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Intrathecal Nalbuphine an Addition to Anaesthesia Armamentarium to Prolong Postoperative Analgesia

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ABSTRACT

Background: Nalbuphine is a synthetic opioid. It has mixed agonist-antagonist action. When used as an adjuvant to intrathecal bupivacaine it acts on kappa receptors in the dorsal horn of the spinal cord producing analgesia. We aimed the present study to evaluate the effectiveness of intrathecal nalbuphine as an adjuvant. At the same time, the efficacy of nalbuphine for sensorimotor characteristics and postoperative analgesia was also judged.

Method: A total of 100 patients were enrolled. They were randomly allocated into two equal groups. Group B: received 15 mg hyperbaric bupivacaine (3ml) 0.5% + 0.5ml normal saline and Group BN: received 15 mg hyperbaric bupivacaine (3ml) 0.5% + Inj. Nalbuphine 500µg (0.5ml). The sensorimotor characteristics, duration of effective analgesia, any hemodynamic alterations, and side effects were noted.

Results: The sensory and motor block characteristics were significantly faster in group BN than group B. The duration of sensory and motor block, as well as duration of effective analgesia, was significantly prolonged in group BN in comparison with group B. Quality of analgesia during the procedure was excellent in 90% and 94% in group B and BN, respectively. Sedation score, hemodynamic parameters, and respiratory rate changes were comparable between both groups. In group B, 4% patient complained of nausea/vomiting, intraoperative hypotension noted in 4% and post-dural puncture headache was recorded in 1 patient while in group BN bradycardia was observed in 3 patients.

Conclusion: Addition of 500µg of nalbuphine as an adjuvant to hyperbaric bupivacaine 0.5% for spinal anaesthesia provides excellent analgesia with a longer duration of effective analgesia in comparison to intrathecal hyperbaric bupivacaine 0.5% alone.

Key Words: Nalbuphine, Opioid, Analgesia, Bupivacaine, Sensorimotor, Hypotension, Bradycardia

INTRODUCTION

Spinal anesthesia is the most popular regional anesthesia technique¹. The technique is simple to perform. The onset of action is rapid. Also, it gives profound muscle relaxation^{2,3,4}. The major limitation is the fixed duration of action of the local anaesthetic used. Therefore, the adjuvants such as opioids, alpha 2 agonists, neostigmine, magnesium, etc. came into picture⁵.

The intrathecal opioids as an adjuvant to local anaesthetic have been found to augment intra-operative and post-operative quality of analgesia⁶. They act synergistically with local anesthetics and intensify the sensory block without having any effect on the sympathetic blockage. It's a routine practice that opioids are added to local anaesthetic for enhancing

their effects, decreasing their dosage, and therefore decreasing the potential side effects and complications. The prolongation of the duration of postoperative analgesia is an advantage^{7,8,9}. The major drawback of the addition of opioids is their side effects. Out of which, respiratory depression can be serious and pruritus can be bothersome.

One of the best ways to control the intrathecal Opioid related side effects is the use of mixed agonist-antagonist opioids. Nalbuphine is one of the most recently used additives to spinal bupivacaine, considering its μ antagonist and κ agonist mechanisms of action¹. As adjunct to intrathecal local anesthetics nalbuphine can provide good intra- and post-operative analgesia. It can also decrease the incidence and obtund the severity of μ receptor side effects⁹. The present study was undertaken to evaluate the efficacy of intrathecal nalbuphine

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as a spinal adjuvant to hyperbaric bupivacaine 0.5% in comparison with bupivacaine 0.5% alone.

MATERIALS AND METHODS

The present prospective observational study was undertaken from December 2014 to November 2016 (2years) in the Department of Anaesthesiology at a Tertiary Care Centre in Maharashtra, India. Total 100 adult patients of American Society of Anaesthesiologists ASA grade I and II, age between 18-60 years, height 150-170cm, either sex undergoing elective lower abdominal or lower limb surgeries under regional anaesthesia were included in the study. We divided them into two equal groups (Group B-control group and group BN- nalbuphine group). Institutional Ethical Committee approval and written informed consent was taken from all. Patients with height <150cm or > 170cm, physical ASA status greater than III, contraindication to spinal anaesthesia, history of hypersensitivity to local anaesthetics or opioids, spinal deformities, patients with cardiovascular, respiratory, neurological, renal or endocrine diseases or psychiatric illness, hypovolemia, severe anaemia, pregnancy, and patients not willing for the procedure were excluded from the study.

After a detailed history and clinical examination, all relevant investigation was done for every patient with note down of demographic data. All patients were kept starving for an overnight period prior to surgery as per routine.

In the preoperative room, pulse rate, BP, respiratory rate, SpO₂ were noted. On the table, the intravenous cannula of 18/20 G was secured, and the patient was preloaded with 10ml/kg of Ringer lactate solution over 10-30mins. A multipara monitor was used to monitor vital parameters. A baseline record of NIBP, SpO₂, ECG, RR was made. None of the patients were administered sedatives in premedication. Under all aseptic precautions, in lateral decubitus position, L3- L4 interspace was identified. Quincke's 25 G needle was inserted via the midline approach till the free flow of CSF was obtained. After positive aspiration of CSF fluid, drug mixture was injected slowly (approx. 30 secs) as per group allotment as: - Group B: 15mg hyperbaric Bupivacaine 0.5 % (3ml) + 0.5ml normal saline and Group BN: 15mg hyperbaric Bupivacaine 0.5% (3ml) + Inj. Nalbuphine 500µg(0.5ml). Inj. Nalbuphine 500µg was measured in an insulin syringe and its volume made up to 0.5ml with N.S before adding to Bupivacaine which itself was drawn in a 5ml syringe. The total volume injected was 3.5ml in both the groups. Nalbuphine used in the study was preservative-free.

The time of drug injection was noted and recorded as 0. After injection patient was turned supine slowly, sensory and motor characteristics, duration of surgery, the total duration of effective analgesia assessed on VAS score, quality of analgesia, sedation score, and vital parameters were monitored

and noted. Intra and postoperative side effects were noted and treated accordingly. All patients were observed in post-anaesthesia recovery area of operation theatre till the administration of rescue analgesia which was the end-point of the main study. Patients were visited at 12 and 24 hours to note about side effects and complications if any.

Statistical Analysis

Mean, standard deviation, and range were used to express the results. Frequencies were denoted number and percentage. One-way analysis of variance (ANOVA) used for multiple group comparison with POST HOC multiple comparisons between groups with LSD correction and categorical data analyzed by chi-square test. *P* value of <0.05 was taken as statistically significant and *P*-value <0.001 as statistically highly significant. The statistical analysis was done using Statistical Package for Social Science evaluation (SPSS) version 20.0.

OBSERVATIONS AND RESULTS

The demographic profiles of the patients and type of procedure were comparable and found no difference between two groups to be considered as significant (Figure 1). Male preponderance was observed in both the groups. The mean duration of surgery was found to be less in group B (67.62±20.02; ranged from 45-105 minutes) as compared to groups BN (88.12±18.03; ranged 45- 140 minute), (*p*=0.0001).

Figure 1: Comparison of demographic data and type of procedure between two groups.

The onset of sensory and motor block was significantly faster and prolonged in group BN as compared to group B. The difference between the two groups was statistically significant (*P*= 0.0001). The time duration for effective analgesia in group B was significantly shorter (234.57±41.34 min) in comparison with group BN (371.22±40.24 min) as depicted in Figure 2.

The quality of analgesia during the procedure was excellent at 91% and 95% in group B and BN, respectively. Quality of analgesia was reported as good in 9% of patients in group B and 5% in group BN.

Figure 2: Comparison of sensorimotor characteristics between two groups.

The highest sensory level was T4 in the maximum number of patients in group BN (56%) while 58% of patients in group B achieved the T6 level, which was achieved by 36% patients in group BN as shown in table 1.

Table 1: Highest Sensory Level (HSL) Achieved (Der-matome)

HSL	Group B	Group BN
T4	9 (18%)	28 (56%)
T5	0 (0%)	0 (0%)
T6	29 (58%)	18 (36%)
T7	12 (24%)	4 (8%)

There was a significantly higher mean VAS score observed in group B than group BN at 90 - 330 minutes. At 330 min a mean of VAS= 4 was noted in group B, hence rescue analgesia was given and no further evaluation for this group was done. The analysis showed that group BN had a significantly lower mean VAS score between the time intervals of 90 – 240 mins, the mean VAS score of 4 was achieved at 450 minutes in group BN (Figure 3).

Figure 3: Mean VAS Score at Various Time Intervals.

Sedation score, hemodynamic parameters, and respiratory rate changes were comparable in two groups. In group B, 2 (4%) patients complained nausea/ vomiting, intraoperative

hypotension was noted in 2 (4%) patients and post-dural puncture headache was recorded in 1 (2%) patient. In group BN, bradycardia was observed in 3 (6%) patients, (Table 2).

Table 2: Incidence of Complications

Complications	Group B	Group BN
Intra-operative		
Nausea/Vomiting	2 (4%)	0 (0%)
Hypotension	2 (4%)	0 (0%)
Bradycardia	0 (0%)	3 (6%)
Pruritus	0 (0%)	0 (0%)
Post-operative		
Postdural puncture headache	1 (2%)	0 (0%)

DISCUSSION

Neuraxial anaesthesia along with neuraxial opioids is one of the important components of enhanced recovery after surgery. It is also one of the important modalities in multimodal analgesia¹⁰. With the advancement in the medical field, there has been a paradigm change from the use of general anaesthesia to regional anaesthesia wherever possible. The major drawback of spinal anaesthesia is hypotension and bradycardia. To some extent, it can be managed by reducing the dose of local anaesthetic. Intrathecal opioids added to local anaesthetics will decrease their dose¹¹⁻¹³.

Nalbuphine, an agonist-antagonist drug, binds to both receptors *i.e.* μ and kappa, but it has a divergent action. At μ receptor, it only displaces other μ agonists from the receptor in a competitive manner without displaying any agonist activity comparable to naloxone but it has agonist activating effect when it binds to a kappa receptor. Such binding patterns and effects characterize nalbuphine as a mixed agonist-antagonist. After intrathecal administration, it binds to the kappa receptors in the brain and spinal cord. These receptors are involved in nociception, thus producing analgesia and sedation without μ side effects⁹. Also, it improves the quality of block, gives prolonged postoperative analgesia. It is also a cost-effective drug¹⁴. Mukherjee et al.¹⁵ used different doses of nalbuphine intrathecally (200, 400, and 800 μ g) along with 0.5% hyperbaric bupivacaine. They concluded that the duration of sensory block and the duration of effective analgesia were prolonged with 400- μ g and 800- μ g doses. They also noted that the side effects were higher with 800- μ g dose. Therefore, we chose to add 500 μ g of preservative-free nalbuphine, which is very close to the best-recognized dose earlier and is practically easier to calculate. The same dose (0.5 mg) of intrathecal nalbuphine was used in the study done by Saad et al.¹ and Dubey and Bisht¹⁶.

In our study, the onset of sensory and motor block was faster as compared to plain bupivacaine. Time to achieve T10 level, highest sensory level as well as time for the complete motor

block was shorter in group BN as compared to group B. The difference found to be statistically significant. Similar results are reported by Parveen et al.⁶ and Kumaresan et al.¹⁷. The two-segment regression of sensory block, duration of sensory and motor block was prolonged when nalbuphine was used as an adjuvant to intrathecal bupivacaine. There was a significant prolongation of effective analgesia duration too. These results correlated well with the previous studies [9, 18-20]. The study conducted by Lin¹⁹ found that nalbuphine 0.4 mg with intrathecal tetracaine improved the quality of intraoperative analgesia. Culebras et al.²¹ also found that intrathecal nalbuphine 0.8-1.6 mg improved the quality of intraoperative analgesia during cesarean deliveries with good visceral analgesia. In the present study, quality of analgesia during the procedure was excellent in 94% with nalbuphine as an adjuvant to spinal bupivacaine.

Patients receiving 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.¹⁸ and Mostafa et al.²⁰ also reported that nalbuphine prolonged duration of analgesia with reduced VAS pain score. Sedation score, hemodynamic parameters, and respiratory rate changes were comparable between the two groups and found no significant difference among groups.

A large number of animal studies have been carried out to prove that intrathecal nalbuphine is not neurotoxic. Rawal et al.²² studied the behavioral and histopathological effects following intrathecal administration of butorphanol, fentanyl, and nalbuphine in sheep. They found that nalbuphine was the least irritating to neural tissues even at higher doses of 15–24 mg. It was not associated with any histopathological changes in the spinal cord. Later human studies were also conducted to test the efficacy of nalbuphine which confirmed the same results. There have been no reports on the neurotoxic effects of using intrathecal nalbuphine for over 10 years. There are some studies on pregnant women, which do not reveal any unwanted action²³.

CONCLUSION

With 500µg of nalbuphine added to heavy hyperbaric spinal bupivacaine 0.5% as an adjuvant, both sensory and motor block onset are faster. Time to two-segment regression and time duration of sensory and motor block are prolonged. Intraoperative analgesia is excellent with a longer duration of extended duration of postoperative analgesia. Thus, the drug nalbuphine proves to be an effective adjuvant to hyperbaric 0.5% bupivacaine for spinal anaesthesia.

Limitations of the study

There is a need for more work on the side effect profile by increasing the number of cases. In existing study rescue analgesia was the endpoint; we need to follow further to find

out the total doses of analgesics needed to keep VAS score below 4. Further study is needed to determine how much we can reduce the dose of local anesthetic.

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REFERENCES

1. Saad S, Afifi E et al. Intrathecal nalbuphine as an adjuvant to bupivacaine in spinal anesthesia for lower-limb surgeries: intraoperative and postoperative effects. *Benha Med J* 2018; 35: 297-306.
2. Rudra A, Halder R et al. Efficacy of low dose propofol for control of emetic episodes during cesarean delivery with spinal anesthesia. *Indian J Anesth.* 2004; 48: 31-4.
3. Bogra J, Arora N, Srivastava P et al. Synergistic effect of intrathecal fentanyl and bupivacaine in spinal anesthesia for caesarean section. *BMC Anesthesiol.* 2005; 5:5.
4. Palan, A., and N.K. Agrawal. "Control of Intraoperative Shivering under Spinal Anaesthesia- A Prospective Randomized Comparative Study of Butorphanol with Tramadol." *Journal of Krishna Institute of Medical Sciences University* 2017; 6(1): 57–65.
5. Varghese, L, and K. Taksande. "A Comparison between Intrathecal Dexmedetomidine with Hyperbaric Bupivacaine and Intrathecal Fentanyl with Hyperbaric Bupivacaine in Lower Abdominal Surgeries: A Prospective Double-Blinded Study." *Journal of Datta Meghe Institute of Medical Sciences University* 2017; 12(2): 99–109.
6. Parveen S, Prasad PK, Lakshmi BS. Evaluation of the Effect of Intrathecal Nalbuphine as an Adjuvant to Spinal Bupivacaine for Post-operative Analgesia in Patients Undergoing Abdominal Hysterectomy: A Randomized, Double-Blinded Control Trial. *Int J Sci Stud* 2015; 3(8):141-146.
7. Rajan, R., Gosavi S et al. A Comparative Study of Equipotent Doses of Intrathecal Clonidine and Dexmedetomidine on Characteristics of Bupivacaine Spinal Anesthesia." *Journal of Datta Meghe Institute of Medical Sciences University* 2018; 13(1): 4–8.
8. Swain A, Nag D et al. Adjuvants to local anesthetics: Current understanding and future trends. *World J Clin Cases.* 2017; 5(8): 307–323.
9. Jyothi B, Gowda S, Shaikh S. 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. Ituk U, Habib AS. Enhanced recovery after cesarean delivery. *F1000 Faculty Rev*-513. Published 2018 Apr 27.
11. Gupta K, Gupta A et al. Efficiency of nalbuphine as an adjuvant to bupivacaine in lower limb orthopaedic surgery- a prospective study. *Int J Res Med Sci* 2017; 5: 623-6.
12. Tang J, Weinberg L. A Literature Review of Intrathecal Morphine Analgesia in Patients Undergoing Major Open Hepato-

- Pancreatic-Biliary (HPB) Surgery, *Anesth Pain Med*. Online ahead of Print ; 9(6): e94441.
13. Merchea A, Lovely J et al. Efficacy and Outcomes of Intrathecal Analgesia as Part of an Enhanced Recovery Pathway in Colon and Rectal Surgical Patients. *Surgery Research and Practice* 2018; 1-5.
14. Sapate M, Sahu P et al. A randomized, double blind, control study of the effects of adding nalbuphine to spinal bupivacaine for lower abdominal surgeries in elderly patients. *Anaesth Pain Intensive care* 2013; 17:145–148.
15. Mukherjee A, Pal A et al. Intrathecal nalbuphine as an adjuvant to subarachnoid block: what is the most effective dose? *Anesth Essays Res* 2011; 5:171–175.
16. Dubey R, Bisht S. The effect of addition of nalbuphine to intrathecal bupivacaine used to elderly patient in lower abdominal surgeries under spinal anesthesia. *J Evol Med Dent Sci* 2014; 70:14963–14970.
17. Kumaresan S, Raj A. Intrathecal Nalbuphine as an Adjuvant to Spinal Anaesthesia: What is Most Optimum Dose?. *Int J Sci Stud* 2017;5(1):57-60.
18. Tiwari A, Tomar G, Agrawal J. Intrathecal bupivacaine in comparison with a combination of nalbuphine and bupivacaine for subarachnoid block: A randomized prospective double blind clinical study. *Am J Ther* 2013; 20:592-5.
19. 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.
20. Mostafa M, Mohamad M, Farrag W. Which has greater analgesic effect; Intrathecal nalbuphine or intrathecal tramadol. *J Am Sci* 2011;7: 480-4.
21. Culebras X, Gaggero G et al. 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.
22. Rawal N, Nuutinen L, Raj PP. Behavioral and histopathologic effects following intrathecal administration of butorphanol, sufentanil, and nalbuphine in sheep. *Anesthesiology* 1991; 75:1025–1034.
23. Shakooch S, Bhole P. Intrathecal nalbuphine an effective adjuvant for post-operative analgesia. *Innov J Med Health Sci* 2014; 4: 79–82.