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COMPARISON OF POST-OPERATIVE ANALGESIA AFTER INTRATHECAL NALBUPHINE WITH BUPIVACAINE AND INTRATHECAL FENTANYL WITH BUPIVACAINE FOR SUBARACHNOID BLOCK IN PATIENTS UNDERGOING LOWER ABDOMINAL AND LOWER LIMB SURGERIES: A RANDOMIZED DOUBLE BLINDED CLINICAL TRIAL.

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ABSTRACT The study was made to compare clinical efficacy of nalbuphine and fentanyl as adjuvant to hyperbaric bupivacaine in patients undergoing infraumblical surgeries under subarachnoid block.

Patients and methods: A total of 100 patients of ASA status I and II aged 20 to 60 years undergoing lower abdominal and lower limb surgeries under spinal anaesthesia were randomized into two groups as Group N: receiving inj. Bupivacaine hyperbaric 0.5% 3 ml + inj. Nalbupine 500mcg and Group F: receiving inj. Bupivacaine hyperbaric 0.5% 3 ml + inj. Fentanyl 25mcg intrathecally.

Results: The onset of sensory and motor blocks and the duration of sensory and motor blocks were comparable in both the groups. The duration of postoperative analgesia (in min) was 322.10±20.39 in Group N and 248.28±17.73 in Group F ($p<0.005$) with statistically significant difference between groups.

Conclusion: Intrathecal nalbuphine when added to hyperbaric bupivacaine as an adjuvant provides clinically more efficient and better quality of block as compared to fentanyl. It also prolongs postoperative analgesia for 6-7 hrs (322 ±20min) when compared to fentanyl (248±17 min) when used as an adjuvant without any significant adverse effects for patients undergoing lower abdominal and lower limb surgeries under subarachnoid block.

KEYWORDS : Nalbuphine, Fentanyl, Bupivacaine, Intrathecal, Post-Operative Analgesia.

INTRODUCTION:

In the field of anaesthesiology spinal anaesthesia is still the most popular regional anaesthesia technique performed for below umbilical and lower limb surgeries because of its simplicity, rapid onset of action, adequate sensory and motor blockade. However the disadvantage is its inadequate duration of postoperative analgesia. Hence post-operative pain management under spinal anaesthesia still remains a continuous challenge for the anaesthesiologists.

Many drugs like Morphine, Buprenorphine, Fentanyl, Midazolam, Clonidine etc. have been used intrathecally as an adjuvant to local anaesthetic to prolong postoperative analgesia with variable success and associated side effects. Opioids are the most frequently used local anaesthetic adjuvants and their use in neuraxial blocks have evolved over the last 50 years.[1]

Adding adjuvant drugs to intrathecal local anesthetics improves quality and duration of sensory blockade and prolongs postoperative analgesia. Intrathecal opioids are synergistic with local anesthetics thereby intensifying the sensory block without increasing sympathetic block.[2] Among the intrathecal adjuvants fentanyl is the most commonly used drug in our institution. Fentanyl is an opioid agonist and acts on μ-opioid receptors.[3]

Nalbuphine is an opioid, structurally related to oxymorphone. It is highly lipid soluble opioid with an agonist action at the kappa and an antagonist activity at the mu opioid receptors.[4,5] Nalbuphine and other kappa agonists have provided reasonably potent analgesia in certain models of visceral nociception. It has a moderate duration of action consistent with their lipid solubility and rapid clearance compared with other opioids like Morphine.[6]

Nalbuphine is recently introduced in India. There are very few studies in literature comparing nalbuphine and fentanyl as an adjuvant to bupivacaine during subarachnoid block. Therefore attempt was made to compare nalbuphine and fentanyl as adjuvant to hyperbaric bupivacaine in patients undergoing lower abdominal and lower limb surgeries under subarachnoid block.

METHODOLOGY:

After obtaining the approval of the institutional ethical committee and written informed consent from the patient, a total of 100 patients of ASA status I and II aged between 20 to 60 years who were undergoing lower abdominal and lower limb surgeries under spinal anaesthesia from December 2017 to June 2018 at The Oxford Medical College, Hospital & Research Centre, Yadavanahali, Bengaluru were included in this hospital based prospective randomized double-blind study. Patients who refused to participate, allergic to the study drugs-bupivacaine or nalbuphine or fentanyl, patients on long standing opioids, patients with coagulation abnormalities, spine defects or infection at the site, history of mental dysfunction, morbid obesity, or any significant systemic disease, pregnant females posted for caesarean section were excluded from the study.

Included patients were kept nill orally for 6 hours. Randomization was done into two groups by computer generated method as Group N: receiving Inj. Bupivacaine hyperbaric 0.5% 3 ml + Inj. Nalbupine 500mcg diluted with Normal saline to 3.5ml intrathecally and Group F: receiving Inj. Bupivacaine hyperbaric 0.5% 3 ml + Inj. Fentanyl 25mcg making it to volume of 3.5ml intrathecally.

An 18G i.v. cannula was secured. All patients were preloaded with 10 ml/kg of crystalloid solution. Baseline oxygen saturation (SpO_2), heart rate(HR), NIBP and ECG were recorded before performing the procedure. The study medication was prepared by the person who is not involved in the study making the drug to 3.5ml volume of transparent solution for all the patients in a 5ml syringe to ensure blinding. Under aseptic conditions, subarachnoid block was performed using 25G Quinke's spinal needle at L3 –L4 level in sitting position. Study drug was injected. The assessment of the hemodynamic parameters like heart rate, BP and SpO_2 were noted.

Following observations were made by the attending anaesthesiologist who is also blinded for the drug administered:
T0 – Time of spinal anaesthesia.
T1 – Time of onset of sensory block.
T2 – Time of onset of motor block.
T3 – Two segment regression of sensory block.
T4 – Duration of motor block.
T5 – Time to first dose of post-operative rescue analgesia.

Sensory block: Sensory level is assessed by loss of cold sensation to swab in mid-clavicular line, every 5 minutes and peak sensory level achieved during study was noted down.

Motor block:

Using modified bromage scale[7]: 0- no motor block; 1- inability to flex the hip; 2- inability to flex the knee; 3- inability to flex the ankle.

Onset of motor block was defined as the time taken to achieve Bromage scale 3. Time taken to achieve complete motor blockade was also noted. It was measured until patient returned to score of 0 in both

lower limbs.

Vital parameters were monitored every 5 min for 20 min then every 10 min till end of surgery. Peri-operatively patients were observed carefully for the side effects like nausea, vomiting, hypotension, pruritus etc.

VAS score was calculated on a 10 cm long scale with '0' on one end, meaning 'no pain', while '10' representing 'worst pain imaginable'. Patients were rating the degree of pain by making a mark on the scale every 15min. Thus the pain score was obtained by measuring the distance from the '0' end to the indicated mark.

Postoperative analgesic drug was given when patient's VAS score reached >3 and this time was taken as duration of post-operative analgesia. Inj. Diclofenac 75 mg (Aq) in 100ml saline was given i.v. route over 10min as rescue analgesia.

STATISTICALANALYSIS:

Results were expressed as means ± standard deviation of the means (SD) or number (%) and frequencies. Comparison between different parameters in the two studied groups was performed using unpaired t test. Comparison between categorical data was performed using Chi square test/ fisher exact test. The data were considered significant if p value was equal to or less than 0.05 and highly significant if p value < 0.01. Statistical analysis was performed with the aid of the SPSS computer program (version 20.windows).

RESULTS:

One hundred patients were enrolled in the current study. There were no significant differences in demographic data regarding age, weight, height, sex ratio, and duration of surgery, among the different groups as shown in [Table 1].

Table 1: Demographic data and duration of surgery

Variable	Group-N	Group-F	T-Value	P value
Age(yrs)	41.18 ± 9.04	39.90± 9.02	0.7090	0.4800
Weight(kg)	73.80 ± 8.31	74.14 ± 7.98	0.2087	0.8351
Height(cm)	165.26 ± 7.54	166.12 ± 7.24	0.5819	0.5620
Sex(M:F)	24:26	27:23		0.6891
Duration of surgery(min)	130.48 ± 25.90	129.92 ± 25.66	0.1086	0.9137

The results regarding the characteristics of sensory and motor blocks have been shown in [Table-2]. The time of onset of sensory and motor blocks were significantly less in than group F. Time of two segment sensory regression and the duration of motor block was comparable in both the groups and was significantly more (p>0.05) in N group than F group.

The duration of post operative analgesia (in minutes) was 322.10±20.39 in Group N and 248.28±17.73 in Group F (p<0.005). There was statistically significant difference in the duration of post operative analgesia between Group N and Group F [Table-2].

Table-2: Characteristics of sensory and motor blocks

Variable	Group-N	Group-F	T-Value	P value
So (time of onset of sensory block)	1.886±0.532	2.212 ±0.386	3.5068	0.0007
Mo (time of onset of motor block)	3.136±0.718	3.994±0.780	5.7211	0.0001
S2 (two segment sensory regression)	213.60±14.09	123.50±6.43	41.1415	0.0001
M (motor duration)	241.04±20.58	145.96±8.12	30.3913	0.0001
Rescue Analgesia	322.10±20.39	248.28±17.73	19.3183	0.0001

Adverse effects among the groups have been summarised in [table 3]. The adverse effects like incidence of hypotension, nausea-vomiting and shivering were comparable in both the groups with insignificant statistical difference. The incidence of pruritus was more in group F than group N with insignificant statistical difference.

Table 3:Adverse effects in the two studied groups.

Characteristics	Fentanyl(n=50)	Nalbuphine (n=50)	p Value
Hypotension	1(2%)	1(2%)	1(NS)
Nausea and vomiting	2(4%)	2(4%)	1(NS)
Shivering	1(1%)	2(4%)	0.4173(NS)
Pruritus	3(6%)	0	0.2424(NS)

The mean Heart rate(HR), mean arterial pressure(MAP) and SpO2 were almost similar in both the groups with no statistically significant difference. (Figure 1 & 2), Table 4.

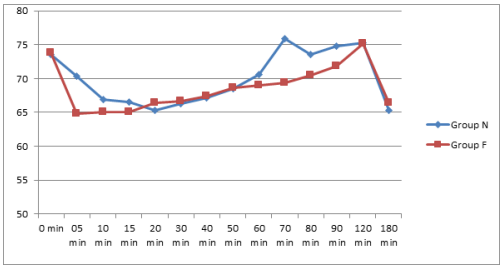

Figure 1: mean Heart rate(HR)

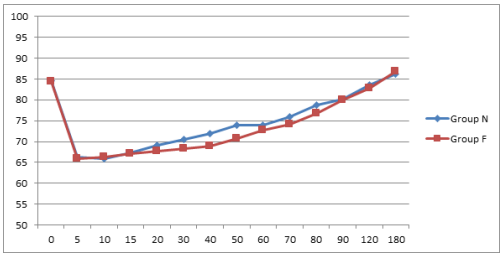

Figure:2 - mean arterial pressure(MAP)

Table 4: Comparison of Vital Parameters:

Parameters	Group N(n= 50) (Mean ± SD)	Group F(n=50) (Mean ± SD)	p-value
HR	70.01±5.01	68.56 ±4.28	>0.001
MAP	74.87 ±3.72	73.75 ±3.17	
SPO2	99.94 ±0.23	99.93 ±0.24	

DISCUSSION:

Newer techniques and drugs are always the need of the day in anesthesiology and pain management. Even though subarachnoid block is the most commonly used technique for lower abdominal and lower limb surgeries, it is limited by its inadequate duration of postoperative analgesia. Hence many adjuvants have been tried for prolonging post-operative analgesia after subarachnoid block but with their own side effects.

Opioids intrathecally decrease nociceptive inputs from A delta and C fibers without affecting dorsal root axons or somatosensory evoked potentials.[8] Nalbuphine when binds to mu(μ) receptors, competitively displaces other μ antagonists from the receptors without itself displaying any agonistic effect. When it binds to kappa receptors, it has agonistic effect. Hence, it is a mixed agonist-antagonist. It produces analgesia and sedation without μ side effects. Animal studies have ruled out any neurotoxicity of intrathecal nalbuphine.[9]

In the current prospective randomized double blind study we have used nalbuphine 500mcg as an adjuvant to 0.5% hyperbaric bupivacaine and compared with fentanyl 25mcg to 0.5% hyperbaric bupivacaine for assessing the duration of postoperative analgesia as the primary end point and characteristics of sensory and motor blockade, intraoperative hemodynamic changes and side effects like nausea, vomiting, hypotension, pruritus etc. as the secondary end points.

The first study which used intrathecal nalbuphine was conducted by Culebras et al who compared intrathecal morphine (0.2 mg) added to hyperbaric bupivacaine with different doses of intrathecal nalbuphine (0.2 mg), (0.8 mg) and (1.6 mg) added to hyperbaric bupivacaine in cesarean section and their study concluded that intrathecal nalbuphine 0.8 mg provides good intra-operative and early post-operative analgesia without side effects.[10]

Mukherjee et al.[11] in 2011 conducted a study on 100 patients undergoing only lower limb orthopaedic surgery using subarachnoid block. But our study was conducted on same sample size of 100 patients of ASA status I and II aged between 20 to 60 years who were undergoing different kinds of infra umbilical surgeries which include lower abdominal & lower limb surgeries under spinal anaesthesia.

In our study we excluded Pregnant females posted for caesarean section as the dose and volume of drug administered is higher than usually administered dose for caesarean section, but Mostafa et al compared post-operative analgesia after intrathecal nalbuphine with bupivacaine and intrathecal fentanyl with bupivacaine after caesarean section with a lower dose and concluded that The duration of post-operative analgesia was more prolonged in nalbuphine group but the difference was insignificant. This can be explained by lower drug volume(2.5ml) used in their study.[12]

In a study done in 2014 evaluating the effect of nalbuphine as an adjuvant to bupivacaine compared with bupivacaine alone on elderly patients 500mcg of intrathecal nalbuphine was used, which was similar to the dose used in our study and concluded that it provides better quality of block as compared to bupivacaine alone.[13]

The present study revealed no statistically significant difference in the demographic data which was comparable in both the groups with respect to means of age, sex ratio, height, weight and duration of surgery.[Table 1]

In our study there was no significant difference between onset of sensory and motor block and there was also no significant difference between peak sensory and motor block and duration of motor block in both the groups which was similar to study done by AB Pawar etal in 2017.[14][Table 2]

The duration of effective post-operative analgesic time was more (322.10±20.39) in Group N when compared to(248.28±17.73) Group F with high statistical significance($p<0.01$). The results of the present study correlates well with other studies where it was observed that addition of nalbuphine allowed a significant reduction in pain score and prolongation of duration of postoperative analgesia.[15]

Gupta et al in 2015-16 conducted a study on orthopaedic surgeries and concluded that duration of analgesia was also extended in patients of Nalbuphine Group (378.0 ± 35.72 min) as compared to Fentanyl Group (234.0 ± 24.10 min) with highly significant difference ($P <$ 0.001). No drug-related side effects were observed in either group. which was similar to current study.[16]

Lin et al. found that the addition of intrathecal nalbuphine 0.4 mg to hyperbaric tetracaine, compared with intrathecal morphine 0.4 mg for subarachnoid block, improved the quality of intraoperative and postoperative analgesia, with fewer side-effects.[17]

Also in the present study no statistically significant difference was found between both groups as regards the hemodynamics like HR, Mean arterial pressure and oxygen saturation. Neither bradycardia nor oxygen desaturation was recorded in our study which is similar to other studies.[1011]

In 2011 study by Tiwari and Tomar showed that nalbuphine hydrochloride (400 µg) significantly prolongs the duration of sensory blockade and postoperative analgesia without any side effect or complication when introduced intrathecally along with hyperbaric bupivacaine.[18] similar to our study very few side effects like nausea, vomiting, itching etc.

In a study done by Sapate et al.[19] on adding intrathecal nalbuphine to bupivacaine for patients undergoing infraumbilical surgeries, they concluded that intrathecal nalbuphine added to bupivacaine provides better quality of block and longer post-operative analgesia than our study (8–9) hours than bupivacaine alone without any significant adverse effects, this may be due to prolongation of duration of action in elderly due to reduced metabolism.

As regards to neurotoxicity of intrathecal nalbuphine, it has been used in modern practice for more than 10 years without any reports of neurotoxicity.[20,21]

CONCLUSION:

Intrathecal nalbuphine added to hyperbaric bupivacaine as an adjuvant provides clinically more efficient and better quality of block as compared to fentanyl as an adjuvant to bupivacaine. It also prolongs postoperative analgesia for 6-7 hrs (322 ± 20min) when compared to fentanyl 4hrs (248±17 min) when used as an adjuvant to bupivacaine without any significant adverse effects for patients undergoing lower abdominal and lower limb surgeries under subarachnoid block.

There are no conflicts of interest regarding the current study.

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