ORIGINAL ARTICLE

Comparison of 0.4 mg versus 0.6 mg of Intrathecal Nalbuphine as an Adjuvant to Hyperbaric Bupivacaine in Lower Abdomen and Lower Limb Surgeries

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Abstract:

Background: Intrathecal administration of nalbuphine causes lower incidences of respiratory depression, nausea or vomiting, pruritus when compared to other opioids. Previous studies have compared various doses of nalbuphine including higher doses as an adjuvant to local anaesthetic. *Aim and Objectives:* To compare different doses of nalbuphine and to find out the most optimum amount. *Material and Methods:* One hundred twenty patients were assigned to Group A or B, each comprising of sixty patients after randomization. Group A, B patients received 0.4, 0.6 mg of nalbuphine respectively as an adjunct to 0.5% hyperbaric bupivacaine 3 ml. Primary outcomes were sensory, motor block duration, post-operative pain relief while secondary outcomes were assessment of haemodynamic parameters. Undesirable effects namely pruritus, shivering, nausea, vomiting were noted if any. *Results:* The onset of sensory, motor blocks didn't differ significantly (p=0.801, 0.616). However, the span of sensory, motor block, and analgesia after surgery were significantly more in group B (p=0.0005). Group A required more rescue analgesics (p=0.0005). The pulse rate was significantly lesser in group B, although it was clinically insignificant. The mean arterial pressures didn't differ significantly (P>0.05). *Conclusion:* Nalbuphine 0.6 mg significantly prolonged the span of sensory, motor blocks, and analgesia after surgery with stable haemodynamics and negligible incidence of nausea, vomiting. We believe that 0.6 mg is the optimum amount of nalbuphine as a supplement in spinal anaesthesia.

Keywords: Nalbuphine, Opioids, Adjuvant, Intrathecal Injection

Introduction:

Subarachnoid block is a type of central neuraxial block frequently advocated for abdominal and lower-limb surgical procedures. Although various regional blocks of both surface landmarks and ultrasound-guided techniques are available, the subarachnoid block is still a preferred technique because of its ease of administration and lesser time consumption. Bupivacaine, a local anaesthetic has duration of action of about 90-120 minutes only. Hence, adjuvants are added to overcome this drawback as well as to provide postoperative analgesia. The commonly added opioid adjuvants are fentanyl, morphine, buprenorphine, tramadol and nalbuphine.

The use of opioids intrathecally dates back to 1979 where Wang *et al.* [1] used morphine. Since then, various opioids such as morphine, nalbuphine, fentanyl, buprenorphine, sufentanil and tramadol have been evaluated [2-7]. Intrathecal administration of nalbuphine results in lower incidences of nausea, vomiting, respiratory depression and pruritis when compared to other opioids [8].

Mukherjee *et al.* have analysed the efficacy of nalbuphine by comparing three different doses (0.2, 0.4, 0.8 mg) as an adjunct to bupivacaine and concluded that 0.4 mg was most effective without side effects when compared to 0.8 mg [9].

However, another subsequent study observed that 0.8 mg was optimum for duration of analgesia as well as safe when compared to 1.6 or 2.5 mg [10]. Hence, we have taken this study to find whether 0.6 mg would be better than 0.4 mg or not?

Material and Methods:

After the approval received from Institutional Ethics Committee, the study was prospectively registered with Clinical Trials Registry (CTRI/2019/01/017240). This clinical study was carried out on a total of 120 patients of American Society of Anaesthesiologists (ASA) I and II physical status, 60 in each group, after obtaining the informed consent. Patients of 18–60 years of age (both male and female) were included. Unwilling patients, pregnant population, patients with any contraindications to subarachnoid block were excluded. After assessment, patients were allotted to either Group A or B by sealed envelope technique of randomisation. Group A received hyperbaric bupivacaine 0.5% (3 ml) with 0.4 mg (0.4 ml) of nalbuphine and 0.2 ml of isotonic saline while Group B received the same amount of bupivacaine with 0.6 mg (0.6 ml) of nalbuphine. Hence, total volume of 3.6 ml was administered for all patients. Nalbuphine (1 ml=10 mg) was first diluted to 10 ml to make it 1mg/ml and 1 ml of this was further diluted to 10 ml to make it 0.1 mg/ml. Preparation of injection was done by another anaesthesiologist who was not involved in any other part of study to ensure double-blinding. All the patients were premedicated with tablet ranitidine 150 mg and metoclopramide 10 mg. On the day of surgery, 18 G intravenous cannula was secured for all the patients and baseline vitals (heart rate, blood pressure, SpO_2, ECG) were checked and continuously monitored and recordings made at every 5 minutes during the first half-an-hour, every 10 minutes during the next half-an-hour and then every 15 minutes for the next hour and finally at 30 minutes till the end of surgery. Preloading with 10 ml/kg of lactated Ringer's solution was carried out for all the patients before performing the block. Spinal anaesthesia was performed by providing the patients a comfortable sitting position, with 25 GQuincke needle at L3-L4 or L4-L5 level, taking aseptic precautions. The completion of injection was noted as "Zero time". Times to onset, block duration (sensory and motor) were noted. Sensory block was evaluated by pinprick/spirit swab, while motor block was graded as per the modified Bromage scale. Ramsay sedation scoring was used for grading the level of sedation and pain during the post-operative period was evaluated by Visual Analogue Scale (VAS). Adverse effects viz. nausea/vomiting 0: no symptoms; 1: symptomatic, requiring no treatment and 2: symptomatic, requiring treatment as well respiratory depression (rate<12/minute or saturation<92%), pruritus (0: none, 1: mild, 2: moderate, 3: severe) were recorded if any.

Sensory blockade was assessed using the pinprick method or using spirit swab which was done every one minute till T6 level is reached and surgery was allowed to proceed only after achieving an adequate level of block. The onset of sensory block was taken from "zero time" to achievement of sensory level at T6 and the duration of sensory block was defined as the time from the highest sensory block to regression of two segments. Achievement of grade 3 motor block was taken as

the time of commencement of the block and total duration was taken from this time to regression to Grade 6. Pain during the post-operative period was evaluated by VAS at 30 minutes interval until first rescue analgesia (intravenous tramadol 50 mg if VAS >4) was given and noted as the end-point of duration of analgesia.

Onset time of sensory blockade (min) in a previous study using 0.4 mg nalbuphine as an adjuvant was 1.63 ± 0.24 [9]. Assuming alpha=0.05, beta = 0.8, error = 9% (0.09), sample size estimated was 60 per group. The data were analysed by Statistical Package for Social Science (SPSSvs23). Quantitative data like age, weight, blood pressure, pulse rate, span of analgesia, onset and span of motor and sensory block were analysed using descriptive statistics and student 't' test was used for the comparison of two groups. Qualitative data viz. pruritus, nausea, vomiting, shivering were analysed using Chi-square test.

Results:

The groups were comparable in parameters such as age, gender, weight, ASA status (Table 1). The duration of surgery was also comparable between groups (mean 83.2 vs 85.6 minutes, SD 15.6 vs 18.8, t-value=0.766, p=0.445).The onset of sensory and motor block did not differ significantly (Table 2). However, the span of sensory, motor block, and post-operative pain relief were significantly more in group B (Table 3). Also, Group A required more rescue analgesics (total 5400 mg in Group A vs 3150 mg in group B) which was statistically significant (Table 4). The mean VAS were significantly higher in Group A until 12 hours and comparable after that, while sedation scores were comparable between groups. The pulse rate was significantly lesser in group B (p=0.0005). However, it was clinically insignificant as it was above 55 per minute (Fig.1) and did not require any intervention. The mean arterial pressures were comparable between groups (Fig.2). Pruritis was observed in one (1.7%) patient in group B versus none in group A and was statistically insignificant (p=1.000). The incidences of nausea, vomiting were more in group B, albeit with no clinical (Grade 0, 1 only) or statistical significance (13.3% vs 1.7% p= 0.032). No patient in the study had shivering.

Table 1: Comparison of Demographic Variables, ASA Status

Parameters	Group A	Group B	Mean	*p*
Male	29 (48.3%)	30 (50.0%)	59 (49.2%)	0.855
Female	31 (51.7%)	30 (50.0%)	61 (50.8%)	
Mean Age (in years)	39.6 ± 12.4	39.3 ± 11.4		0.606
Mean Weight (in Kg)	62.5 ± 9.6	61.5 ± 5.2		0.508
ASA status	ASA I - 43 (71.7%)	ASA I – 36 (65.8%)	ASA I – 79 (65.8%)	0.178
	ASA II - 17 (28.3%)	ASA II – 24 (34.2%)	ASA II – 41 (34.2%)	

Table 2: Comparison of Onset of Sensory, Motor Block by Unpaired t-test

		N	Mean ± S.D	t	*p*
Onset of Sensory Block (min)	**Group A**	60	1.9 ± 0.5	0.253	0.801
	Group B	60	1.9 ± 0.5		
Onset of Motor Block (min)	**Group A**	60	3.5 ± 1.2	0.503	0.616
	Group B	60	3.4 ± 1.2		

Table 3: Comparison of Onset of Sensory, Motor Block by Unpaired t-test

		N	Mean ± S.D	t	*p*
Duration of Sensory Block (min)	**Group A**	60	118.9 ± 14.8	10.459	0.0005
	Group B	60	152.8 ± 20.3		
Duration of Motor Block (min)	**Group A**	60	160.6 ± 27.9	6.135	0.0005
	Group B	60	190.3 ± 25.0		
Duration of Post-Operative Analgesia (min)	**Group A**	60	171.1 ± 21.9	10.261	0.0005
	Group B	60	210.3 ± 19.8		

Table 4: Comparison on Rescue Analgesics

			Group A	Group B	Total	$\chi 2$	*p*
Number of Rescue Analgesia	**I**	**Count (%)**	22(36.7)	57(95.0)	79(65.8)	45.748	0.0005
	II	**Count (%)**	26(43.3)	3(5.0)	29(24.2)		
	III	**Count (%)**	12(20.0)	0(0)	12(10.0)		
Total		**Count (%)**	60(100.0)	60(100.0)	120(100.0)		

$\chi 2$

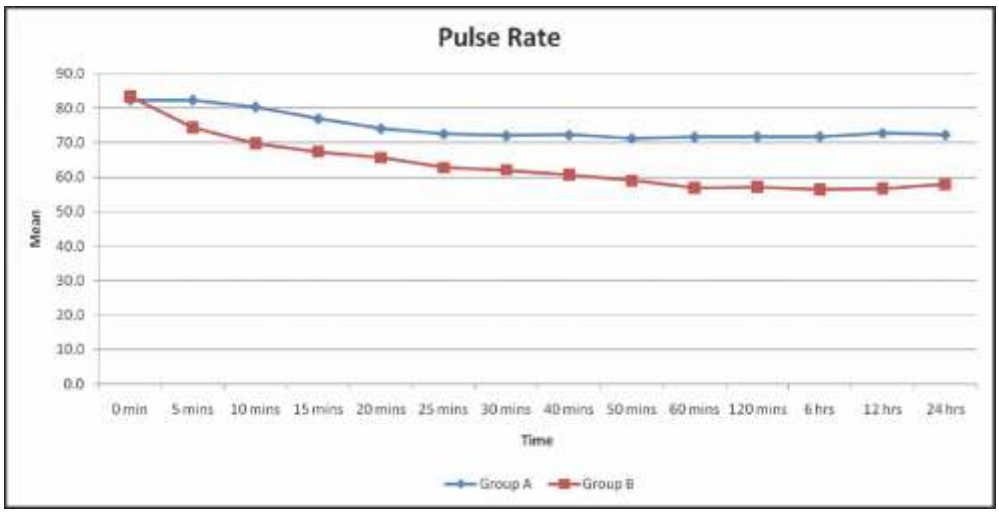

Fig. 1: Comparison of Pulse Rate between Groups: Group B had significantly lesser values than Group A

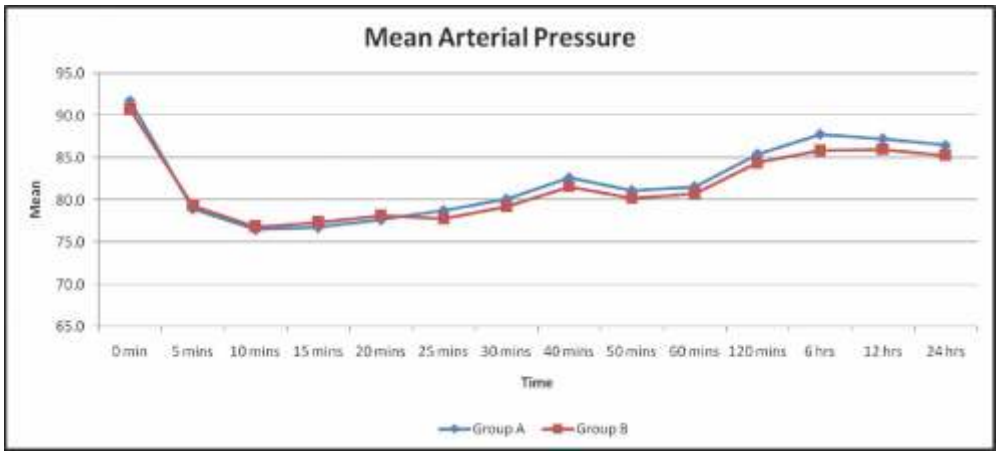

Fig. 2: Comparison of Mean Arterial Pressure between Groups

Discussion:

In our study, we observed that 0.6 mg nalbuphine as a supplement to intrathecal hyperbaric bupivacaine 0.5% (3 ml) significantly prolonged the span of postoperative pain relief thereby reducing the consumption of rescue analgesics compared to 0.4 mg, with stable haemodynamics and negligible incidence of nausea, vomiting**.** Mukherjee *et al*. [9] reported that 0.8 mg nalbuphine resulted in the maximum duration of analgesia (270 minutes) followed by 0.4 mg (240 minutes) and 0.2 mg (210 minutes) as a supplement to 0.5% bupivacaine 2.5 ml, while in our study, the mean duration of post-operative analgesia were 171, 210 minutes respectively for 0.4, 0.6 mg of nalbuphine added to 0.5% bupivacaine 3 ml. Also, the undesirable effects viz. bradycardia, hypotension, pruritis, nausea, and vomiting were significantly more in 0.8 mg group of that study, resulting in a conclusion

that 0.4 mg was the optimum amount [9]. We have used tramadol as a rescue analgesic despite one of our secondary objectives being to note the incidences of nausea and vomiting as we commonly prescribe it for postoperative analgesia in this set of patients. Although the incidences of nausea, vomiting were more in group B while requiring lesser doses of tramadol, it was clinically and statistically insignificant. In contrast to the study by Mukherjee *et al*. [9], Jyothi *et al.* [10] subsequently observed that 0.8 mg was the optimum dose regarding prolongation of duration of analgesia as well as safety when compared to 1.6 or 2.5 mg as a supplement to 0.5% bupivacaine 3 ml.

Previous studies have used higher doses of nalbuphine in various populations [10-11]. While Jyothi *et al*. [10] have used up to 2.5 mg of nalbuphine, Gupta *et al*. [11] have compared nalbuphine (2 mg) versus fentanyl (25 mg) as a supplement to 0.5% bupivacaine (3.5 ml) and adjudged that nalbuphine produced more duration of analgesia, motor block without any adverse effects. Other studies have used 0.8 mg or above of nalbuphine intrathecally, even in the pregnant population [12-13] and observed that nalbuphine 0.8 mg was optimum and safer than morphine 0.2 mg [12] or better than fentanyl 25 mg [13]. Indeed, a study has used 1 mg of nalbuphine plus 0.1 mg of morphine in pregnant population [14].

Tiwari *et al.* [15] compared 0.2 or 0.4 mg of nalbuphine versus placebo as a supplement to 0.5% hyperbaric bupivacaine (2.5 ml) and observed that nalbuphine (0.4 mg) significantly extended the span of pain relief without any adverse effects. Sapate *et al.* [16] observed that 0.5 mg nalbuphine as an additive provided a higher-grade quality of block in contrast to 0.5% hyperbaric bupivacaine (3 ml) alone, in patients aged between 50 and 70 years without any side-effects. After analyzing all these studies [9-16], we have chosen 0.6 mg as a comparator dose to 0.4 mg and avoided 0.8 mg or higher doses for comparison as there is a possibility of ceiling effect.

Limitations:

Main limitation of our study is that we have not added a placebo group in our study despite choosing appropriate doses of nalbuphine for comparison after careful analysis of previous studies. We avoided a placebo because of ethical concerns and believe that it would not have produced a major impact on the study. We have not chosen newer local anaesthetics such as levo-bupivacaine or ropivacaine (available as isobaric in our geographical area) because we commonly preferred hyperbaric bupivacaine at the time of commencing this study.

Conclusion:

We conclude that both doses of nalbuphine 0.4 mg and nalbuphine 0.6 mg are effective adjuvants to hyperbaric bupivacaine in spinal anaesthesia. Nalbuphine 0.6 mg resulted in significant extension of span of sensory, motor blockade and postoperative pain relief and reduction in the necessity of analgesic aids, with stable haemo-dynamics and negligible incidence of nausea, vomiting when compared to 0.4 mg. Therefore, we believe that nalbuphine 0.6 mg is the optimum dose as a supplement to local anaesthetics in intrathecal administration.

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