Original Research Article

A randomized double blind comparative study of analgesic efficacy of different doses of intrathecal nalbuphine in patients undergoing abdominal hysterectomy

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Abstract

Background: To assess and compare the analgesics efficacy of two different doses of Intrathecal nalbuphine (1 mg and 2mg) when added to hyperbaric bupivacaine(17.5mg) as compared to bupivacaine alone in spinal anesthesia for abdominal hysterectomy. **Methods:** After taking IEC approval and informed written consent a prospective randomized double blind controlled study was conducted on 75 patients of ASA I-II female aged b/w 30-60 years weight 30 to 70 kg and height≥ 140 cm. All patients were randomly divided into 3 groups; Group C: Bupivacaine 0.5%, 3.5ml (n=25) [control group], Group N1: Bupivacaine 0.5%, 3.5ml plus 1mg Nalbuphine (n=25) Group N2:Bupivacaine 0.5%, 3.5ml plus 1 mg Nalbuphine (n=25). **Results:** All the three groups were statistically comparable regarding demographic and hemodynamic profile. Time to T6 (sensory onset) was 6.8±1.00 min. in group C, 6.56±0.92 min in group N1 and 6.08± 0.91in group N2. The difference was statistically significant b/w group C and group N2 [P=0.009]. Duration of analgesia (Time to first pain) was 190.01±15.20 min in group C, 240.52±19.71 min in group N1 and 281.92±31.64 min in group N2. The difference was statistically significant among all the three groups, [P=0.00]. 100% complete success rate was achieved in three groups. **Conclusions:** We conclude that Nalbuphine 2mg as an Intrathecal adjuvant to bupivacaine seems to be promising technique in providing prolonged postoperative analgesia following abdominal hysterectomy in spinal anesthesia

Key Word: Abdominal hysterectomy, Analgesia, Nalbuphine , Spinal anaesthesia,

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INTRODUCTION

In initial days of anaesthesia, it was common and only method to use general anaesthesia for all types of surgeries, whether it happened to be short or long, or of upper or of lower part of body [1]. Amongst all regional techniques, the spinal anaesthesia emerged as a convenient, fast and effective method for variety of surgical procedures and especially for lower abdominal surgeries. Spinal anaesthesia is very economical and easy to administer. Studies have shown that resumption of the different physiologic functions were more rapid, hospital stay shorter and compliance greater when abdominal gynaecologic surgeries were performed under spinal anaesthesia than with general anesthesia[2]. However, postoperative pain control is a major problem because spinal anaesthesia using only local anaesthetics is associated with relatively short duration of action, and thus early analgesic intervention is needed in the postoperative period [2]. Adjuvants are drugs that increase the efficacy or potency of other drugs when given

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concurrently. Neuraxial adjuvants are used to improve or prolong analgesia and decrease the adverse effects associated with high doses of a single local anaesthetic agent. Hence aims of our study was to assess and compare the analgesic efficacy of two different doses of intrathecal nalbuphine (1mg and 2mg) when added to hyperbaric bupivacaine (17.5mg) as compared to bupivacaine alone in spinal anaesthesia for abdominal hysterectomy.

MATERIALS AND METHODS

A prospective randomized double blind controlled clinical study was conducted in the Department of Anaesthesiology, Pannadhaya Zanana Hospital attached to RNT Medical College, Udaipur (Raj.) after the approval of institutional ethical committee (IEC) and obtaining written informed consent from all patients before participation.

Sample Size: Sample size is calculated on the basis of previous study Pallavi Ahluwalia *et al* [3], a minimum sample size of 19 patients in each group is required to study the difference of 20 minutes in duration of analgesia in two groups at 80% power and Confidence interval of 95%. We are taking sample size of 25 patients in each group to compensate for dropouts.

Study Population: The present study was conducted on 75 patients of ASA I-II of both sex, posted for total abdominal hysterectomy (Duration of surgery 30-90min.), aged between 30-60 yrs. weight 30 to 70 kg and height ≥ 140 cm. All patients under study were subjected to a detailed pre-anaesthetic examination and investigations were carried out accordingly during this evaluation.

Group Allocation: 75 patients were randomly divided into three groups (25patients in each group) by sealed envelope techniques, based on intrathecal dose regime as follows:

- **Group C**: Intrathecal Bupivacaine 0.5% (Hyperbaric) 3.5ml (17.5mg), (n=25) [control group].
- **Group N1**: Intrathecal Bupivacaine 0.5% (Hyperbaric) 3.5ml (17.5mg) plus 1 mg Nalbuphine (n=25)
- **Group N2**: Intrathecal Bupivacaine 0.5% (Hyperbaric) 3.5ml (17.5mg) plus 2 mg Nalbuphine (n=25)

Double blindness: To ensure double blindness to the study, the intrathecal drugs was prepared by the one anaesthesiologist as per group allocation and also performed all subarachnoid block and was not further involved in the study. Another anesthesiologist, conducting the study recorded all the data who was not aware of group allocation. The patient, surgeon and postoperative staff were also not aware of group allocation.

Anaesthesia technique: After taking informed written consent from patient and confirming overnight fasting, patient was taken on the operation table, connected to monitors and baseline vitals like pulse rate, blood pressure, respiratory rate were recorded. ECG and pulse oximetry (SpO_2) were monitored continuously, while non-invasive blood pressure (NIBP) was measured at 5 min. intervals or earlier if needed. After a 20gauge intravenous (IV) cannula inserted at the forearm level, Lactated Ringer's solution was administered as a bolus of 10 ml/kg before subarachnoid block to all patients. Vital parameters just before lumbar puncture were noted. Spinal anaesthesia was performed at L3-L4 interspace with the patient in left lateral position by using a 25 Gauge Quincke needle in midline under strict aseptic conditions. Free flow of cerebrospinal fluid was verified before injection of the anaesthetic solution, which was administered over 30 seconds according to allocated group. End of intrathecal injection was taken as time zero for further data recording. All patients were immediately placed in supine position following the injection with a 15° head down tilt to achieve level of block of T5-T6. Monitoring was done using continuous electrocardiography,heart rate, non-invasive blood pressure, continuous pulse oximetry and patients were given 5.0 L/min of oxygen by venti-mask. Intravenous fluid and blood were administered as per need.

Sensory Block: Sensory block was assessed by pinprick method using 24 gauge hypodermic needle and graded as:1- Sharp pain, 2- Touch sensation only, 3- Not even touch sensation. Grade 2 was considered as sensory block The onset of sensory block was defined as the time from the intrathecal injection of the study drug to the time taken to achieve the T6 level of sensory block. Peak sensory level and time taken to achieve it was also noted. Sensory-motor block was assessed at 2, 4, 6, 8 and 10 minutes after subarachnoid block and at the end of surgery, thereafter every 30 minutes postoperatively till complete sensory and motor recovery achieved. Duration of sensory block was defined as the time taken for the sensory block to regress upto S1 dermatome (i.e. lateral side of foot) from the end of spinal injection.

Motor Block: Motor block was assessed using Modified Bromage Score at the same time interval when sensory block was assessed. Onset of motor block was defined as the time from intrathecal injection of the study drug to the time taken to achieve complete motor block (Time to Bromage 3). Duration of motor block was assessed by recording the time elapsed from the end of spinal injection to return to Bromage 0.

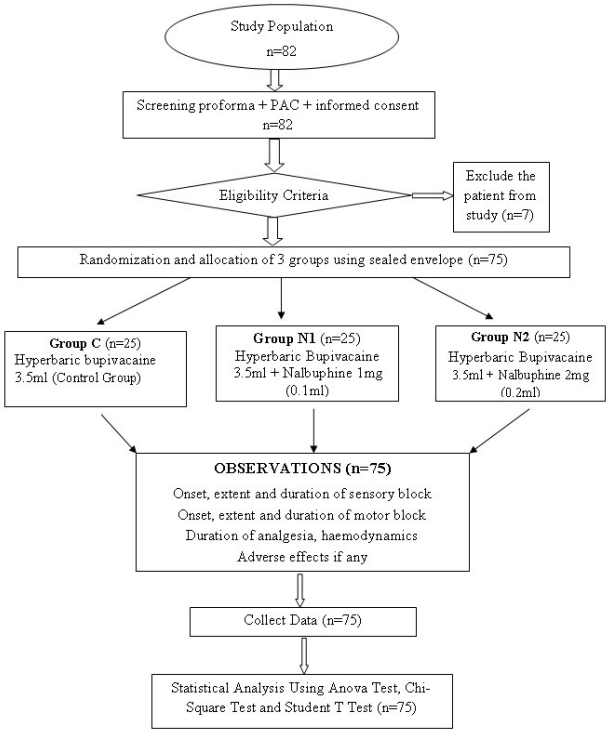
Modified bromage Score	Criteria
0	Able to move hip, knee, and ankle
1	Unable to move hip, able to move knee and ankle
2	Unable to move hip and knee, able to move ankle
3	Unable to move hip, knee, and ankle

When adequate spinal block (T6 Sensory level and Bromage score 2 or 3) was achieved, the time from the end of intrathecal injection to readiness for surgery was recorded. Then the patient was positioned for planned surgery.

Analgesia Duration: Time from intrathecal injection to the first complaint of postoperative pain was defined as duration of analgesia and noted. Intramuscular injection Diclofenac 75mg and / or Tramadol 100 mg (IV) was given as rescue analgesia in postoperative period as per hospital protocol. Patient was kept under observation for total period of 24 hours to look for any side effects. The incidence of perioperative adverse effects such as nausea, vomiting (PONV), shivering, pruritus, respiratory depression, sedation hypotension and headache etc. were recorded.

Statistical Analysis: Data were entered and analysed with the help of MS Excel and SPSS version 16.0. Qualitative or categorical data were presented as number (proportion) and compared with chi-square test. Quantitative or continuous variable were presented as mean ± SD and compared using student't' test. Analysis of variance (ANOVA) was applied as per need as test of significance. $p<0.05$ was considered as statistically significant.

Flowchart



OBSERVATIONS

Table 1: Patients distribution according to age and weight in three groups

	Group C (n=25)	Group N1 (n=25)	Group N2 (n=25)	P value
Age (yrs)	35-51	35-50	30-52	
Mean± SD	41.80±5.72	42.56±4.73	42.36±5.50	0.873
Weight(Kg)	45-65	38-62	41-70	
Mean± SD	50.16±5.79	49.24±7.32	52.52±9.26	0.295

Test used- Chi-Square Test

Table-1 shows that all three groups were statistically comparable regarding age and weight distribution of patients ($p>0.05$)

Table 2: Sensory Block Characteristics after subarachnoid block

		Group C (n=25)	Group N1 (n=25)	Group N2 (n=25)	P value		
					C/N1	C/N2	N1/N2
Time to reach T_6 sensory level (min)		6.80±1.00	6.56±0.92	6.08±0.91	0.371	0.009	0.076
Peak sensory level	T4	1 (4%)	1 (4%)	2 (8%)			
(PSL)	T5	2 (8%)	3 (12%)	2 (8%)			
	T6	22 (88%)	21 (84%)	21 (84%)			
Mean±SD(PSL)		T 5.84±0.47	T 5.80±0.50	T 5.76±0.59	0.789	0.592	0.789
Median of PSL (Range)		T6 (T4-T6)	T6 (T4-T6)	T6 (T4-T6)			
Time to PSL(min)		7.12±1.17	6.96±1.17	6.48±1.05	0.618	0.049	0.137

Data are n (%), mean ±S D, median (Range), T=Thoracic level

Sensory onset (Time to T6): Table 2 shows that time to T6 (sensory onset) was 6.80±1.00 min in group C,6.56±0.92min. in group N1 and 6.08±0.91min. in group N2. The difference was statistically significant between group C and group N2(P=0.009), however this difference was of less than 1 min. While it was statistically comparable between group C and group N1 (P=0.371) and group N1 and group N2 (P=0.076).

Peak sensory level (PSL) and time to PSL: Median value of PSL was T6 with range of T4-T6 in all three groups. There was no significant inter group difference in mean PSL in all three group (P>0.05). Time to PSL was 7.12± 1.17 in group C, 6.96±1.17 in group N1, 6.48±1.05 in group N2. The difference was statistically significant between group C and N2 (P=0.049) while it was comparable between group C and group N1 (P=0.618) and group N1 and N2 (P=0.137).

Table 3: Motor block characteristics after sub-arachnoid block

		Group C (n=25)	Group N1 (n=25)	Group N2 (n=25)	P value		
					C/N1	C/N2	N1/N2
Maximum Bromage Score(MBS) (Patients distribution)	0	0	0	0			
	1	0	0	0			
	2	0	0	0			
	3	25	25	25			
Time to MBS (min.) Mean±SD		5.80±1.01	5.76±1.33	5.72±1.05	0.50	0.08	0.57
Range (min.)		4-8	4-8	4-8			

Table 3 shows that maximum Bromage Score as 3(complete motor block) in all patients in all three groups. Time to achieve maximum Bromage score of 3 (motor onset) was 5.80±1.01min. in group C, 5.76±1.33min. in group N1, 5.72±1.05min. in group N2. There was no significant difference in motor onset time in three groups (p>0.05).

Table 4: Comparison of sensory block duration and duration of analgesia in all three groups

	Group C	Group N1	Group N2	P	Value	
				C/N1	C/N2	N1/N2
Duration of analgesia (min) (time to first pain)	190.01±15.20	240.52±19.71	281.92±31.64	0.00	0.00	0.00
Prolongation in duration of analgesia as compared to Group C (%)	-	26.58%	48.37%			
Sensory block duration(Return to S1)	215.20±15.30	260.80±18.86	307.00±31.39			
Prolongation in sensory block duration compared to Group C (%)	-	21.18%	42.65%			

Duration of analgesia (Time to first pain) was 190.01±15.20min. in group C, 240.52±19.71min. in group N1 and 281.92±31.64min. in group N2. The difference was statistically significant among all the three groups (P = 0.00). Thus duration of analgesia was in order of group N2> group N1> groupC.Duration of analgesia was prolonged by 26.58% by intrathecal addition of 1 mg Nalbuphine (Group N1) and 48.37% by 2 mg Nalbuphine(Group N2) as compared to bupivacaine alone (Group C). Sensory block duration was (Time toS1 sensory regression) 215.20±15.30 min. in group C, 260.80±18.86 min. in group N1 and 307.00±31.39 min. in group N2. The difference was statistically significant among all three groups (P value =0.00). Sensory block duration was in order of group N2 > group N1 > group C. Sensory block duration was prolonged by 21.18 % by intrathecal addition of 1 mg Nalbuphine and 42.65 % by 2 mg Nalbuphine as compared to bupivacaine alone. There was no significant difference in motor block duration (Time to return to Bromage 0) in all the three groups. It was 197.20±15.01min. in group C,202.06±15.09min. in group N1 and199.60±14.71min. in group N2. (p>0.05).

Table 5: Incidence of intraoperative side effects and complications

	Group C(n=25)	Group N1(n=25)	Group N2(n=25)	P Value
Bradycardia (HR<50bpm)	2 (8.0%)	1(4.0%)	1(4.0%)	0.768
Hypotension (SBP<90mmHg)	4 (16.0%)	4 (16.0%)	5 (20.0%)	0.911
PONV Nausea	1 (4.0%)	3 (12.0%)	4 (16.0%)	0.376
PONV Vomiting	0	*0*	1 (4.0%)	0.363
Respiratory Depression	0 (0%)	0(0%)	0(0%)	--
Pruritus	0 (0%)	0(0%)	0(0%)	--

Table 5 shows that Incidence of bradycardia, hypotension and PONV were minimal and comparable in three groups (p>0.05). None of the patient had pruritus, respiratory depression or other side effect.

DISCUSSION

Opiate analgesics provide effective pain relief and are a standard of care for control of mild to severe pain. Parenteral opioids remain an integral part of most postoperative analgesic plans but the techniques which improve pain control and reduce opioid requirements may lead to decrease in opioid related adverse effect, provide better patient satisfaction and may reduce the incidence of long term pain following surgery. Regional techniques, such as spinal anesthesia may offer advantages over general anesthesia including reduced stress response to surgery and analgesia extending into the postoperative period.[4,5] Nalbuphine is an opioid analgesic. Nalbuphine has an analgesic (agonist action) potency equivalent to that of morphine on a milligram basis. Receptor studies show that nalbuphine binds to mu (μ), kappa (k), and delta (δ) receptors. Nalbuphine acts as antagonist at the mu receptor and as agonist at the k-receptor. Nalbuphine has the potential to maintain or even enhance μ-opioid based analgesia while simultaneously mitigating the μ-opioid side effect [6]. Nalbuphine as an adjunct to local anaesthetic were found as effective doses to prolong analgesia as compared to control group but none of the study compared 1mg versus 2mg nalbuphine intrathecally to find which is optimum dose for spinal anaesthesia. Therefore we aimed present study in which nalbuphine was used in 1mg and 2mg dose as an adjunct to 3.5ml 0.5% hyperbaric bupivacaine, with an aim to find its better dose in spinal anaesthesia for abdominal hysterectomy.

1. Demographic data: In present study, all the three groups were statistically comparable regarding mean age, mean weight, mean height, sex, ASA grading, diagnosis and duration of surgery which was in accordance with the previous studies conducted by other authors like Parveen *et al*, in 2015 [7] and Ahmed *et al*, in 2016 [8] in abdominal hysterectomy patients.

2. Hemodynamic parameters: All the three groups in present study were comparable regarding hemodynamic parameters like heart rate, systolic blood pressure, diastolic blood pressure and oxygen saturation during intra-operative period as observed by other authors like Parveen *et al*, in 2015 [7] and Ahmed *et al*, in 2016 [8] in abdominal hysterectomy, Ahluwalia *et al*, in 2015 [3] in lower abdominal surgery, Tiwari *et al*, in 2013 9 in lower abdominal and lower limb surgery, Devendra Verma *et al*, in 2013 [10] and Mukherjee *et al*, in 2011 [11] in lower limb orthopedic surgery. It shows that Intrathecal nalbuphine has no hemodynamic adverse effects.

3. Sensory block characteristics:

(A) Onset of sensory block: - In our study time to T6 (sensory onset) was 6.80±1.00 min. in group C, 6.56±0.92 min. in group N1 and 6.08±0.91 min.in group N2. The difference was significant in between group C and group N2 (p=0.009).

Time to peak sensory level were 7.12±1.17 min. in group C, 6.96±1.17 min.in group N1 and 6.48±1.05 min.in group N2. The difference was significant between group C and group N2. (p=0.049). Time to T6 and time to PSL were statistically comparable between group C and group N1 and group N1 and group N2, (p>0.05).It shows that nalbuphine when added in 2mg dose, significantly accelerated sensory onset both in terms of time to T6 and time to PSL. Similar to our study Parveen *et al*, in 2015 [7] also mentioned that 1mg dose of nalbuphine accelerated the sensory onset significantly. Time to L1 (sensory onset) was 3.23±1.03min. in group B and 1.63±0.57min. in group N, (p<0.001). The study by Ahluwalia *et al*, in 2015 [3] found that the onset time of sensory block (time to T10) in group B was 3.78±1.31 min. while in group N (nalbuphine 0.8mg) was 1.29±0.43 min. (p<0.05), The onset of sensory block was significantly faster among patients receiving nalbuphine as compared to group B, because of the high lipophilic nature of nalbuphine. Intrathecal local anesthetics work by inhibiting voltage gated sodium channels in the spinal cord, which interferes with afferent and efferent sensory and motor impulses [5]. Opioids work in the intrathecal space by activating opioids receptors in the dorsal gray matter of spinal cord, which modulates the function of afferent pain fibers 5].

Receptors studies shows that nalbuphine binds to μ, κ and δ receptors, nalbuphine acts as antagonists at the μ receptors and as agonist at the κ receptors. It has been proven that opioids are found synergistic with bupivacaine in central neuraxial block, that's why addition of nalbuphine in 2mg dose significantly accelerated the sensory onset in N2 group, as compared to group C in our study.

(B) Peak sensory level (PSL):

In our study median level of PSL (peak sensory level) was T6 (T4-T6). In all the three groups mean value of PSL was comparable (p>0.05) Similar to our study Ahmed *et al*, in 2016, Parveen *et al*, in 2015, Ahluwalia *et al*, in 2015, Tiwari *et al*, in 2013, Devendra Verma *et al*, in 2013, A Mukherjee *et al*, in 2011 also found that peak sensory level in control group and various doses of nalbuphine groups were also statistically comparable.

4. Motor block characteristics:

Onset of motor block: Present study shows that onset of motor block as defined by time to reach Bromage score-3 was comparable in three groups. 5.80±1.01min. in group C, 5.76±1.33 min. in group N1 and 5.72±1.05 min. in group N2). There was no statistically significant difference found in onset of motor block (p>0.05). Opioids work in the intrathecal space by activating opioids receptors in the dorsal gray matter of spinal cord, which modulates the function of afferent pain fibers[5]. Opioids were found synergistic with bupivacaine in reducing pain without measurably increasing sympathetic or motor blockade in dog modals [12].

Time to first rescue analgesia (duration of analgesia): In our study duration of analgesia 190.01±15.20 min in group C, 240.52±19.71 min. in group N1 and 281.92±31.64 min. in group N2. Intergroup difference was significant among all the three groups, in the group C/N1 (p=0.00), group C/N2 (p=0.00), group N1/N2 (p=0.00). Thus duration of analgesia was in order of group N2 > group N1 > group C. Duration of analgesia was prolonged by 26.58% by intrathecal addition of 1 mg Nalbuphine (Group N1) and 48.37% by 2 mg Nalbuphine (Group N2) as compared to bupivacaine alone (Group C).

Sensory Block duration : Sensory blockade as defined as regression to S1 was 215.20±15.30 min. in group C, 260.80±18.86 min. in group N1 and 307.00±31.39 min. in N2.Sensory block duration was prolonged by 21.18% by intrathecal addition of 1 mg Nalbuphine and 42.65% by 2 mg Nalbuphine as compared to bupivacaine alone. Ahmed *et al*, in 20168 Parveen *et al*, in 20157 Mukherjee *et al*, in 2011[11]. Above study including ours shows that sensory block duration increase significantly when nalbuphine added, because of synergistic effect of nalbuphine with local anesthetics as explained earlier.

Duration of motor blockade: In our study duration of motor block as defined by return of Bromage 0 was 197.20±15.01 min. in group C, 202.06±15.09 min. in group N1 and 199.60±14.71 min. ingroup N2, Which was comparable.

5. Adverse effects: In our study incidence of hypotension (In group C-16%, group N1-16% and in group N2 20%) and bradycardia (8% in group C, 4% in group N1 and 4% in Group N2) during intraoperative period was minimal and statistically comparable in all three groups (p=0.911, p=0.424)

LIMITATION OF THE STUDY

We compared 1 mg and 2 mg dose of Nalbuphine as intrathecal adjuvant to bupivacaine in spinal anaesthesia to find which is better dose and our results showed that 2 mg dose is superior. This study was not planned as a dose finding study in which a range of multiple doses of drug are used to find optimum dose.

CONCLUSION

We conclude that

1. Use of Nalbuphine (1 mg and 2 mg) as an intrathecal adjuvant to bupivacaine is effective in prolonging the duration of analgesia and sensory block significantly as compared to bupivacaine alone in spinal anaesthesia.
2. Among two doses, Nalbuphine 2 mg was found superior, because both duration of analgesia and sensory block were significantly longer than with 1mg dose, without increasing any adverse effect; moreover, 2 mg dose also accelerated the sensory onset significantly.

Hence, Nalbuphine 2 mg as an intrathecal adjuvant to bupivacaine seems to be a promising technique in providing prolonged postoperative analgesia following abdominal hysterectomy in spinal anaesthesia.

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