
GROUP B	4	0	0	0	0	0
GROUP C	4	1	2	0	0	0
GROUP D	8	5	5	0	0	0

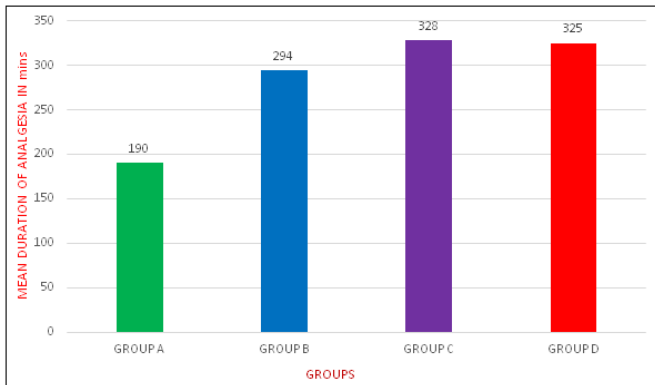


Figure 1: Duration of Analgesia

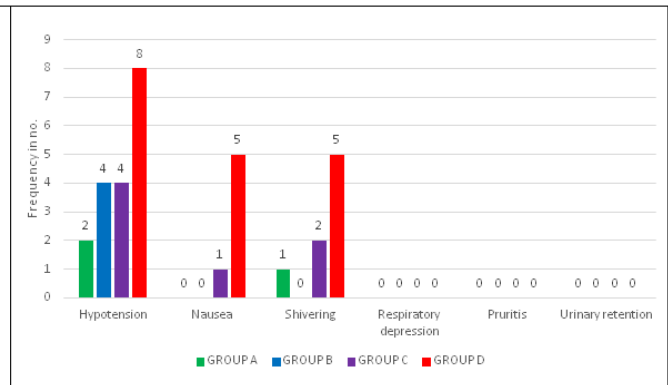


Figure 2: Incidence of Side Effects

DISCUSSION

Nalbuphine, a mixed agonist-antagonist drug, binds both to mu and kappa receptors, but its action on these receptors is divergent. When Nalbuphine binds to μ receptor, it serves only to competitively displace other μ agonists from the receptor without itself displaying any agonist activity similar to those of naloxone. However, when it binds to kappa receptor, it has agonist activating effect. This pattern of binding and effects defines Nalbuphine as a mixed agonist-antagonist. Nalbuphine, administered Intrathecally, binds to Kappa receptors in the brain and spinal cord areas which are involved in nociception, producing analgesia and sedation without μ side effects. The rationale for the combination of opioids and local anaesthetics is that these two types of drugs eliminate pain by acting at two different sites. Local anaesthetics act at the nerve axon and the opioid at the receptor site in the spinal cord^{7,8}. The major site of action of opioid is within the second and third laminae of substantia gelatinosa in the dorsal horn of the spinal cord. Intrathecal opioids used as adjuncts are capable of producing analgesia of prolonged duration, but allow early ambulation of patients because of their sympathetic and motor nerve-sparing activities. The popularity of intrathecal opioids was undermined by reports of side-effects such as respiratory depression, pruritus and postoperative nausea and vomiting. There are few studies suggest that neuraxial administration of Nalbuphine has minimal side effects such as respiratory depression, pruritis, nausea, vomiting, and significant prolonged duration of analgesia⁵. In our study, all the four groups were comparable in distribution of patients according to age, sex, weight, and height. The mean onset time of sensory block and motor block of Group C and D was significantly early as compared to Group A and B. Two segment regression of sensory blockade was significantly prolonged by addition of intrathecal Nalbuphine as seen in Group B, C and D when compared with Group A Bupivacaine alone and this result correlates with that of

study done by Jyothi B, Shruthi Gowda, Safiya I Shaikh who had compared 100 patients undergoing lower abdominal and lower limb orthopaedic surgeries under subarachnoid block. They used different doses of Nalbuphine 0.8mg, 1.6mg, 2.4mg added to 0.5% heavy Bupivacaine and they concluded that addition of 0.8mg of Nalbuphine to 0.5% Bupivacaine for subarachnoid block provides excellent analgesia with longer duration of action compared with 1.6 and 2.4mg of Nalbuphine⁹. Tiwari *et al.*, who compared intrathecal Nalbuphine 0.2mg and 0.4mg added to hyperbaric Bupivacaine with Bupivacaine alone. They concluded that prolonged duration of analgesia was seen in Nalbuphine 0.4mg without adverse effects.¹⁰ Mukherjee *et al.* had compared 100 patients undergoing orthopaedic lower limb surgeries under spinal anaesthesia. They used different doses of Nalbuphine 0.2, 0.4, and 0.8 mg added to 0.5% Bupivacaine and they concluded that 0.4 and 0.8 mg have significant prolonged duration of analgesia¹¹. Nalbuphine also provided hemodynamic stability. Similar findings are seen in the study conducted by Culebras *et al.*⁶, Tiwari *et al.*¹⁰, Mostafa *et al.*¹², where there was no gross hemodynamic changes throughout their study. From our study, we can conclude that use of Nalbuphine hydrochloride along with Bupivacaine causes no gross hemodynamic disturbances even with increasing the dosage from 1.0mg to 2.0mg. In our study, none of patient had respiratory depression (respiratory rate below 10 bpm, SPO2 <90%). Nalbuphine exhibits ceiling effect for respiratory depression. This is proved in studies done by Romagnoli and Keats¹³, Thomas *et al.*¹⁴. Since respiratory depression is predominantly μ receptor-mediated and Nalbuphine is a μ receptor antagonist, respiratory depression effect is expected to be attenuated by Nalbuphine. Increasing the dosage from 1.0mg to 2.0mg did not cause any respiratory complications. This result correlates that of the studies done by Culebras *et al.*⁶, Tiwari *et al.*¹⁰, and Mostafa *et al.*¹². Since Nalbuphine is a mixed agonist-antagonist, studies by Pugh and

Drummond GB¹⁵, Thomas *et al.*¹⁴, have proved that it exhibits a ceiling effect to analgesia that is increasing doses of drug produce increasing analgesia only up to a certain point. Beyond that point, further increase in dose does not result in increased intensity of analgesia. In our study, Nalbuphine exhibits analgesic ceiling effect at 1.5 mg dosage, above which will not increase analgesic efficacy. This analgesic ceiling effect can be a significant limitation of Nalbuphine usage. In our study, addition of Nalbuphine significantly prolonged duration of analgesia which correlates to results of studies done by Lin¹⁶, Culebras *et al.*⁶, Tiwari *et al.*¹⁰, Mostafa *et al.*¹². Patient who received Bupivacaine alone had significantly higher pain scores earlier than patients who received Nalbuphine-Bupivacaine combinations as assessed by VAS. Studies done by Tiwari *et al.*¹⁰, Mostafa *et al.*¹², also reported that Nalbuphine prolonged duration of analgesia with reduced VAS pain score. Adverse effects like nausea, vomiting, urinary retention, and shivering were statistically insignificant in Group B (1.0mg) and Group C (1.5mg) comparing with patients in Group D (2.0mg). Nalbuphine 1.5mg (Group C) has significant prolonged duration of analgesia with minimal adverse effects ($P < 0.0001$) than Nalbuphine 2.0mg (Group D), while Nalbuphine 1.0mg (Group B) have significant lesser duration of analgesia compared to Group C and D. Nalbuphine 2.0mg (Group D) have prolonged duration of analgesia but increased adverse effects. With all the above observations we conclude that addition of Nalbuphine to Bupivacaine provides prolonged analgesia, and superior pain relief with minimal side effects in Group C (1.5mg) compared to the other Groups B and D and Bupivacaine alone in spinal anaesthesia. Since Nalbuphine reaches ceiling effect at lower intrathecal dosage i.e, at 1.5mg the increased drug dosage is not required and this increases the safety margin.

CONCLUSION

We conclude that intrathecal Nalbuphine 1.5mg added to 0.5% hyperbaric Bupivacaine for spinal anaesthesia in patients undergoing lower abdominal surgeries and lower limb surgeries provides excellent analgesia with prolonged duration of sensory block and motor block without adverse effects.

REFERENCES

1. Veering B. Focus on adjuvants in regional anesthesia. *Euro Anaesth.* 2005;50:149-51.

2. Morgan M. The rational use of intrathecal and extradural opioids. *Br J Anaesth* 1989;63:165-88.
3. Chen JC, Smith ER, Cahill M, Cohen R, Fishman JB. The opioid receptor binding of dezocine, morphine, fentanyl, butorphanol and nalbuphine. *Life Sci* 1993;52:389-96.
4. Pick CG, Paul D, Pasternak GW. Nalbuphine, a mixed kappa 1 and kappa 3 analgesic in mice. *J Pharmacol Exp Ther* 1992;262:1044-50.
5. Fournier R, Van Gessel E, Macksay M, Gamulin Z (2000) Onset and offset of intrathecal morphine versus nalbuphine for postoperative pain relief after total hip replacement. *Acta Anaesthesiol Scand* 44(8): 940-945.
6. Culebras X, Gaggero G, Zatloukal J, Kern C, Marti RA. Advantages of intrathecal nalbuphine compared with intrathecal morphine, after cesarean delivery: An evaluation of postoperative analgesia and adverse effects. *Anesth Analg* 2000;91:601-5.
7. Yaksh TL, Rudy TA. Analgesia mediated by a direct spinal action of narcotics. *Science* 1976;192(4246):1357-8.
8. Gwirtz KH, Young JV, Byers RS, *et al.* The safety and efficacy of intrathecal opioid analgesia for acute post-operative pain: seven years' experience with 5969 surgical patients at Indiana University Hospital. *Anaesthesia and Analgesia* 1999;88(3):599-604.
9. Jyothi B, Shruthi Gowda, Safiya Shaikh . A comparison of analgesic effect of different doses of intrathecal nalbuphine hydrochloride with bupivacaine and bupivacaine alone for lower abdominal and orthopedic surgeries. *Indian J Pain* 2014;28:18-23.
10. Tiwari AK, Tomar GS, Agrawal J. Intrathecal bupivacaine in comparison with a combination of nalbuphine and bupivacaine for subarachnoid block: A randomized prospective double blind study. *Am J Ther* 2013;6:592-5.
11. Mukherjee A, Pal A, Agrawal J, Mehrotra A, Dawar N. Intrathecal nalbuphine as an adjuvant to subarachnoid block: What is the most effective dose? *Anesth Essays Res* 2011;5:171-5.
12. Mostafa M G, Mohamad MF, Farrag WS. Which has greater analgesic effect; Intrathecal nalbuphine or intrathecal tramadol. *J Am Sci* 2011;7:480-4.
13. Romagnoli A, Keats AS. Ceiling effect for respiratory depression by nalbuphine. *Clin Pharmacol Ther* 1980;27:478-85.
14. Gal TJ, DiFazio CA, Moscicki J. Analgesic and respiratory depressant activity of nalbuphine: A comparison with morphine. *Anesthesiology* 1982;57:367-74.
15. Pugh GC, Drummond GB. A dose-response study with nalbuphine hydrochloride for pain in patients after upper abdominal surgery. *Br J Anaesth* 1987;59:1356-63.
16. Lin ML. The analgesic effect of subarachnoid administration of tetracaine combined with low dose of morphine or nalbuphine for spinal anaesthesia. *Ma Tsui Hsueh Tsa Chi* 1992;30:101-5.

Source of Support: None Declared
Conflict of Interest: None Declared