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Original Research Article

A CONTROLLED AND RANDOMIZED STUDY OF COMPARING ANAESTHETIC EFFICACY OF INTRATHECAL NALBUPHINE HYDROCHLORIDE WITH BUPIVACAINE AND BUPIVACAINE ALONE FOR INFRAUMBILICAL SURGERIES:A PROSPECTIVE STUDY

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Abstract

Over the years, the technique has been refined and has evolved into the modern concept of intrathecal, spinal or subarachnoid block. Spinal effects are produced by slow injection of a small volume of local anaesthetic solution containing dextrose (to make ithyperbaric).Among the regional techniques available, spinal anaesthesia is an attractive option when the surgical site is below umbilicus.

Keywords: Infraumbilical, Surgery, Spinal Block, Neuroaxaial

Introduction

Central neuraxial blockade is one of the most commonly performedtechnique in modern anaesthesia. In 1898, August Bier first described "cocainisation of the spinal cord". Over the years, the technique has been refined and has evolved into the modern concept of intrathecal, spinal or subarachnoid block. Spinal effects are produced by slow injection of a small volume of local anaesthetic solution containing dextrose (to make ithyperbaric). Among the regional techniques available, spinal anaesthesia is an attractive option when the surgical site is below umbilicus[1]. It produces dense sensory, motor and sympathetic blockade. It has the advantages of low cost, better postoperative pain relief, decreased PONV, low incidence of thromboembolism when compared to general anaesthesia. Subarachnoid block is associated with reduced stage I recovery time and patients can resume their normal oral intake quickly. Because of these benefits, spinal anaesthesia is one of the emerging technique in day care surgeries in recent times. Spinal anaesthesia is beneficial in terms of decreasing intraoperative blood loss, blunting the stress response to surgery and reducing mortality and morbidity in high risk surgical patients. Subarachnoid block is a preferred technique in patients who are prone to aspiration like obesity, full stomach, GERD and in patients with reduced respiratory drive.In spite of the above benefits, the major limitation of subarachnoid block is short lived duration of anaesthesia. Normally, spinal anaesthesia with bupivacaine heavy (H) lasts for 2 to 2.5 hours[2]. Addition of adjuvants like opioids, neostigmine and epinephrine to the local anaesthetics intrathecally, results in prolongation of duration of anaesthesia. In 1979, Wang and his colleagues[3] first used intrathecal opioidsfor acute pain treatment. Intrathecal opioid is widely used in treating intraoperative, postoperative, obstetric, traumatic and chronic cancer

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pain. The technique of intrathecal opioid administration along with local anaesthetics is to improve the quality of analgesia and decrease the requirement of postoperative analgesics[4].The basis for the combination of local anesthetics and opioids is that these two groups of drugs provide analgesia by their action at two different sites. Local anesthetics have their action at the spinal nerve axon and opioids act at the receptor site in the spinal cord[5]. Various opioids have been used intrathecally like morphine, fentanyl, buprenorphine and nalbuphine to fasten the onset and prolong the duration of sensory and motor blockade. Nalbuphine is an opioid, synthetically prepared with mixed μ antagonist and κ agonist properties[6]. Nalbuphine when administered intrathecally binds to kappa receptors in the spinal cord and brain producing analgesia and sedation without μ adverse effects. It has minimal respiratory depressant effect and low abuse potential compared to other centrally acting opioid analgesics. Side effects like shivering, nausea, vomiting and urinary retention are infrequent with nalbuphine hydrochloride. Increased drug dosage is not required, Since nalbuphine reaches ceiling effect at lower intrathecal dosage. This also explains the safety margin of the drug. In this study, we investigated the addition of nalbuphine hydrochloride as an adjuvant to hyperbaric bupivacaine in subarachnoid block, in comparison with hyperbaric bupivacaine alone in order to evaluate the beneficial effects of nalbuphine.

MATERIALS AND METHODS

"Prospective randomized controlled study evaluating anaesthetic efficacy of mixture of intrathecal bupivacaine 0.5% heavy and nalbuphinehydrochloride with intrathecal bupivacaine 0.5% heavy alone for infra umbilical surgeries".

SAMPLE SIZE CALCULATION

The study population comprised of 60 adult patients classifiedunder the ASA PS 1 or 2 posted for lower abdominal surgery and lower limb orthopaedic surgery.

INCLUSION CRITERIA

- 30 - 60 years of age
- ASA physical status 1 or 2
- Patients who gave valid informed written consent
- Patients undergoing lower abdominal surgery and lower limborthopaedic surgery.

EXCLUSION CRITERIA

- 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

RESULTS

Sample size was calculated using n.master 2.0 software. Sample size based on clinical trials-parallel design-hypothesis equivalence/ bioequivalence. Equivalence margin is 1, observed / expected difference - 0.68, Standard deviation - 0.5, Effect size - 0.64, Power (1-β) - 80,

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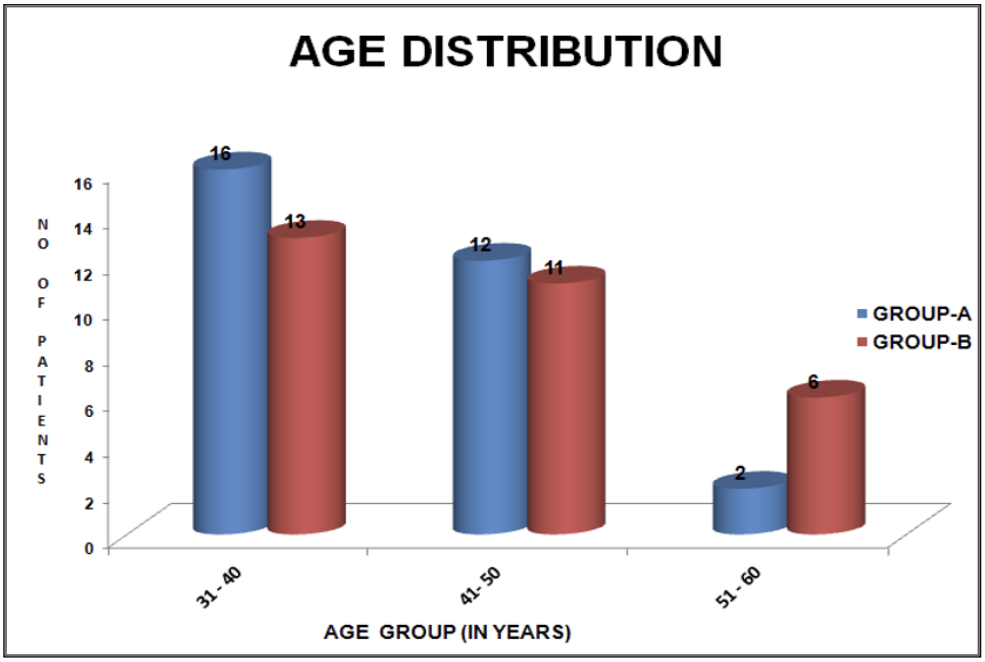
α Error (%) - 5, Group A-30, Group B - 30. For Statistical analysis IBM SPSS (Version 21) software was used. The demographic data of thepatients in both the groups were studied and the analysis revealed no significant difference between the two groups.

Table 1: AGE DISTRIBUTION

Age	GROUP-A		GROUP-B	
(Years)	No of Patients (N)	Percentage(%)	No of Patients(N)	Percentage(%)
31 - 40	16	53.33	13	43.33
41 - 50	12	40.00	11	36.67
51 - 60	2	6.67	6	20.00
TOTAL	30	100	30	100
Chi-squareValue				2.35
p-value	0.31			
Significant	Not Significant			



GROUP A - BUPIVACAINE + NALBUPHINE GROUP B - BUPIVACAINE + NORMAL SALINE

Both the groups are identical in distribution in terms of age.

Mean Age (in Years)

Group	Mean	Standard Deviation
GROUP-A	39.90	7.60
GROUP-B	42.57	8.40

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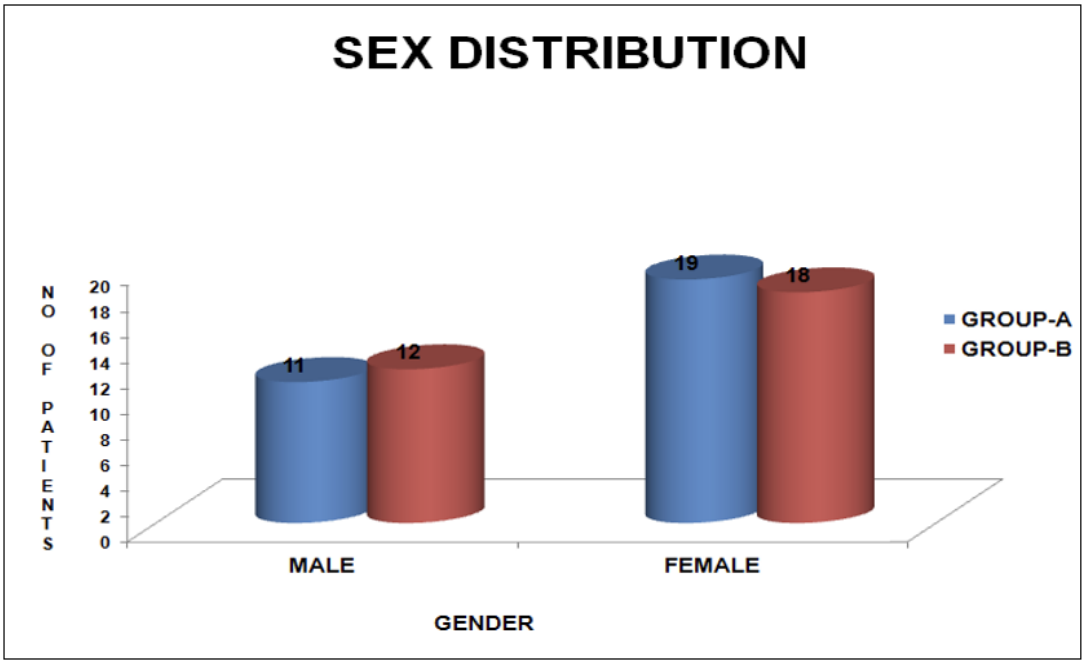
t-value	1.29
p-value	0.20
Significant	**Not Significant**

Table 2: SEX DISTRIBUTION

	GROUP-A		**GROUP-B**		**TOTAL**	
SEX	**No of Patients(N)**	**%**	**No of Patients(N)**	**%**	**No of Patients (N)**	**%**
MALE	11	36.67	12	40.00	23	38.33
FEMALE	19	63.33	18	60.00	37	61.67
TOTAL	30	100	30	100	60	100
ni-squarevalue	0.07					
p-value	0.79					
Significant	**Not Significant**					



GROUP A - BUPIVACAINE + NALBUPHINE GROUP B - BUPIVACAINE + NORMAL SALINE

No statistically significant difference in sex distribution betweentwo groups.

Table 3:WEIGHT DISTRIBUTION

	GROUP-A		**GROUP-B**	
Weight in kgs	**No of Patients(N)**	**%**	**No of Patients(N)**	**%**
51 – 60	9	30.00	5	16.67

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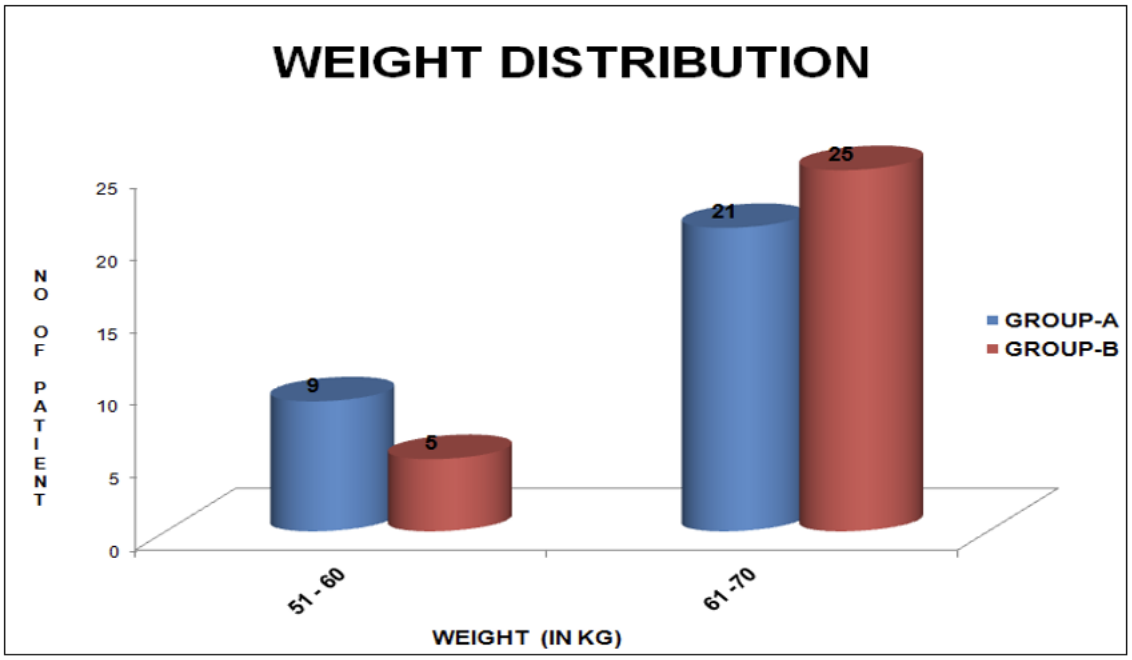
61 -70	21	70.00	25	83.33
TOTAL	30	100	30	100
Chi-square Value	1.49			
p-value	0.22			
Significant	**Not Significant**			



GROUP A - BUPIVACAINE + NALBUPHINE GROUP B - BUPIVACAINE + NORMAL SALINE

Table 4 : HEIGHT DISTRIBUTION

	GROUP- A		**GROUP- B**	
Height in cms	**No of Patients (N)**	**%**	**No of Patients (N)**	**%**
151 – 160	11	36.67	12	40.00
161 – 170	19	63.33	17	56.67
171 –180	0	0	1	3.33
TOTAL	30	100	30	100
Chi-square Value	1.16			
p-value	0.56			
Significant	**Not Significant**			

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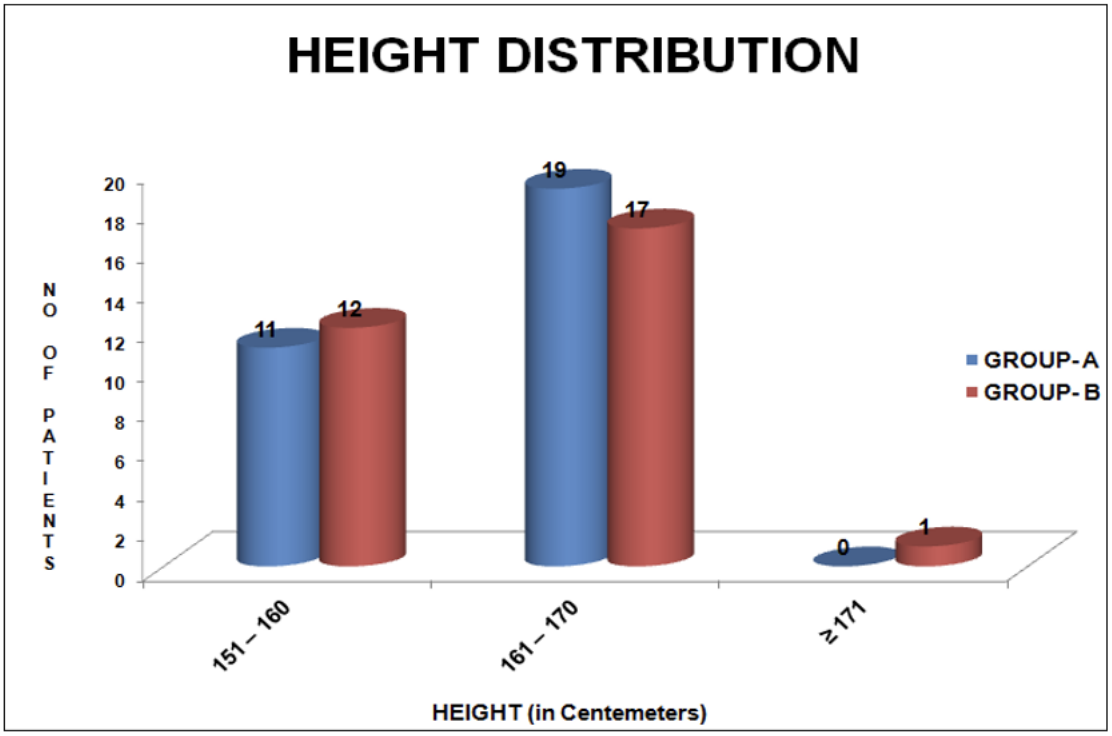

GROUP A - BUPIVACAINE + NALBUPHINE GROUP B - BUPIVACAINE + NORMAL SALINE

Mean Height (Centimeter)

Group	Mean	Standard Deviation
GROUP-A	162.60	4.52
GROUP-B	162.30	4.94
t-value	0.25	
p-value	0.81	
Significant	**Not Significant**	

The mean height distribution between the two groups are similar.

Table-5: ASA DISTRIBUTION

ASA	GROUP-A		GROUP-B	
	No of Patients(N)	%	No of Patients(N)	%
I	23	76.67	21	70.00
II	7	23.33	9	30.00
TOTAL	30	100	30	100
Chi-square Value	0.34			
p-value	0.56			
Significant	**Not Significant**			

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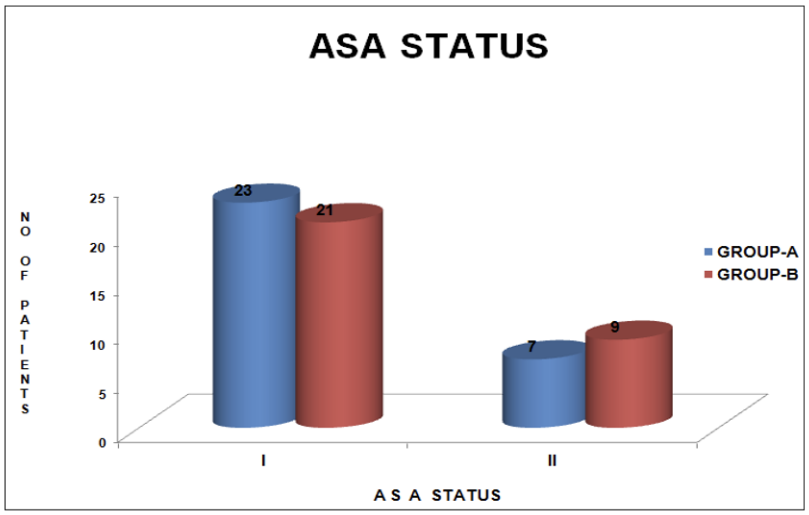


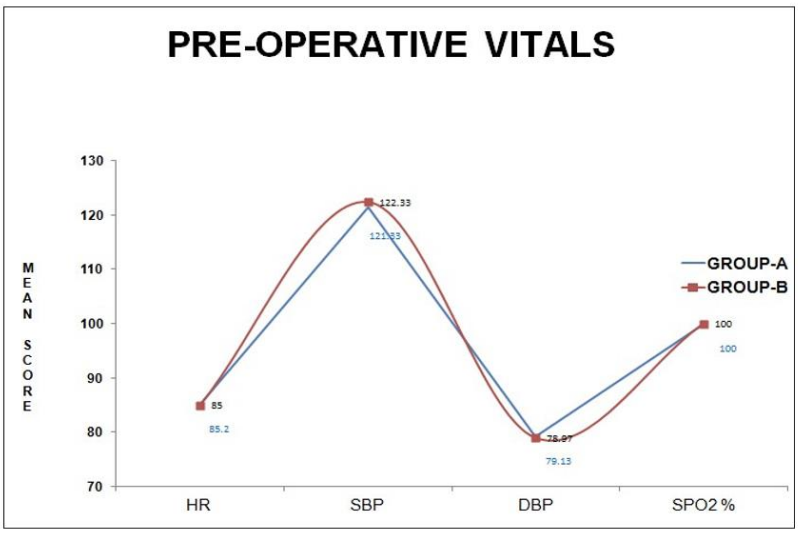
GROUP A - BUPIVACAINE + NALBUPHINE GROUP B - BUPIVACAINE + NORMAL SALINE

ASA - American Society of Anesthesiologist

Table 6:PRE-OPERATIVE VITALS

Variables	GROUP-A		GROUP-B		t-value	p-value	Significant
	MEAN	SD	MEAN	SD			
PR (Min)	85.20	4.39	85.00	4.09	0.18	0.86	NS
SBP (mmHg)	121.33	7.45	122.33	8.02	0.50	0.62	NS
DBP (mmHg)	79.13	4.33	78.97	3.38	0.17	0.87	NS
SPO2 %	100	0	100	0	-	-	-

NS-Not Significant



GROUP A - BUPIVACAINE + NALBUPHINE GROUP B - BUPIVACAINE + NORMAL SALINE

No statistically significant difference between the two groups interms of preoperative vitals

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STUDY PERIOD

Table 7:PULSE RATE (beats/min)

TIME	GROUP-A		GROUP-B		t-value	p-value	Significant
	MEAN	SD	MEAN	SD			
2 Sec	88.47	4.00	86.63	4.23	0.16	0.88	NS
2 Min	89.30	3.64	89.23	3.14	0.08	0.94	NS
4 Min	90.70	4.04	91.47	3.49	0.79	0.44	NS
6 Min	91.27	4.74	91.53	3.96	0.24	0.81	NS
8 Min	89.17	5.36	90.80	5.32	1.19	0.24	NS
10 Min	85.97	5.70	86.70	5.33	0.52	0.61	NS
15 Min	81.57	6.29	83.00	5.02	0.98	0.33	NS
20 Min	78.67	5.88	80.07	5.30	0.97	0.34	NS
25 Min	76.03	6.57	76.37	5.01	0.22	0.83	NS
30 Min	73.00	7.05	74.30	5.25	0.81	0.42	NS
40 Min	70.67	7.47	71.70	6.25	0.58	0.56	NS
50 Min	68.67	7.01	69.43	4.57	0.50	0.62	NS
1 Hour	67.73	5.51	69.50	5.85	1.20	0.23	NS
2 Hour	70.93	5.08	72.83	6.49	1.26	0.21	NS
3 Hour	74.80	6.04	77.27	6.06	1.59	0.12	NS
4 Hour	77.83	6.11	82.73	5.60	3.24	0.002	Significant
5 Hour	81.30	5.77	86.37	4.45	3.81	0.001	Significant
6 Hour	84.30	5.47	88.67	4.71	3.31	0.002	Significant
8 Hour	85.50	5.33	89.00	3.92	2.90	0.005	Significant
10 Hour	87.53	4.62	90.27	4.39	2.34	0.002	Significant
12 Hour	89.00	4.47	91.53	3.93	2.33	0.002	Significant
14 Hour	88.57	3.36	90.03	5.73	1.21	0.23	NS
16 Hour	88.47	3.09	89.80	5.39	1.18	0.25	NS
18 Hour	88.93	3.81	90.01	4.05	1.13	0.04	NS
20 Hour	89.67	4.06	90.07	3.64	0.30	0.05	NS
22 Hour	90.73	3.37	91.00	3.17	0.36	0.75	NS
24 Hour	90.40	2.82	91.87	4.24	1.58	0.12	NS

NS- Not Significant

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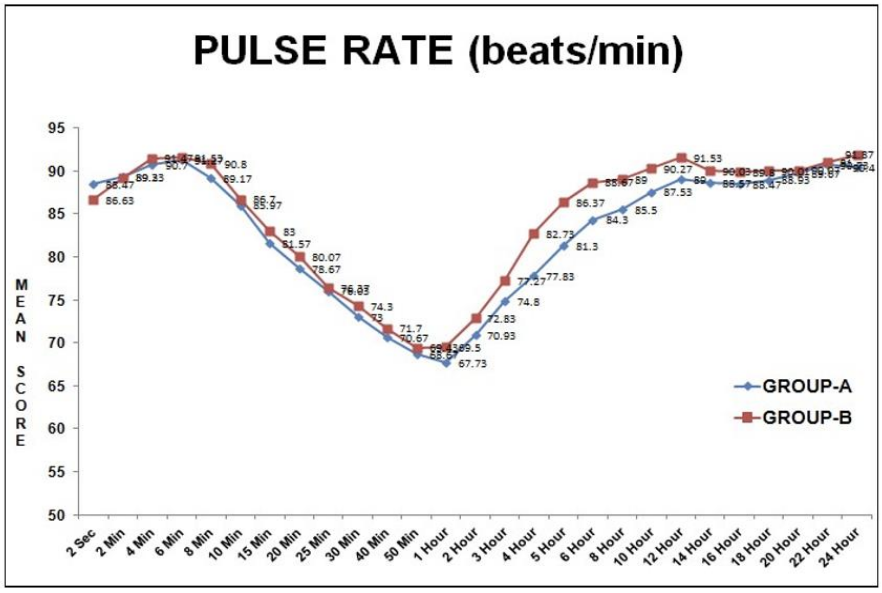

GROUP A - BUPIVACAINE + NALBUPHINE GROUP B - BUPIVACAINE + NORMAL SALINE

From the above graph, it was clearly evident that the mean pulse rate for the first three hours after spinal anaesthesia was similar in boththe groups, after that patients in the nalbuphine group had significantly lower pulse rate than the control group from 4 to 10 hours.

Mean Weight (Kg)

Group	**Mean**	**Standard Deviation**
GROUP-A	63.13	5.20
GROUP-B	64.67	4.27
t-value	1.25	
p-value	0.22	
Significant	**Not Significant**	

The mean weight distribution between the two groups are similar.

DISCUSSION

Over the years, extensive research have been done to improve the quality of spinal anaesthesia by varying drug regimens and technical methods. Normally adjuvants are added to hyperbaric bupivacaine 0.5% and administered intrathecally to prolong the anaesthetic effects. They produce antinociceptive effect by acting perineurally or at different receptor sites in the spinal cord. Intrathecal opioids when used as adjuvants are capable ofproducing early onset of sensory, motor blockade and prolonged postoperative analgesia. They also allow early ambulation of patients due to their sympathetic and motor sparing activities. Nalbuphine hydrochloride is a mixed μ antagonist and κ agonist opioid. It has been found to cause prolongation of the effects of local anaesthetics in intrathecal, epidural and peripheral nerve blocks with the advantages of minimal respiratory depression and better hemodynamic stability.This prospective randomised controlled study performed in 60 patients who underwent infraumbilical surgeries under spinal anaesthesia demonstrated that nalbuphine in the dose of 0.5mg when added to hyperbaric bupivacaine had earlier onset of sensory and

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motor blockade and prolonged duration of analgesia. Both the study and control groups were comparable in demographic parameters like age, weight and height. The mean age of the patients in the nalbuphine group (A) was 39.90±7.60 years. The mean ageof the patients in the control group (B) was 42.57±8.40 years. The mean weight of the patients in the nalbuphine group was 63.3±5.20 kgs. The mean weight of the patients in the control group was 64.67±4.27 kgs. Themean height of the patients in the nalbuphine group was 162±4.52 cm. The mean height of the patients in the control group was 162.30±4.97 cm.The variables were compared using independent sample test and Levene'stest for equality of variances and p value was found to be not significant. The mean pulse rate of the patients in the nalbuphine group was around 77 bpm whereas in the control group it was around 83 bpm at 4^{th}hour. The systolic and diastolic pressures of the patients in the nalbuphine group were 114±6.24 mmHg and 74.40±5.61 mmHg respectively, whereas in the control group it was around 119±5.73 mmHgand 78.20±4.01 mmHg at 4^{th} hour. Statistical analysis of the mean blood pressure and mean pulse rate was done and p value was found to be significant between 3 to 6 hrs.The sensory and motor block were checked after performance of subarachnoid block using pinprick and modified Bromage scale respectively. The mean onset time of sensory block (T10) in the nalbuphine group was found to be 1.93±0.45 mins whereas in the control group it was found to be 3.30±0.54 mins. The mean onset time of motor block was found to be 2.97±0.56 mins in the nalbuphine group whereas inthe control group it was found to be 4.50±0.63 mins. The statisticalanalysis by the independent sample test and the t test for equality of means has shown faster onset time for sensory and motor block significantly with a p value of 0.0001 in the nalbuphine group. More number of patients in the nalbuphine group (A) achieved higher sensory level (T4) than the patients in the control group (B).The mean time to regression of sensory block upto L1 in the nalbuphine group was found to be 4.65±1.03 hrs, whereas in the control group it was found to be 3.21±0.57 hrs. Mean duration of motor blockadein the nalbuphine group was 2.87±0.39hrs and in the control group was 2.05±0.34hrs. Statistical analysis were done and p value (0.0002) was found to be significant.The patients were followed in the postoperative period for the presence of pain by the Visual Analog Scale. The VAS score of 4 is considered as the termination of analgesia. When the patients had a VAS score of 4 rescue analgesic (1g IV paracetamol) was given. The mean duration of analgesia in the nalbuphine group was found to be 5.54±1.05 hrs and in the control group it was found to be 3.62±0.61hrs. Statistical analysis revealed significant p value (0.0001) between the two groups. Shakooh[7] et al in their study of 60 patients had demonstrated similar faster onset of sensory and motor block - 1.43±0.57 minutes and 3.47±1.01 minutes respectively on addition of 0.8mg of nalbuphine to 0.5% hyperbaric bupivacaine. They also demonstrated significant ($p<0.05$) prolongation of the duration of two segment sensory regression& motor blockade - 218.50±34.72 mins and 243.3±56.46 mins. The duration of postoperative analgesia in their study was 298±51.02 mins. Side effects like bradycardia and urinary retention were not reported. Hence in our study, we decided to add a low dose of nalbuphine intrathecally to hyperbaric bupivacaine to produce desired results without adverse effects. The results obtained in this study was comparable with them. Pallavi Ahluwalia[8] et al in their study of 70 patients demonstratedthat the onset time of sensory block was found to be earlier in nalbuphinegroup (1.29±0.43 mins) compared to the control group (3.78±1.31mins).

The duration of motor blockade and the duration of analgesia in the nalbuphine group were 256.41 mins and 298.43 mins. We obtained similar results in our study. Mukherjee[9] et al formulated 'a study to determine whether nalbuphine prolongs analgesia by comparing with control group and also to determine the optimum dose of intrathecal nalbuphine'. It was

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observedthat 0.4mg of nalbuphine with 0.5% hyperbaric bupivacaine produces prolongation of the duration of postoperative analgesia without any side effects. Hence we used 0.5mg of nalbuphine intrathecally. Lin[10] et al demonstrated 'the analgesic effect of subarachnoid administration of tetracaine combined with 0.4 mg of nalbuphine or 0.4 mg of morphine'. They reported 0.4 mg of nalbuphine or morphine improves the effectiveness of intraoperative and postoperative analgesia but the side effects are less in nalbuphine group compared to morphine group. In our study we added nalbuphine to bupivacaine intrathecally andobtained similar quality of analgesia. Intrathecal nalbuphine was in practise over 20 years with no neurotoxic side effects. Earlier studies have been conducted on parturient women did not reveal any untoward effects. There was an animal study by Rawal[11] et al that examined the effects of intrathecal nalbuphine and reported no behavioral and systemic histo-pathologic abnormalities.All the patients in our study both nalbuphine and control groups were monitored in the postoperative period and oxygen was supplemented at the rate of 2 litres/minute through ventimask.

CONCLUSION

Nalbuphine hydrochloride in the dose of 0.5mg when added as an adjuvant to hyperbaric bupivacaine 0.5% in subarachnoid block had a faster onset of sensory and motor blockade. The two segment dermatome regression time was significantly prolonged and the duration of postoperative analgesia was also increased in nalbuphine group. There was no increase in the risk of side effects like pruritus, hypotension, bradycardia and urinary retention.

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