ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

Comparison of intrathecal Nalbuphine and Clonidine as adjuvants to Bupivacaine heavy for spinal anesthesia in elective infraumbilical surgeries in adult patients – a prospective study

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Submission: 09-01-2021 Revision: 03-03-2022 Publication: 01-04-2022

ABSTRACT

Background: Post-operative analgesia is a major problem associated with relatively short duration of action of spinal-anesthetics. Intrathecal adjuvants can prolong the duration of analgesia giving better success rate & patient satisfaction. **Aims and Objectives:** To assess the duration of postoperative analgesia with intrathecal bupivacaine supplemented with either nalbuphine or clonidine as adjuvants and also to assess the time of onset, maximum level and duration of sensory and motor blockade, and any postoperative complications. **Materials and Methods:** Following institutional ethical committee approval 60 patients scheduled for elective infra umbilical surgeries duration of less than 2 hours, under spinal anesthesia, were included in this prospective randomized interventional study. Patients were randomly allocated to one of two groups into Group-N received 2.5 ml of 0.5 % hyperbaric bupivacine + 0.5ml of nalbuphine (0.4mg). Group-C received 2.5 ml of 0.5% hyperbaric bupivacine + 0.5 ml of clonidine (30 μg). The onset of sensory and motor blockade, duration of sensory and motor blockade, two-segment regression time from highest level of sensory blockade, and duration of analgesia was recorded. **Results:** Total duration of postoperative analgesia was significantly higher in group-C(351.00 ± 31.00 min) than in group-N(256.00 ± 8.14 min). Though the mean time for onset of sensory and motor block among both groups was not significantly different, the mean time for complete sensory and motor recovery was significantly longer in Group-C than Group-N. **Conclusion:** Intrathecal clonidine has more prolonged analgesia and motor blockade compared to nalbuphine, and hence clonidine can be preferred over nalbuphine as an intrathecal adjuvant.

Key words: Adjuvants; Clonidine; Nalbuphine; Spinal anesthesia

Access this article online

Website: http://nepjol.info/index.php/AJMS

DOI: 10.3126/ajms.v13i4.42201

E-ISSN: 2091-0576

P-ISSN: 2467-9100

INTRODUCTION

In rural and semi-urban areas of the developing countries, spinal anesthesia is the most common anesthetic technique for surgical procedure because due to lack of sophisticated anesthetic equipment, anesthetic gases for general anesthesia, and also for economic reasons. However, post-operative analgesia is a major problem associated with relatively short duration of the action of spinal anesthetics. Hence, early analgesic intervention is needed in post-operative period.

In recent years, the use of intrathecal adjuvants has gained popularity with the aim of prolonging duration of analgesia, better success rate, patient satisfaction, and decreased resources utilization. Various adjuvants including opioids have been used with local anesthetics in spinal anesthesia.

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The first report on the use of intrathecal opioids for acute pain treatment was in 1979 by Wang et al.[1] Various opioids have been used along with bupivacaine to prolong its effect, to improve the quality of analgesia, and to minimize the requirement of post-operative analgesics. Nalbuphine is a semisynthetic opioid with mixed μ antagonist and k agonist properties.[2,3]

Alpha-2 agonists possess analgesic properties and augmentation of local anesthetic effects.[4-6] Perioperative anesthetic and analgesic requirements get reduced to a huge extent by adding opioid or alpha-2 agonists as adjuvants. Clonidine, a partial alpha-2 adrenoreceptor agonist, has long been used to treat hypertension. Addition of clonidine to local anesthetics during spinal anesthesia prolongs the duration of both motor and sensory blockade.[7-9]

Hence, this study was undertaken to compare intrathecal bupivacaine 12.5 mg (0.5%) supplemented with either nalbuphine 0.4 mg or clonidine 30 μg as adjuvants in infraumbilical surgeries with the primary aim to assess the duration of post-operative analgesia and the secondary aim is to assess the time of onset, maximum level and duration of sensory and motor blockade, intraoperative hemodynamic variations, post-operative complications such as post-operative nausea and vomiting, pruritus, respiratory depression, and sedation.

Aims and objectives

This study aims to assess the duration of post-operative analgesia with intrathecal bupivacaine supplemented with either nalbuphine or clonidine as adjuvants and also to assess the time of onset, maximum level and duration of sensory and motor blockade, and any post-operative complications.

MATERIALS AND METHODS

The study was pre-approved by the Institutional Ethics Committee for the final permission. After approval by the Institutional Ethical Committee, 60 patients of the American Society of Anesthesiologist (ASA) physical status Classes I and II, age between 18 and 65 years, scheduled for elective infraumbilical surgeries duration of <2 h, under spinal anesthesia, were included in this prospective randomized interventional study.

Pre-anesthetic checkup was done previous day of the surgery. Patients were evaluated for any systemic disease and laboratory investigations recorded. Patients with ASA Class III and above, history of known sensitivity to the drugs used, patients with gross spinal deformity, peripheral neuropathy or with contraindications to neuraxial block – local/systemic infections, coagulation disorders, hypovolemia, signs of raised intracranial tension, uncontrolled hypertension, pregnant, and obese patients were excluded from the study.

The procedure of SAB explained to the patient and written informed consent was obtained. Patients were randomly allocated to one of the two groups using computer generated random numbers (n=30). Group N (n=30) receives 2.5 ml of 0.5% hyperbaric bupivacaine + 0.5 ml of nalbuphine (0.4 mg of nalbuphine with 0.1 ml of normal saline) = 3 ml. Group C (n=30) receives 2.5 ml of 0.5% hyperbaric bupivacaine + 0.5 ml of clonidine (30 μg of clonidine in 0.2 ml with 0.3 ml of normal saline) = 3 ml. The baricity of the study drugs varies slightly but was statistically insignificant.

All the patients fasted for at least 6 h for solids and 2 h for clear liquids before the procedure. Basal vital data such as temperature, pulse rate (PR), blood pressure (BP), respiration rate (RR), and oxygen saturation (SpO_2) were recorded. After securing intravenous (20G) access in dorsum of the hand, 10 ml/kg body weight of ringer lactate infused over 30 min. The patient was shifted to the OT table, all monitors were connected to the patient and baseline PR, BP, and RR recorded.

SAB was performed and the study drug injected in L3/4 or L4/5 intervertebral space, using a 25 gauge Quincke spinal needle, in the lateral position, maintaining aseptic precautions, according to the standard institutional protocol. Following free flow of CSF, drugs were injected slowly over 10 s. Thereafter, patients were immediately placed in the supine position for surgery. Intraoperative fluid replacements were given as necessary depending on the blood loss and hemodynamic parameters. Intraoperative hypotension and bradycardia were managed with crystalloids and atropine 0.6 mg, respectively. In case of any respiratory depression, oxygen through facemask at 6 L was administered. Advanced equipment and drugs for resuscitation, airway management, and ventilation were kept ready.

The onset of sensory blockade and motor blockade, duration of sensory blockade, two-segment regression time from the highest level of sensory blockade, duration of motor blockade and duration of complete analgesia, and duration of effective analgesia are recorded.

The changes in PR, systolic and diastolic BP, SpO_2, and respiratory rate were recorded at 0, 5, 10, 20, and 30 min and then at 30 min intervals up to 120 min after SAB. Any side effects in the form of hypotension, bradycardia, respiratory depression (judged by respiratory rate <10 or SpO_2 <90%), nausea and vomiting (in presence of stable

hemodynamic parameters), sedation (Ramsay sedation scale), and pruritus were recorded.

Intensity of pain was assessed by visual analog scale (VAS) score at 0, 10, 15, 30, and 60 min and then at 30 min intervals until the patient received a rescue analgesic.

The level of sensory block was evaluated by loss of pinprick sensation. The test was performed every 5 min till loss of discrimination to pinprick for the first 10 min and then every 10 min until its full recovery. Onset of sensory block was taken as time interval between the complete injections of local anesthetic solution to the achievement of complete loss of sensation at T10 dermatome level. Maximum level of sensory analgesia was taken as highest level of cephalad spread of analgesic. Two-segment regression time was noted. Total duration of sensory block was taken from onset of sensory block to return of pin prick at T10.

Quality of motor blockade

The motor blockade was assessed using modified Bromage scale (1978).

Onset time is to achieve Bromage score 1, duration of total motor blockage was recorded. After the subarachnoid blockade, all the patients were monitored for pulse rate, BP, RR, and SpO_2 at 1, 5, 10, 20, 30, 60, 90, and 120 min intraoperatively and every hour postoperatively until the effect of subarachnoid block was disappeared.

Duration of complete analgesia is the time from intrathecal injection to first pain (VAS 1–3) and was noted.

Duration of effective analgesia is the time from intrathecal injection to unbearable pain when rescue analgesia was given in the form of inj. diclofenac sodium 1.5 mg/kg intramuscularly and the time of rescue analgesia was noted.

During the procedure, all the patients were infused with appropriate quantity of intravenous fluids. Any untoward effects such as bradycardia, hypotension, nausea, vomiting, and shivering were noted and treated appropriately.

All the statistical methods were carried out through the SPSS for Windows (version 16.0).

Statistical analysis

All the statistical methods were carried out through the SPSS for Windows (version 16.0).

RESULTS

In our study, we observed that the mean time for onset of sensory block at shin of tibia in Group N was 67±11.49 s and 64.67±14.08 s in Group C (Table 1), whereas the mean time for onset of motor block in Group N was 83±14.42 s and in Group C was 82.67±15.52 s (Table 2). With regard to the highest sensory level attained, both groups were comparable (Table 3).

The time for two segment regression was 72±9.15 min in Group N when compared to 72.3±10.44 min in Group C. The time for complete sensory recovery in groups was 211.33±16.13 min in Group N and 251.33±25.43 min in Group C (Table 4 and Figure 1). The mean of total duration of motor block in Group N was 195.83±18.57 min compared to 232.00±25.51 min in clonidine group (Table 5 and Figure 2). Total duration of post-operative analgesia was 256.00±8.14 min in Group N and 351.00±31.00 min in Group C (Table 6 and Figure 3). In both the groups, hemodynamic stability was maintained and side effects were comparable.

DISCUSSION

Neuraxial anesthetic techniques are preferred for infraumbilical surgeries due to their rapid onset of surgical anesthesia with complete muscular relaxation. It is also beneficial in patients of anticipated difficult airway or who are suffering from comorbid conditions. These advantages are sometimes offset by a relatively short duration of the action of local anesthetics.

The duration of subarachnoid block can be improved using intrathecal adjuvants in the form of opioid analgesics or non-opioid drugs, which act synergistically with local anesthetic agents to intensifying the sensory block without increasing the level of sympathetic block as they act independently through different mechanism. Several clinical studies have shown that opioids and α2-adrenergic agonists are able to do so.

Nalbuphine is a semi-synthetic opioid agonist-antagonist analgesic of the phenanthrene series. It is an agonist-antagonist opioid that is structurally related to oxymorphone and naloxone. It binds to μ-receptors, as well as to κ- and δ-receptors. It acts as an antagonist at the μ-receptor and as an agonist at the κ-receptor. Activation of supraspinal and spinal κ-receptors results in limited analgesia, respiratory depression, and sedation. Nalbuphine, like other agonist-antagonist compounds, interferes with the analgesia produced by pure μ-agonists.

Clonidine hydrochloride, an imidazoline derivative, was originally developed as a nasal decongestant and vasoconstrictor. Its hypotensive and bradycardia effects were first appreciated in 1962. It is a centrally acting adrenergic agonist that lowers BP by decreasing basal

Table 1: Onset time of sensory block

Characteristics	Time (Sec)	Group N	Group C	"P" value	Inference
Onset of sensory block	21–30	0	0		
	31–40	2	2		
	41–50	2	6		
	51–60	7	8		
	61–70	11	7		
	71–80	8	4		
	81–90	0	3		
	Range	43–80	40–90	P=0.791	NS
	Mean	67	64.67		
	SD	11.49	14.08		

Table 2: Onset of motor block

Characteristics	Time (Sec)	Group N	Group C	"P" value	Inference
Onset of motor block (Sec)	40–50	2	1		
	51–60	2	2		
	61–70	2	8		
	71–80	9	6		
	81–90	10	5		
	91–100	4	6		
	101–110	1	2		
	111–120	0	0		
	Range	50–110	50–110	P=0.902	NS
	Mean	83	82.67		
	SD	14.42	15.52		

Table 3: Maximum level of sensory block

	Sensory height	Number of patients			
		Nalbuphine	%	Clonidine	%
Maximum cephalic spread of sensory block	T4	3	10	1	3.3
	T6	5	16.7	3	10
	T8	18	60	24	80
	T10	4	13.3	2	6.6
	T12	0	0	0	0

Table 4: Duration of sensory block

Characteristics	Time (Min)	Group N	Group C	"P" value	Inference
Duration of sensory block (Min)	161–180	2	0		
	181–200	10	1		
	201–220	12	4		
	221–240	6	7		
	241–260	0	8		
	261–280	0	6		
	281–300	0	4		
	Range	180–240	200–290	P<0.0005	S
	Mean	211.33	251.33		
	SD	16.13	25.43		

sympathetic nervous system activity. It was introduced first in Europe in 1966 and subsequently in the U.S. for use as an antihypertensive agent.

The analgesic effect of clonidine is mediated spinally through the activation of post-synaptic α2-adrenergic receptors in substantia gelatinosa of the spinal cord to enhance the sensory and motor blocks of bupivacaine without increasing the incidence of respiratory depression while intrathecal nalbuphine activates opioids receptors in the dorsal gray matter of spinal cord (substantia gelatinosa) to modulate the function of afferent pain fibers.

Bupivacaine acts mainly by blockade of voltage gate Na+ channels in the axonal membranes and presynaptic inhibition of calcium channels. Synergism is characterized

Table 5: Duration of motor block

Characteristics	Time (Min)	Group N	Group C	"P" value	Inference
Duration of motor block (Min)	151–170	4	0		
	171–190	12	3		
	191–210	8	4		
	211-230	6	7		
	231–250	0	8		
	251–270	0	8		
	Range	160–230	180–270	P<0.0005	S
	Mean	195.83	232		
	SD	18.57	25.52		

Table 6: Duration of effective post-operative analgesia

Characteristics	Time (Min)	Group N	Group C	"P" value	Inference
Duration of effective post-operative analgesia (min.)	226–250	14	0		
	251–275	16	0		
	276–300	0	3		
	301–325	0	5		
	326–350	0	7		
	351–375	0	9		
	376–400	0	5		
	401–425	0	1		
	Range	240–270	290–410	P<0.0005	S
	Mean	256	351		
	SD	8.14	31		

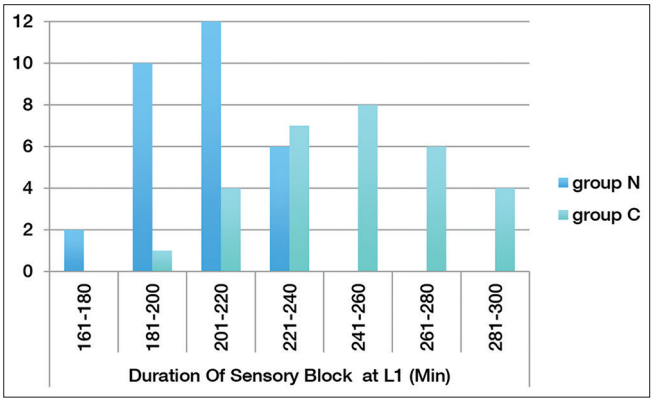

Figure 1: Duration of sensory block

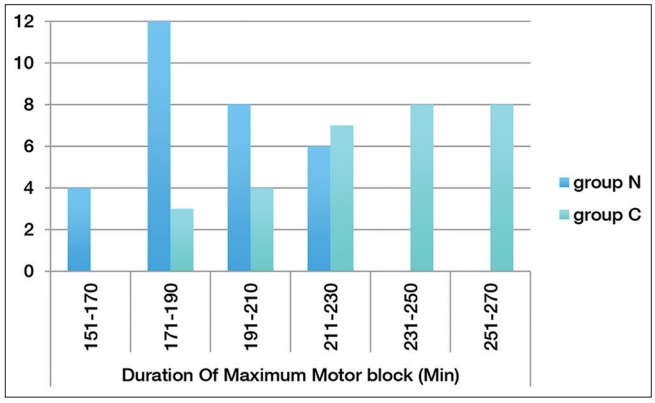

Figure 2: Duration of sensory block

by enhance somatic analgesia without affecting the cephalic spread of bupivacaine.

It was observed in the previous studies with clonidine that 30 μg of clonidine was the minimum dose to provide significant increase in the duration of sensory and motor block and without increasing the incidence of side effects.

Various authors have used intrathecal nalbuphine in doses from 0.4 mg to 2 mg. Mukherjee et al.,[8] have compared three doses of 0.2, 0.4, and 0.8 mg nalbuphine along with 12.5 mg of 0.5% hyperbaric bupivacaine. The authors concluded that a dose of 0.4 mg and 0.8 mg prolongs the duration of post-operative analgesia but 0.4 mg had least incidence of side effects. Tiwari et al., [9]have compared 0.2 mg and 0.4 mg of nalbuphine along with bupivacaine for intrathecal anesthesia and found out that 0.4 mg of nalbuphine prolonged the post-operative analgesia.

Results of our study concurs with the study done by Mostafa et al.,[10] who compared nalbuphine 0.8 mg with 25 μg fentanyl in patients undergoing cesarean section found that the duration of post-operative analgesia in nalbuphine as 231.83±15.73 min. Another study by Gupta et al.,[11] using nalbuphine 2 mg the time to first request for analgesia was 278.7±29.6 min in fentanyl group

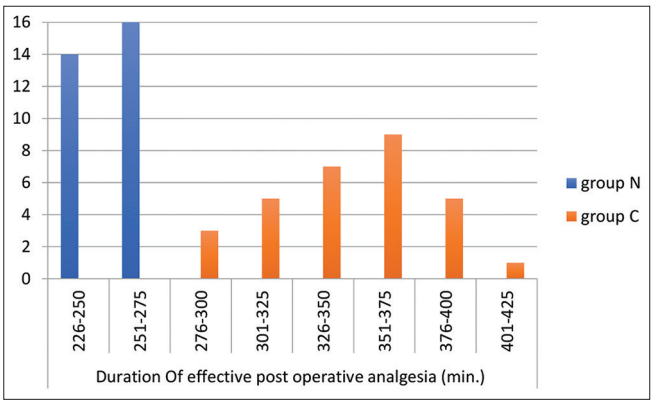

Figure 3: Duration of effective post-operative analgesia

and 318.6±21.9 min in patients of nalbuphine group. Prolonged duration of analgesia in the nalbuphine group in this study compared to our study is due to higher dose of nalbuphine used.

In a study conducted by Strebe[12] et al., using three different doses of clonidine for spinal anesthesia, group using dose of 37.5 μg duration of post-operative analgesia was 342±75 min whereas in our study, it is 351.00±31.00 min. Results of this study well correlated with our study.

Saxena et al.,[13] conducted a study, who used different doses of clonidine as 15 μg, 30 μg, and 37.5 μg. It was observed that the duration of analgesia was lesser for the group receiving 15 μg of clonidine than the group receiving 30 μg, which was less than the 37.5 μg of clonidine group. It was concluded that the duration of analgesia is dose dependent. Duration of analgesia in group which received 30 μg clonidine was 285.60±36.59 min.

In our study, the total duration of post-operative analgesia was 256.00±8.14 min in nalbuphine group and 351.00±31.00 min in clonidine group. The difference is highly significant (P<0.005). All the above-mentioned studies support our results.

Hence, in our study, we have selected 0.4 mg of nalbuphine to compare with 30 μg of clonidine as intrathecal adjuvant.

The hypothesis used for our study was the alternate hypothesis, with clonidine producing more prolonged post-operative analgesia than nalbuphine.

Limitations of the study

Sample size was not adequate for the present study, hence, more studies need to be done to get conclusive results.

CONCLUSION

After comparing 30 μg of clonidine with 0.4 mg of nalbuphine as adjuvants to 0.5% hyperbaric bupivacaine 2.5 ml, in adult patients for infraumbilical surgeries, it is concluded that – intrathecal clonidine has more prolonged analgesia and motor blockade compared to nalbuphine, and hence, clonidine can be preferred over nalbuphine as an intrathecal adjuvant.

ACKNOWLEDGMENT

The authors acknowledge assistance of Head of the Department, all staff members and postgraduates of the department of Anesthesiology of JSS Hospital, Mysuru in undertaking this study.

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Authors Contribution:
GBK- Concept and design of the study, prepared first draft of manuscript, reviewed the literature, and manuscript preparation; **MBP-** Interpreted the results, reviewed the literature, and manuscript preparation; **AHM-** Concept, coordination, statistical analysis and interpretation, preparation of manuscript, and revision of the manuscript; **SKKG-** Reviewed the literature and manuscript preparation; **ND-** Concept, coordination, statistical analysis, and interpretation; and **NVB-** Prepared first draft of manuscript

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Source of Support: None, **Conflicts of Interest:** None.