



# Comparative evaluation of sequential and premixed administration of hyperbaric bupivacaine with fentanyl in subarachnoid block for lower limb surgeries – A randomized prospective study

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## ABSTRACT

**Background:** Subarachnoid block is the most commonly used anesthetic technique for lower limb surgeries. Fentanyl is very often combined with hyperbaric bupivacaine as an adjuvant. This study was conducted to compare the block characteristics by administering bupivacaine and fentanyl in a sequential and premixed manner. **Aims and Objectives:** The primary objective was to compare the effects of hyperbaric bupivacaine and fentanyl administered either as a premixed solution or sequentially on block characteristics-onset of sensory and motor blockade, regression of block and duration of analgesia. The secondary objective was to study the hemodynamic changes and adverse effects. **Materials and Methods:** A total of 72 patients scheduled to undergo lower limb surgery were allocated to three groups. Patients in Group A received 15 mg of 0.5 % bupivacaine heavy (H), followed by 25 mcg of fentanyl intrathecally using different syringes. Group B received 25 mcg of fentanyl, followed by 15 mg of 0.5% bupivacaine H in a separate syringe. Group C received premixed 0.5 % bupivacaine H 15 mg and fentanyl 25 mcg in single syringe. The block characteristics-onset and regression of sensory and motor blockade, duration of analgesia, and adverse effects were studied. **Results:** The mean time (minutes) taken for onset of sensory block was  $2.40 \pm 0.51$  in group A,  $4.80 \pm 0.53$  in Group B and  $6.70 \pm 0.50$  in Group C. Mean time (minutes) taken for onset of motor block was  $4.35 \pm 0.43$  in Group A, while it was  $5.64 \pm 0.65$  and  $7.32 \pm 0.64$  in Groups B and C, respectively. Two segment regression and duration of motor blockade were found to be longer in Group A. **Conclusion:** Sequential intrathecal administration of bupivacaine followed by fentanyl has a faster onset and prolonged duration of block when compared to the premixed group.

**Key words:** Intrathecal injection; Fentanyl; Bupivacaine

## INTRODUCTION

Subarachnoid block (SAB) has been the choice of anesthetic technique for lower limb surgeries as it offers an advantage of profound nerve block that can be achieved by a relatively simple intrathecal injection of a small amount of local anesthetic.<sup>1</sup> The most widely used local anesthetic in SAB is bupivacaine heavy (H), which

provides a more reliable block and has lesser adverse effects. Bupivacaine H has been used with opioid and non-opioid adjuvants to lengthen the duration of action, maintain hemodynamic stability, and provide prolonged post-operative analgesia.<sup>2</sup> Intrathecal opioids selectively decrease nociceptive afferent input from A $\delta$  and C fibers without affecting dorsal root axons or somatosensory evoked potentials.<sup>3</sup>

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The combination of bupivacaine H and fentanyl is widely used in SAB as it is synergistic and is known to improve the quality of block.<sup>4</sup> This combination has been administered in different methods; while some choose to combine both the drugs in a single syringe, others prefer to use separate syringes and administer these drugs in a sequential manner with fentanyl being administered first or later.

When fentanyl and bupivacaine H are premixed in a single syringe the baricity of the solution gets altered which can affect the spread of the drugs in the intrathecal region and this can have a bearing on the characteristics of the block. There is limited data on this aspect and hence this study was conducted to compare the block characteristics by administering bupivacaine H and fentanyl in a sequential and premixed manner.

### Aims and objectives

The primary objective was to compare the effects of hyperbaric bupivacaine and fentanyl administered either as a premixed solution or sequentially on SAB characteristics—onset of sensory and motor blockade, regression of block and duration of analgesia. The secondary objective was to study the hemodynamic changes and adverse effects. We also studied the impact of administering fentanyl before and after bupivacaine H on these parameters.

## MATERIALS AND METHODS

This randomized clinical study was conducted at a tertiary care teaching hospital in Bengaluru over a period of 2 years. After obtaining institutional ethics committee clearance (IEC Study Ref No. 366/2020) 72 patients of either sex, aged between 18 and 60 years and belonging to American Society of Anesthesiologist physical status 1 and 2, scheduled to undergo elective lower limb surgeries were allocated according to computer generated random numbers into three groups— Group A, Group B, and Group C after obtaining written and informed consent. Any patient with contraindications to spinal anesthesia and pregnant patients were excluded from the study.

### Sample size calculation

Required sample size was calculated based on the study conducted by Malhotra et al.<sup>5</sup> Using the mean $\pm$ SD criteria, with 5% level of significance and 90% power of the study, the sample size calculated was 72 with 24 patients in each group.

A detailed pre-anesthetic evaluation and all the relevant investigations were done. Patients were kept nil per oral - 6 h for solid food and 2 h for clear liquids. In the

operation theater, the standard monitoring devices—pulse oximeter, ECG, non-invasive blood pressure were attached and base line vitals recorded. Large bore intravenous (IV) cannula was secured and IV fluids started.

With the patient in a sitting position, under strict aseptic precautions, 2% lignocaine was infiltrated at the lumbar puncture site (L2-L3 OR L3-L4). Lumbar puncture was done with a 25 gauge Quincke needle. After the free flow of clear cerebrospinal fluid (CSF), drugs were injected intrathecally as per the group allocation. Group A received 15 mg of 0.5% bupivacaine H, followed by 25 mcg of fentanyl using two different syringes. Group B received 25 mcg of fentanyl followed by 15 mg of 0.5% bupivacaine H in another syringe. Group C received premixed 0.5% bupivacaine H 15 mg and fentanyl 25 mcg in a single syringe.

After injecting the drug, the patient was made to lie down in a supine position, and sensory block (T1) was assessed by sterile pin prick every 2 min until the T12 dermatome level was achieved. Time of onset of motor blockade (T2) was noted (time taken to reach a modified Bromage score of 3). Highest level of sensory block achieved was recorded. Time of sensory block regression (T3) was assessed (time taken for 2-segment regression from the highest sensory block). Time of regression of motor block (T4) was assessed (from a modified Bromage score of 3 to regression of motor blockade to 0). Total duration of analgesia (T5) was noted (from the onset of sensory block T12 to the first requirement of analgesia). Patients BP was recorded every 2 min for the first 10 min, then every 5 min till the end of the procedure. Episodes of hypotension (systolic blood pressure below 90 mmHg or a fall in blood pressure by more than 20% from baseline values) and bradycardia (heart rate <60 beats/min) were noted down. Undesirable effects of fentanyl such as nausea, vomiting, and pruritus were also noted. The patient and the person assessing the block characteristics were blinded to the sequence of the injection.

### Statistical analysis

Data were collected, coded, and tabled using Statistical Package for the Social Science (IBM Corporation Released 2017. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corporation) Mean and standard deviation ( $\pm$ SD) were used for numerical data. Qualitative variables are expressed as frequency and percentages and quantitative variables are expressed as mean and standard deviation. To compare the proportion between groups, Chi-square test was used. To compare the mean values between groups, ANOVA was used. Significance level was fixed as 5% ( $\alpha=0.05$ ).

## RESULTS

The demographic characteristics of patients were comparable across all the groups (Table 1). The SAB characteristics in all the groups are compared and summarized in Table 2. Onset of sensory and motor blockade was faster in sequential groups (A, B) as compared to the premixed group. Regression of the block was slower in Groups A and B as compared to Group C. Total duration of analgesia was longest in Group A followed by Group B and was least in Group C (Figure 1). The difference noted in block characteristics among the groups was statistically significant.

Incidence of hypotension was 20.8% in Group A and B while it was high in Group C (45.8%). The mean systolic blood pressure was noted to be low in Group C between 5 min and 45 min interval as compared to Group A and B (Figure 2). The p-value in this interval remained statistically significant. No episodes of bradycardia were observed in any of the study groups. Four patients in Groups A and B, and three patients in Group C experienced nausea. Pruritus was observed in one patient in Group A, two in Group B,

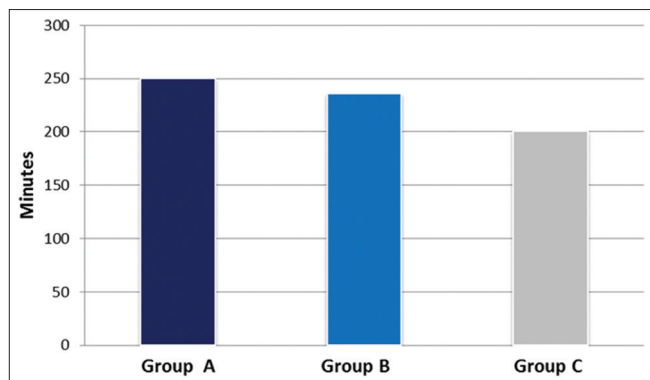


Figure 1: Comparison of total duration of analgesia

Table 1: Demographic data of patients

Demographic parameters	Group A	Group B	Group C
Age (years)	43±11.0	39.0±10.7	41.0±13.0
Gender M/F	15/9	20/4	18/6
BMI	26.0±3.4	25.1±3.7	27.0±3.3
ASA I/II	10/14	13/11	15/9

ASA: American Society of Anesthesiologists, BMI: Body mass index

Table 2: SAB characteristics among the three groups

SAB characteristics	Group A	Group B	Group C	P-value
T1-Sensory block onset (min)	2.40±0.51	4.80±0.53	6.70±0.50	<0.001
T2-Motor block onset (min)	4.35±0.43	5.64±0.65	7.32±0.64	<0.001
T3-Sensory regression time (min)	120.5±12.0	108.5±9.5	95.7±12.3	0.002
T4-Motor regression time (min)	150.6±10.7	135.2±11.2	125.2±8.3	0.001
T5-Total duration of analgesia (min)	250.2±15.5	235.6±10.5	200.6±12.8	0.000

SAB: Subarachnoid block

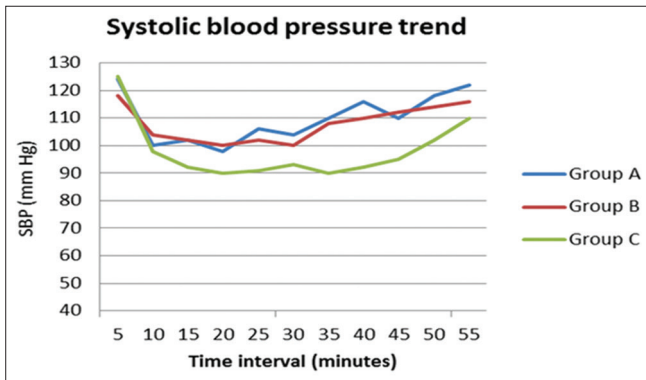
and none in Group C. There was no statistical difference in adverse effects among the three groups.

## DISCUSSION

SAB is the preferred anesthetic technique for lower limb surgeries due to its simplicity, safety, and reliability. Many adjuvants have been tried along with local anesthetics but opioids continue to be the most commonly used class of drugs. The opioids potentiate anti-nociception of local anesthetics by G protein-coupled receptor mechanisms by causing hyperpolarisation of the afferent sensory neurons.<sup>6</sup> The dose, site of injection, lipophilicity, and the acid-base milieu of the site of drug deposition determine the extent of efficacy of the block.<sup>7,8</sup>

Intrathecal fentanyl in the dose range of 10–25 mcg has been shown to prolong the duration and extent of sensory block with a favorable adverse effect profile.<sup>9</sup> Intrathecal fentanyl has a high lipid solubility, which allows its rapid clearance from the CSF. This increased clearance is postulated to cause less cephalad spread of fentanyl, and thus fewer side effects.<sup>10</sup> Combination of bupivacaine H and fentanyl for SAB has become a standard practise in many centers. The baricity of fentanyl is lower than bupivacaine H<sup>11</sup> and when these two drugs are combined together, the baricity of the mixed solution gets lowered to the extent of 0.006<sup>12</sup> which, in turn, can affect the block characteristics and this forms the crux of our study.

Among the three study groups, a faster onset of sensory and motor blockade was observed in sequential groups as compared to the premixed group. Among the sequential groups, it was faster in Group A wherein bupivacaine H was injected first as compared to Group B where intrathecal fentanyl preceded the local anesthetic. Similar results were seen in a study done by Malhotra et al.,<sup>5</sup> where they reported faster onset of sensory/motor block in the sequential group (2.9±1 min/3.6±1.1 min) and delayed in the premixed group (6.3±1.5 min/7.2±1.5 min). The findings of our study can be logically explained as follows- in sequential groups since bupivacaine H and fentanyl were injected separately, due to the baricity of local anesthetic the drug spread was more toward the most dependent part



**Figure 2:** Comparison of SBP at different time intervals. SBP: Systolic blood pressure

of the spine in supine position, that is, around T7-T8 level, while in the premixed group, the lower baricity restricted the cephalad spread of the drugs. The reason for the early onset of block in Group A as compared to Group B (both are sequential groups) could be the sequence of drug administration; since bupivacaine H was injected first in Group A, it would have resulted in an early block. The early onset of sensory block ( $2.40 \pm 0.51$  min) noticed in our study was probably because of the relatively higher dose (15 mg) of bupivacaine H as compared to the dose of 12.5 mg used in the study by Malhotra et al., and also the definition of sensory block onset was taken at T10 dermatome level in their study while it was T12 in our study. Contrast to our results Kumar et al.,<sup>13</sup> in their study reported that sequential intrathecal injection attained a slower onset of sensory block ( $12.6 \pm 1.929$  min) when compared with the premixed group ( $5.82 \pm 1.892$  min). In their study sensory block of T6 was considered which was different from our definition (T12 dermatome).

In our study, the mean two-segment regression of sensory level was found to be longer in Group A ( $120.5 \pm 12$  min) when compared to the other two groups. Similar results were found in various studies done by Malhotra et al., Singam and Mankhair<sup>14</sup> and Chaudhry et al.<sup>15</sup> The adjuvant used in the study by Chaudhry et al., was dexmedetomidine with 0.5% hyperbaric bupivacaine, which reiterates the fact that irrespective of the adjuvant used, when drugs are premixed in a single syringe and administered intrathecally, the onset of the block gets delayed due to change in baricity. The motor regression time follows a similar trend as that of sensory regression, being longest in the sequential group and lesser in the premixed group (Group A>B>C).

The total duration of analgesia was longer in Group A ( $250.2 \pm 15.5$  min) as compared to Group C ( $200.6 \pm 12.8$  min) which was statistically and clinically significant. Similar results were noted in studies done by Malhotra et al., and Kumar and Balaji. This difference might be due to the

fact that fentanyl and bupivacaine as a mixture dilutes the potency of fentanyl and receptor occupancy might decrease leading to a less pronounced effect.<sup>5</sup> On the other hand, if fentanyl is administered separately it leads to formation of stronger bonds with the mu opioid receptors concentrated in the superficial layers of the dorsal horn in the spinal cord leading to denser and prolonged block.

The incidence of hypotension in sequential Groups (A and B) was 20.8% while it was 45.8% in Group C. Similar results were found in a study done by Singam and Mankhair, the incidence of hypotension was less in sequential group (12.1%) and more in the premixed group (52.1%). In our study, we observed a fall in the systolic blood pressure in Group C between 5 min and 45 min intervals when compared to Group A and Group B which was statistically significant. There was no statistically significant difference in mean heart rate at different time intervals between the groups. The possible explanation for hypotension noted in premixed group could be due to a hypobaric mixture of bupivacaine and fentanyl that ascends faster, causing early and prolonged sympathetic block. The incidence of nausea, vomiting, and pruritus was less in all three groups and not statistically significant.

#### Limitations of the study

This study has some limitations-SAB was performed in sitting position and patients were made to lie down after that, the speed and duration of change in position from sitting to supine can affect the flow dynamics of drugs in the CSF and influence the block characteristics. The surgeries performed on the lower limbs were heterogeneous across all the groups and this can affect the duration of analgesia.

## CONCLUSION

We conclude from our study that sequential intrathecal injection of hyperbaric bupivacaine followed by fentanyl results in the early onset of sensory and motor blockade, delayed regression of the block, prolongation of analgesia, and stable hemodynamics as compared to premixed drug administration.

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**JSN**- Definition of intellectual content, literature survey, implementation of the study protocol, data collection, and data analysis; **VMS**- Concept, design, clinical protocol, manuscript preparation, and submission of the article; **BG**- Design of study, statistical analysis, and interpretation; and **KJM**- Manuscript review and editing.

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