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Comparison of Analgesic Efficacy of subarachnoid Bupivacaine, Bupivacaine with Fentanyl and Bupivacaine with Nalbuphine An Intragroup Prospective Observational Study

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ABSTRACT

Opioids are added to local anesthetics to extend theduration of spinal analgesia/anaesthesia.The present study was undertaken to compare the analgesic efficacy of subarachnoid hyperbaric bupivacaine 0.5% alone as a control,bupivacaine 0.5% with fentanyl and bupivacaine 0.5% with nalbuphine. Total 150 patients of either sex, ASA grade I and II, between 18 to 60 years and height 150 to 170 cm, posted for elective lower abdominal and lower limb surgeries were enrolled. They were divided into three equal groups. Group B: received 15mg hyperbaric bupivacaine 0.5%(3ml) + 0.5ml normal saline, Group BF: received 15mg hyperbaric bupivacaine 0.5% (3ml) + Inj. Fentanyl25μg(0.5ml) and Group BN: received 15mg hyperbaric bupivacaine 0.5%(3ml) + Inj. Nalbuphine 500μg(0.5ml). The sensorimotor blockade was significantly faster and prolonged in group BF and BN than group B. Quality of analgesia during the procedure was excellent in 90%, 94% and 94% in group B, BF and BN respectively. The duration of effective analgesia in group B (229.80$\pm$ 43.542min) was significantly shorter in comparison with group BF (359.40 $\pm$ 45.955min) and BN (364.20 $\pm$ 38.34min), (P= 0.0001). Subarachnoid fentanyl 25μg and nalbuphine 500μg acts as an adjuvant to potentiate localanesthetic bupivacaine with the result that there is prolongation of sensory and motor blockade& extended duration of effective analgesia in early postoperative period, reducing the total consumption of rescue analgesics.

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INTRODUCTION

Pain is an unpleasant experience, not only sensory but emotional as well. It can cause tissue damage if untreated. It can also become chronic. Therefore, acute post-operative pain management is a crucial aspect of post-operative care. Severe pain, regardless of its site, can adversely affect nearly every organ function, thereby affecting the post-operative morbidity and mortality (Morgan, 2006). Pain relief in the perioperative period is the part & parcel of anaesthesia care. Spinal anaesthesia has a limited duration, specific to the drug used (Swain *et al.*, 2017; Dave *et al.*, 2020). Local anaesthetics used

solo will provide a limited period of extended post-operative analgesia. Adding adjuvants to intrathecal local anaesthetics improves the quality and duration of the spinal blockade and prolongs post-operative analgesia. It is also possible to reduce the dose of local anaesthetics, & also the total amount of systemic post-operative analgesics (Taksande and Varghese, 2017; Rajan *et al.*, 2018).

Spinal adjuvants are used to improve spinal anaesthesia quality and to prolong effective post-operative analgesia (Belekar, 2017). Fentanyl and morphine have been the most preferred opioids. Fentanyl, a phenylpiperidine derivative, is a synthetic opioid receptor agonist. It is preferred because of its rapid onset and short duration of action with lesser incidence of respiratory depression (Bhure, 2012). Studies have shown that it improves the duration of sensory anaesthesia and post-operative analgesia without significant side effects (Bogra *et al.*, 2005; Chu *et al.*, 1995).

Nalbuphine is a newer addition to the anaesthetic armamentarium as an adjuvant to local anaesthetics. It is opioids μ-receptor antagonist and κ-receptor agonist (Chen *et al.*, 1993) and is related chemically to oxymorphone and naloxone. Its analgesic potency is substantially equivalent to that of morphine, and one-fourth as potent as nalorphine as an antagonist. Nalbuphine has the potential to maintain or even enhance μ-opioid-based analgesia while simultaneously mitigating the μ-opioid side effect (Gunion *et al.*, 2004). This ability to antagonize the side effects specific to spinal opioids acting on μ receptors such as respiratory depression, pruritus, & urinary retention might prove to be an asset (Penning *et al.*, 1988; Yang *et al.*, 1999).

The present project was undertaken to study and compare the analgesic efficacy of opioid adjuvant fentanyl 25 μg and nalbuphine 500 μg with bupivacaine and bupivacaine alone for a spinal subarachnoid block in patients undergoing lower abdominal and lower limb orthopaedic surgeries.

MATERIALS AND METHODS

Institutional Ethical Committee approval and written informed consent were taken from all the patient. The type of the study was prospective observational, carried out in the Department of Anesthesiology at a Tertiary care centre in Maharashtra during a period from December 2014 to November 2016. Total 150 adult patients of either sex, ASA grade I or II, age between 18-60 years, height 150-170cm, were registered. Elective lower abdominal or lower limb surgeries under spinal anaesthesia predicted to last from 40-150 mins were included in the study. We divided them into three groups—Group B- control group, Group BF-fentanyl group and Group BN- nalbuphine group. We excluded patients with physical ASA status $\geq$III, height <150cm or > 170cm, contraindication to spinal anaesthesia (e.g., -bleeding diathesis, local infection and patients on anticoagulants), spinal deformities, history of hypersensitivity to local anaesthetics or opioids, patients with cardiovascular, neurological, respiratory, renal or endocrine diseases or psychiatric illness, severe anaemia, hypovolemia, pregnant patients and patients not willing for the procedure.

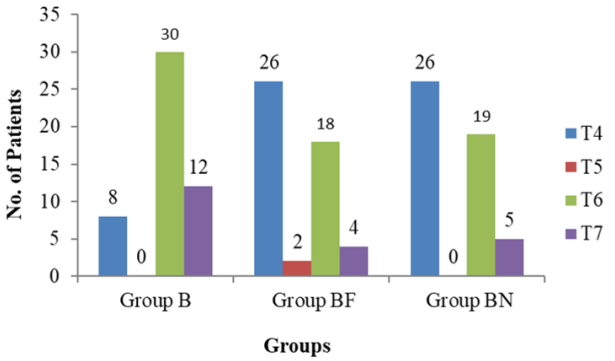

Figure 1: Highest Sensory Level Achieved (Dermatome)

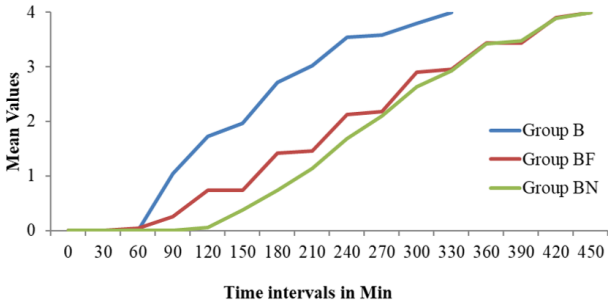

Figure 2: Mean VAS Score at Various Time Intervals

A thorough pre-anaesthetic evaluation was performed by taking history and clinical examination. The demographic data were noted, and minimum necessary investigations like haemogram, blood grouping, bleeding and clotting time, urine analysis and random blood glucose were done for every patient. Electrocardiogram, chest X-ray and other investigations like LFT, KFT, coagulation profile were done in patients above 40 years or as and when required according to history and clinical examination. All patients were kept starving for an overnight period before surgery.

In the preoperative room, pulse rate, BP, respiratory rate, SpO2 were noted. In the operation theatre, after securing intravenous cannula of 18/20 G,

Table 1: Demographic profile of the patients and type of procedure

Demographic data		Group B	Group BF	Group BN
Age (in years)	21-30	10 (20%)	12 (24%)	10 (20%)
	31-40	22 (44%)	11 (22%)	13 (26%)
	41-50	15 (30%)	19 (38%)	20 (40%)
	51-60	3 (6%)	8 (16%)	7 (14%)
Sex	Male	34 (68%)	28 (56%)	37 (74%)
	Female	16 (32%)	22 (44%)	13 (26%)
Height (in cm)	151-160	29 (58%)	23 (46%)	17 (34%)
	161-170	21 (42%)	27 (54%)	33 (66%)
ASA Grade	I	45 (90%)	44 (88%)	45 (90%)
	II	5 (10%)	6 (12%)	5 (10%)
Type of procedure	Orthopaedic	19 (38%)	21 (42%)	18 (36%)
	Surgical	31 (62%)	29 (58%)	32 (64%)

Table 2: Characteristics of subarachnoid (spinal) blockade

Characteristics	Group B	Group BF	Group BN	P value
Onset of sensory block (sec)	122.4±47.27	60.8±21.86	58.3±22.65	0.0001
Onset of motor block(min)	4.02±0.91	2.86±0.64	2.6±0.57	0.0001
Time to achieve T10 level group (min)	5.40±0.81	3.74±0.66	3.78±0.68	0.0001
Time to achieve highest sensory level (Min)	8.42±0.99	6.86±1.26	6.56±1.20	0.0001
Time for 2 segment regression (min)	82.48±5.71	99.88±7.65	98.74±7.84	0.0001
Complete motor block (min)	7.66±1.00	6.16±0.79	6.12±0.94	0.0001
Duration of sensory block (min)	126.28±10.96	154.90±14.67	152.26±15.24	0.0001
Duration of motor block (min)	107.36±10.52	128.72±13.40	124.34±13.46	0.0001
Duration of effective analgesia (min)	229.80±43.54	359.40±45.95	364.20±38.34	0.0001

Table 3: Incidence of Complications

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

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 was 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 until 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, Group BF: 15mg hyperbaric Bupivacaine 0.5 % (3ml) + Inj. Fentanyl 25μg (0.5ml) 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 NS before adding to bupivacaine in a 5ml syringe. The total volume injected was 3.5ml in all three groups. Both Nalbuphine and Fentanyl used in the study were 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, a total duration of effective analgesia assessed on VAS score, quality of analgesia as excellent, good fair & poor, Ramsay sedation score, and vital parameters were monitored and noted.

Intra and post-operative side effects were noted and treated accordingly. A fall in systolic blood pressure by 30% of its absolute value was considered as hypotension and treated with rapid infusion of intravenous fluid Ringer lactate 250ml and 6mg intravenous Inj. Mephenteramine, if there was no response to intravenous fluid administration. The heart rate of less than 60 beats per minute was considered as bradycardia and treated with Inj. Atropine sulphate 0.6mg intravenously. Respiratory depression was defined as a fall in respiratory rate < 10 breaths/min or as a fall in peripheral oxygen saturation <90% treated with oxygen supplementation of 4L/min by the facemask. All patients were observed in the post-anaesthesia recovery area of operation theatre until the administration of rescue analgesia, which was the endpoint of primary study. Patients were visited at 12 and 24 hours to note about side effects and complications if any.

Statistical analysis

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

The rationality of sample size was with the formula of difference in mean as 36 cases per group from the study performed by Thote et al. We included 50 patients in each group in our study. Power of study was 80% with a confidence limit of 95%.

OBSERVATION AND RESULTS

A total of 150 adult patients were enrolled in the study and randomly divided into three groups of 50 patients in each group. Maximum numbers of patients were between the age group of 31 – 50 years. Male preponderance was observed in all the 3 study groups. M: F ratio in group B was 2.12: 1, in group BF it was 1.27: 1, and in group BN it was 2.84: 1. Majority of patients in group BF (54%) and group BN (66%) had height 161-170 cm, whereas a maximum number of patients in group B (58%) had height between 151- 160cm. In all the three groups, the majority of patients had physical status grade I, Table 1.

The mean onset of sensory and motor block as well as time to achieve T10 level, was significantly faster in group BF and BN in comparison with group B and were statistically significant (P= 0.0001). The highest sensory level was T4 in a maximum number of patients in group BF and BN, 52% in each group. However, 60% of patients in group B achieved T6 level, which was achieved by 36% patients in group BF and 38% patients in group BN, Figure 1. The mean time to achieve highest sensory level was found to be significantly faster in group BF and BN than in group B. Two segment dermatomal regressions was seen earlier in group B in comparison with group BF and BN which was statistically highly significant (p=0.0001). Complete motor block occurred significantly earlier in group BF and group BN than in group B. The duration of sensory and motor block was prolonged considerably in group BF, and BN in comparison with group B. All the sensory and motor characteristics were comparable between group BF and BN, Table 2.

Quality of analgesia during the procedure was excellent in 90%, 94% and 94% in group B, BF and BN respectively. Quality of analgesia was reported as good in 10% of patients in group B and 6% each; in group BF and BN. The time duration for effective analgesia in group B was significantly shorter in

comparison with group BF and BN. However, in the group's BF and BN, it was comparable (P= 0.575), Table 2.

The surgery took 45-105 minutes in group B, 40-120 minute in BF and 45- 140 minute in group BN. However, the mean duration of surgery was found to be less in group B (64.74±19.02 min) as compared to groups BF (82.30±25.52) and BN (84.16±22.05), (p=0.0001).

VAS score evaluated at various time intervals showed a significantly higher mean value in group B than group BF and BN at 90 - 330 mins. At 330min, 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 interval of 90 – 240 mins, beyond which the mean VAS scores were comparable in group BF and BN. The mean VAS score of 4 was achieved at 450 mins in group BF and BN, Figure 2.

Sedation score, hemodynamic parameters and respiratory rate changes were comparable in all three groups. Table 3 show intra-operative and post-operative complications. There was no incidence of respiratory depression, urinary retention, shivering, and sedation was observed in this study.

DISCUSSION

Spinal anaesthesia requires a small volume of drug. It is regional anaesthesia almost devoid of systemic pharmacologic effects. It produces rapid (<5 minutes), & profound, sensory analgesia, which is reproducible (RD, 2014). It is well documented that opioid administered intrathecally along with local anaesthetics has a synergistic analgesic effect, thereby providing powerful potentiation of the analgesic effect of local anaesthetic. As a general rule with intrathecal hyperbaric bupivacaine at 0.5% concentration, in a dose of 1mg will block one and one- half segments of the spinal nerve roots in an adult. On this basis, the dose recommended for lower abdominal surgeries is 2.5 to 3.5ml (12.5- 17.5 mg). In the present study, hyperbaric 0.5% bupivacaine, we used in the dose of 15 mg and was identical in all the 3 study groups. Fentanyl in a dose of 25 μg (preservative-free) was used as an additive to 15mg hyperbaric 0.5% bupivacaine. Fentanyl in doses of 10 to 30 μg is commonly used as additive intrathecally (RD, 2014). Nalbuphine in a dose of 500μg (preservative-free) was evaluated in the current study as a spinal adjuvant. In several clinical settings, it has been used in doses from 200 to 1600 μg (Goma *et al.*, 2018).

Thote *et al.* (2015) and Dubey and Bisht (2014) studied nalbuphine in a dose of 500μg as spinal additive. Nalbuphine (500μg) and fentanyl (25 μg) as an intrathecal adjuvant to 0.5% hyperbaric bupivacaine (15mg) both were found to hasten the onset of sensory and motor blockade significantly. Both also prolonged the duration of sensorimotor blockade compared to 0.5% hyperbaric bupivacaine alone. Thus, nalbuphine and fentanyl as adjuvants seem to be more efficient clinically than plain bupivacaine as there was an extended duration of sensory & motor block and post-operative analgesia as well. Group BN and group BF were found to be comparable in sensory, motor and analgesic characteristics. These results are consistent with the findings of previous studies (Thote *et al.*, 2015; Dubey and Bisht, 2014). The mean duration of effective analgesia was significantly prolonged in group BF and BN than in group B (P=0.0001), and these results are in accordance with other studies (Dubey and Bisht, 2014; Parveen *et al.*, 2015). However, the mean duration of effective analgesia in patients of group BF and BN was noted to be similar (P=0.575), which is comparable with the study done by Gomaa *et al.* (2014). Quality of analgesia was found to be comparable in all the three groups (p= 0.715). Thus the addition of fentanyl or nalbuphine only marginally improved quality of surgical analgesia in existing study.

VAS score evaluated at various time intervals showed a significantly higher mean value in group B than group BF and BN at various time interval beginning at 90 min and up to 330 mins. At 330 min, a mean of VAS= 4 was noted in patients of 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 as compared to that in group BF between the time interval of 90 – 240 mins($p<0.05$), beyond which the mean VAS scores were comparable in group BF and BN. The mean VAS score of 4 was achieved at 450 mins in both BF and BN groups. Thus, patients in group B showed increasing VAS score of 90 min onwards and reached a value of 4 early i. e at 330 min, requiring rescue analgesia.

In contrast, patients in groups BF and BN registered delayed increase in VAS score and reached a VAS score of 4 at 450min. Also, the mean VAS score in group BN was significantly lower from 90 to 240 min than in group BF ($p<0.05$). These results are correlated well with the study done by Pal *et al.* (2011) and Jyothi *et al.* (2014). Degree of Sedation scored on the Ramsay sedation scale at various time intervals throughout the study duration showed no statistically significant difference in the three groups.

Maximum patients in the three groups showed a sedation score of 2, reflecting a co-operative, oriented and tranquil state of the patient. Hemodynamic parameters and respiratory rate changes were comparable in all three groups.

As far as side effects are concerned, 2% patient in group B and 6% patients in group BF complained of nausea/ vomiting. They were treated with Inj. Ondansetron 4mg IV. In group B, it can be attributed to a higher level of spinal anaesthesia (T4). Pruritus was observed in 6% of patients in group BF, but was of mild intensity requiring no treatment. Pruritus induced by intrathecal and epidural opioids is likely due to activation of μ opioid receptors (Gauchan *et al.*, 2014) and cephalad migration of drug in cerebrospinal fluid with subsequent interaction with trigeminal nucleus located superficially in the medulla. Intraoperative hypotension was noted in 4% of patients in group B, and 4% in group BF, they were treated with IV fluids and Inj. Mephenteramine 6mg iv, which can be attributed to a higher level of spinal anaesthesia in these patients. Bradycardia was observed in 6% of patients in group BN and 4% patients in group BF. It was treated with Inj. Atropine 0.6 mg IV post-dural puncture headache was reported in 1 patient each in group B and group BF in our study. It is attributed to spinal anaesthesia. We did not encounter even a single case of respiratory depression. Overall side effects observed in the present study were less frequent and required simple measures to treat them.

CONCLUSION

Intrathecal fentanyl 25μg and nalbuphine 500μg are acts synergistically to potentiate intrathecal local anaesthetic bupivacaine with the result that there is a prolongation of both sensory and motor block. It is worthwhile to note that prolongation of sensory block is beneficial to the patient in the sense that duration of effective analgesia is prolonged in the early post-operative period thereby reducing the need for total number rescue analgesic doses. Nalbuphine-bupivacaine combination was comparable to fentanyl-bupivacaine combination in terms of sensorimotor blockade and analgesia.

However, we suggest Nalbuphine-bupivacaine combination as a better alternative than a fentanyl-bupivacaine combination with respect to its lower side effect profile like pruritus & respiratory depression. Its easy availability as it does not come under the Narcotic act is a significant favourable aspect. Narcotics nonviability & its procurement is a concern in Indian hospitals.

Limitations

The study needs further follow up after the first rescue analgesic dose to find out the total consumption of analgesics and also requires more elaboration on the study of side effects.

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Conflict of interest

None.

Ethical approval

Institutional ethics committee.

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