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The spinal adjuvent - intrathecal nalbuphine as effective as intrathecal fentanyl

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ABSTRACT

Opioids are favoured as adjuvants to local anaesthetics for spinal anaesthesia. The present study was aimed to compare the clinical efficiency of intrathecal nalbuphine with fentanyl as an adjuvant to 0.5% hyperbaric bupivacaine. 100 adult patients of either sex, ASA grade I and II, aged 18–60 years were randomized into two groups of 50 each to receive either fentanyl 25 μg (Group BF) or nalbuphine 500μg (Group BN) with 3 ml 0.5% hyperbaric bupivacaine, making drug volume to 3.5 ml in each group. Sensory and motor block characteristics, duration of analgesia, VAS score, haemodynamic and side effects were recorded. The sensorimotor characteristics were comparable and found no significant difference between the two groups, (P>0.05). The time duration for adequate analgesia in group BN was 366.40 $\pm$ 37.32min, and in the group, BF was 361.39 $\pm$ 43.96min, (P= 0.567). In both, the groups, quality of analgesia during the procedure was excellent in a maximum number of patients (96% each group). In group BF, 4 (8%) patients complained nausea/ vomiting, pruritus was observed in 2 (4%), intraoperative hypotension in 3 (6%) and bradycardia in 2 (4%) and post-dural puncture headache in 2 patient (4%). In group BN, only bradycardia was observed in 3 (6%) patients. Nalbuphine and fentanyl were found to be equally efficient, but nalbuphine had a lower side effect profile, readily available as it does not come under the Narcotic act. However, we suggest Nalbuphine-bupivacaine combination as a better alternative than fentanyl-bupivacaine combination.

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INTRODUCTION

The subarachnoid block is a popular technique for lower abdominal and lower limb surgeries (Rajan *et al.*, 2018) for its ease of administration & rapid onset of anaesthesia with extended postoperative analgesia (Bindra *et al.*, 2018; Taksande and Varghese, 2017). Bupivacaine, which is the most commonly used drug for spinal anaesthesia, has a slow onset, high potency, and limited duration of postoperative analgesia (Ahmed, 2019). That is why many intrathecal adjuvants to local anaesthetic have been

addressed to augment the clinical efficacy and duration of analgesia (Gupta *et al.*, 2016).

However, among various adjuvants, intrathecal opioid has provided an effective prolongation of postoperative analgesia after surgical procedures (Roussel and Heindel, 1999; Förster and Rosenberg, 2003). The opioid analgesics activate opioid receptors located on the primary afferent neurons, resulting in the activation of pain modulating systems. Their activation may either directly decrease neurotransmission or inhibit the release of excitatory neurotransmitters. Opioid agonist acts on mu receptors and is principally responsible for supraspinal and spinal analgesia along with sedation, nausea, vomiting, pruritus, and respiratory depression. Opioid, an agonist-antagonist, act primarily on kappa receptors. Site of action in the spinal cord is substantiagelatinosa. Analgesia with neuraxial opioids is doserelated and specific for visceral rather than somatic pain (Gupta *et al.*, 2016).

Fentanyl is an opioid agonist and acts on μ-opioid receptors. As an analgesic, fentanyl is 75 to 125 times more potent than morphine. Since it is extremely lipid-soluble and reaches opioid receptors very rapidly, this accounts for its rapid onset (1-2 min) and relatively short duration of action (Taksande and Varghese, 2017). Nalbuphine is a synthetic opioid analgesic with agonist-antagonist activity and acts as an antagonist at μ-receptors and agonist at κ-receptors to provide reasonably potent analgesia (Flood *et al.*, 2005). Nalbuphine, when used as an adjuvant to hyperbaric bupivacaine, has improved the quality of perioperative analgesia with fewer side effects. Also, it has been used intrathecally by various investigators to enhance the postoperative analgesia (Culebras *et al.*, 2000; Pal *et al.*, 2011). There is no documented report of neurotoxicity with nalbuphine. Morphine, fentanyl, and other μ-opioids come under the Narcotic Act. Thus, their availability is a significant concern, while nalbuphine is readily available (Lin, 1992). Hence, the present study was designed to compare the effects of nalbuphine versus fentanyl to hyperbaric bupivacaine for lower abdominal or lower limb surgeries.

MATERIALS AND METHODS

This prospective observational study was conducted in a total of 100 adult patients of either sex, ASA grade I or II, age 18-60 years, height 150-170cm. We selected elective lower abdominal or lower limb surgeries. The Institutional Ethical Committee approval was obtained and written informed consent was taken from all the patients. This study was carried out in the Department of Anaesthesiology at a Tertiary care centre in Maharashtra during a period from December 2014 to November 2016.

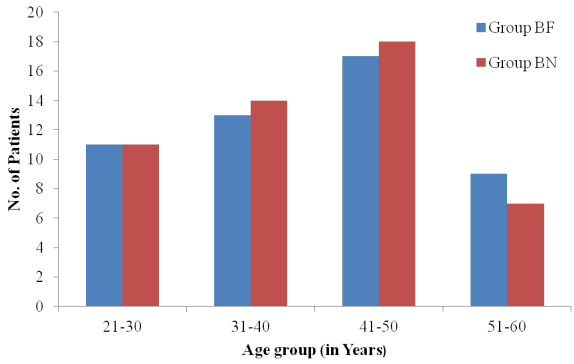

Figure 1: Distribution of patients according to age groups

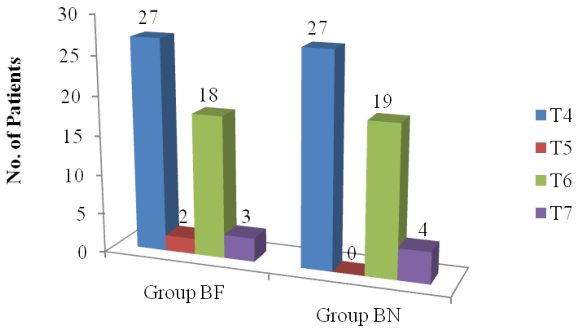

Figure 2: Highest Sensory Level Achieved

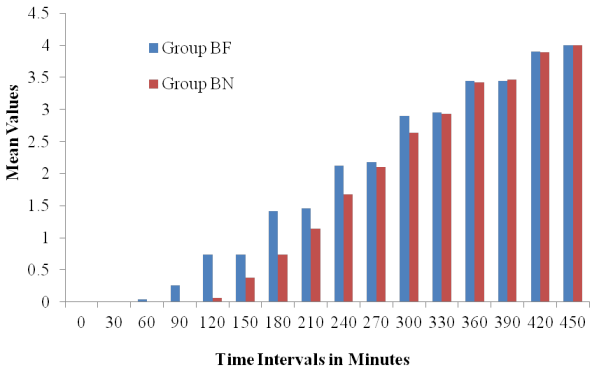

Figure 3: Comparison of mean VAS Score at Various TimeIntervals between two groups

Patients with cardiovascular, neurological, respiratory, renal or endocrine diseases or psychiatric illness, severe anaemia, hypovolemia, pregnant patients, 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 physical ASA status $\geq$III, height <150cm or > 170cm and patients not willing for the

Table 1: Comparison of Sensorimotor Characteristics between two groups

Characteristics	Group BF	Group BN	P value
Onset of sensory block (sec)	61.7±23.76	59.5±24.67	>0.05
Onset of motor block(min)	2.85±0.67	2.61±0.58	>0.05
Time to achieve T10 level group (min)	3.75±0.71	3.79±0.73	>0.05
Time to achieve highest sensory level (Min)	6.89±1.35	6.62±1.28	>0.05
Time for 2 segment regression (min)	99.79±6.75	98.64±7.74	>0.05
Complete motor block (min)	6.12±0.77	6.10±0.92	>0.05
Duration of sensory block (min)	154.85±11.57	152.36±12.34	>0.05
Duration of motor block (min)	129.82±13.42	125.36±12.45	>0.05
Duration of effective analgesia (min)	360.51±46.85	365.43±37.32	>0.05

Table 2: Comparison of complications between two groups

Complications	Group BF	Group BN
Nausea/Vomiting	4 (8%)	0 (0%)
Hypotension	3 (6%)	0 (0%)
Bradycardia	2 (4%)	3 (6%)
Pruritus	2 (4%)	0 (0%)
Postdural puncture headache	2 (4%)	0 (0%)

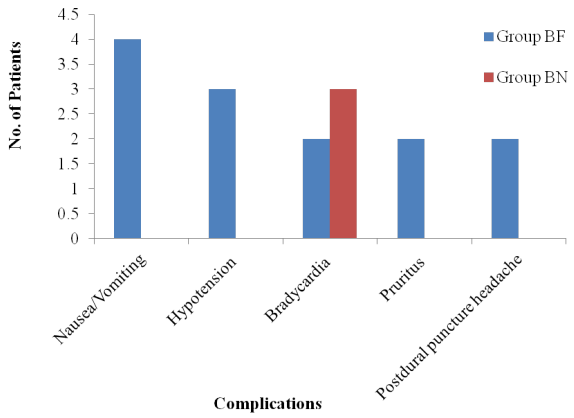

Figure 4: Comparison of complications between twogroups

procedure were excluded from the study.

After a detailed history and thorough clinical examination, all relevant investigations were done. Electrocardiogram, chest X-ray and other investigations like LFT, KFT, and coagulation profile were done as per clinical discretion. 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, the patient was preloaded with 10ml/kg of Ringer lactate solution over 10-30mins. A multipara monitor was used to monitor vital parameters. 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 a midline approach to 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 BF (50 patients): 15mg hyperbaric Bupivacaine 0.5 % (3ml) + Inj. Fentanyl 25μg (0.5ml) and Group BN (50 patients): 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 which was drawn in a 5ml syringe. In both the groups, the total volume injected was 3.5ml. Both Nalbuphine and Fentanyl used in the study were preservative-free 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 postoperative side effects were observed 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. A

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.

OBSERVATIONS AND RESULTS

Total of 100 patients was divided into two groups of 50 patients in each group. In group BF, 30 (60%) patients were males and 20 (40%) females while in group BN, 35 (70%) were males and 15 (30%) were females. Thus, male predominance was observed in both groups. Most of the patients had height between 161-170 cm in group BF (28; 56%) and BN (34; 68%) whereas height between 151-160 cm observed in 22 (44%) cases in group BF and 16 (32%) in group BN. In both the groups, maximum number of patients observed in ASA status I (BF: 86% and BN: 88%) and remaining patients in ASA status II (BF: 14% and BN: 12%). The age distributions of patients are depicted in Figure 1. There were no significant differences in demographic data regarding age, sex, height and ASA grading between the two groups.

In most of the patients, the surgical procedure was done in both the groups (Group BF: 64% and group BN: 60%) while the orthopaedic process was done in 36% and 40% patients in group BF and BN respectively. The mean duration of surgery was found to be 85.50$\pm$26.48 min in groups BF and 87.27$\pm$25.05 min in group BN, (p=0.0001). The difference between the two groups regarding type and duration of surgery was not significant (p>0.05).

All the sensorimotor characteristics were comparable and found no significant difference between the two groups, (P>0.05), as shown in Table 1.

The highest sensory level was T4 in a maximum number of patients in both the BF and BN groups, (54% in each group) as depicted in Figure 2. The quality of analgesia during the procedure was excellent in a maximum number of patients, i.e. 96% in each group. In comparison, the quality of analgesia was reported as good in 4% of patients in each group. The time duration for adequate analgesia in group BN was 366.40 $\pm$ 37.32min, and in the group, BF was 361.39 $\pm$ 43.96min, (P= 0.567), it was comparable between two groups, (p=0.0001).

The pain was evaluated on the visual analogue scale (1-10cm); rescue analgesia was given at VAS $\geq$ 4. The analysis showed that group BN had a significantly lower mean VAS score between the time interval of 90 – 240 minutes, beyond which the mean VAS scores were comparable in group BF and BN. The mean VAS score of 4 was achieved at 450 minutes in both the groups, as shown in Figure 3.

Sedation score, hemodynamic parameters and respiratory rate changes were comparable between two groups. Table 2 show the intra and postoperative complications observed in two groups.

DISCUSSION

The quality of intraoperative analgesia & extended effective relief of pain during the intr postoperative period is of principal importance for anesthesiologist & surgeon as well. It has significant physiological benefit through the smoother postoperative course and earlier discharge from the hospital, and it may also reduce the onset of chronic pain syndromes (Bindra *et al.*, 2018). The present study compared the clinical efficacy of intrathecal nalbuphine with fentanyl as an adjuvant to 0.5% hyperbaric bupivacaine by assessing the sensory and motor blockade characteristics and duration of postoperative analgesia as the primary endpoints. The results of the study showed that the onset of sensory and motor block was comparable between fentanyl and nalbuphine group. This can be explained that both fentanyl and nalbuphine are lipophilic, which can result in the rapid uptake of the drugs resulting in similar onset (Lin, 1992; Wang *et al.*, 1988).

Also, the duration of sensory and motor block was comparable between the two groups. Although the duration of adequate analgesia was slightly shorter in the fentanyl group, it was not statistically significant when compared to nalbuphine. In group BF

and BN, 48 patients each reported excellent quality of analgesia, and two patients in each group reported good quality of analgesia. Quality of analgesia was found to be comparable in 2 groups (p= 0.715). Thus the addition of fentanyl or nalbuphine only marginally improved quality of surgical analgesia in the current study. These results are in agreement with the research performed by Thote et al., where the onset of sensory and motor block with 25 μg of fentanyl and 0.5 mg of nalbuphine was similar and observed longer duration of analgesia with nalbuphine group when compared to fentanyl group (Thote *et al.*, 2015).

Nalbuphine had lower VAS scores and was more efficient in providing a better quality of analgesia in the early postoperative period than compared to fentanyl. However, the analysis showed that group BN had a significantly lower mean VAS score between the time interval of 90 – 240 minutes ($p<0.05$), beyond which the mean VAS scores were comparable in group BF and BN. The mean VAS score of 4 was achieved at 450 minutes in both the groups. These findings are correlated well with the previous studies (Jyothi *et al.*, 2014; Gomaa *et al.*, 2014).

These studies also have shown lesser VAS scores with prolongation of analgesia with nalbuphine group. Lower potency of nalbuphine and its agonist and antagonist property might be the cause. Degree of sedation scored on the Ramsay sedation scale throughout the study duration showed no statistically significant difference in two groups at any time interval, intraoperatively or postoperatively. Thus, the sedation score was equal for both the groups, but the number of rescue analgesia was less in the nalbuphine group. Gupta *et al.* (2016) and Mostafa *et al.* (2011) recorded negligible sedation and comparable mean sedation score in the fentanyl and nalbuphine group; similar results were found in our study.

During the intra and postoperative period, there was no significant difference observed in the mean pulse rate and mean arterial pressure at various intervals in two groups. The other authors did not record any significant variations in the pulse rate of patients with fentanyl and nalbuphine group. Also, no significant difference observed in mean preoperative systolic blood pressure (SBP), but the difference in mean SBP was statistically significant at the intervals of 20, 30, 50 and 60 minutes. At these occasions, the mean SBP was comparable in group BF and BN. This can be attributed to higher sensory level (T4) achieved in these groups. Observations at other intervals and an immediate postoperative period no significant differences were observed in mean SBP in two groups. These findings are correlated with the study done by Gupta *et al.* (2016) and Gomaa *et al.* (2014).

There was no adverse effect on respiratory function evident in 2 groups. The respiratory rate was within the normal range as was the SpO2 levels, which fluctuated between 97% -100% during the intraoperative as well as postoperative period, which is similar to the other studies (Dubey and Bisht, 2014; Padma and Mydhili, 2015).

As depicted in Figure 4, 8% of patients in group BF complained of nausea/ vomiting and was treated with Inj. Ondansetron 4mg IV. Pruritus was observed in 4% of patients in group BF but was of mild intensity requiring no treatment. The fall in SBP was so much so that three patients (6%) of group BF developed hypotension and were treated with IV fluids and Inj. Mephenteramine 6mg, 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. This was treated with Inj. Atropine 0.6 mg IV Incidence of hypotension and bradycardia was not statistically significant between the two groups. This shows that both the opioids did not have any significant sympatholytic activity and instead enhanced the antinociception in the spinal cord. postdural puncture headache was reported in 2 patients in group BF; it is attributed to spinal anaesthesia. The most feared side effect of intrathecal opioid is respiratory depression. High doses of opioid increase the risk of respiratory depression. No incidence of respiratory depression was observed in any patient intra or postoperatively in two groups.

CONCLUSION

Nalbuphine and fentanyl were found to be comparable in sensory, motor and analgesic characteristics and hemodynamic stability in patients undergoing lower abdominal or lower limb surgeries. But, intrathecal nalbuphine had a lower side effect profile as compared to intrathecal fentanyl, and it is cost-effective. Easy availability is an attractive proposition as it does not come under the Narcotic act. However, we suggest Nalbuphine-bupivacaine combination may prove to be a better alternative to the fentanyl-bupivacaine combination.

The limitations of the present study

We did not have the control group. Though the sample size calculated was adequate, we feel that a larger sample size may prove to be more elaborative, especially to be sure about the side effect pro-

file. There is a different pharmacodynamic property exhibited by nalbuphine which needs to be further researched.

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Conflict of interest

None.

Ethical approval

Institutional ethics committee.

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