**ORIGINAL RESEARCH**

# A prospective randomized clinical study of efficacy of premixed versus sequential administration of fentanyl as an adjuvant to intrathecal hyperbaricbupivacaine in lower limb surgeries

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**ABSTRACT**

**Objectives**: This study aims to compare the effects of intrathecal administration of hyperbaric bupivacaine premixed with fentanyl versus sequential administration of the two in separate syringes in lower limb surgeries on block characteristics. Fentanyl is a lipid soluble opioid commonly used as adjuvant to local anaesthetic. It provides a stable hemodynamic profile and prolonged analgesia. The primary outcome of this study was the onset and duration of sensory and motor block. Secondary outcomes were degree of motor block, hemodynamic parameters, sedation score and adverse effects. **Methods & Materials**: A total of 60 patients were randomly assigned to two groups, each consisting of 30 patients. In Group P, patient received 2.5ml of 0.5% heavy bupivacaine (2.5 ml or 12.5 mg) mixed with 0.5 ml (25 micrograms) of fentanyl in 3ml syringe. Group S received 2.5 ml (12.5 mg) of 0.5% heavy bupivacaine in a 3.0 ml syringe, followed by 0.5 ml (25 micrograms) of fentanyl in another 3.0 ml syringe. Statistical calculations performed using the SPSS 21 version statistical program for Microsoft Windows. **Results**: In terms of the onset of sensory and motor block, group S exhibited the short duration, compared to group P. Group S demonstrated prolonged sensory and motor block durations. Group P experienced a higher incidence of hypotension compared to groups S. In conclusion, administering hyperbaric bupivacaine prior to fentanyl resulted in an earlier onset and longer duration of sensory and motor block. **Conclusions**: The sequential administration of hyperbaric bupivacaine followed by fentanyl leads to an accelerated onset and extended duration of sensory and motor block.

**Key words**: Bupivacaine, fentanyl, motor block, premixed, sensory block, sub arachnoid block.



## INTRODUCTION

Subarachnoid block (SAB) is a widely used regional anaesthesia technique for lower limb orthopaedic procedures due to its cost-effectiveness and reduced risk of major perioperative complications, attributed to the localized action of the drug. The selection of the local anaesthetic (LA) for SAB is based on its pharmacological properties [1]. Hyperbaric bupivacaine is commonly preferred due to its predictable block and lower incidence of side effects. To prolong the anaesthetic effect, maintain stable haemodynamics, and provide extended postoperative analgesia,[2] opioids and non-opioid adjuvants are often combined with bupivacaine. Among intrathecal opioids, fentanyl is frequently employed as it effectively reduces visceral and somatic pain, improves block quality, lowers pain scores, and decreases the need for postoperative analgesics.

However, the mixture of opioids and hyperbaric bupivacaine can affect the distribution of the drug within the intrathecal space due to changes in the density of the hyperbaric solution [3]. The density of cerebrospinal fluid (CSF) at 37°Cis 1.00059 g/ml, while the baricity of fentanyl is 0.99410 and that of hyperbaric bupivacaine is 1.02360. 5 After combining fentanyl with LA in the same syringe, the baricity of the solution becomes 1.01850. Even slight alterations of 0.0006 in the baricity of a solution can influence the spread of LA in the CSF [6]. Hyperbaric solutions offer greater predictability, with enhanced gravity-

dependent distribution and reduced variability among patients.

Considering these factors, the objective of this study was to investigate the differences in block characteristics, specifically the onset and duration of the block, as well as their effects on haemodynamics when administering hyperbaric bupivacaine and fentanyl either in a single syringe or separate syringes. By examining these variables, the study aimed to enhance understanding of the optimal administration approach for achieving desired block characteristics and minimizing potential complications.

## METHODS & MATERIALS

A total of 60 patients, aged 18-70 years and classified as American Society of Anaesthesiologists (ASA) grade I or II scheduled for unilateral lower limb surgery (including various orthopaedic procedures such as fractures and implant removals) under subarachnoid block, were enrolled in the study. Prior to the study, written informed consent was obtained from all participants. Patients with allergies to any of the drugs and polytrauma patients were excluded.

The patients were randomly assigned to Two groups, with each group consisting of 30 patients, using computer-generated random numbers before the start of the study. In Group P, patients received a premixed solution of 0.5% hyperbaric bupivacaine (2.5 ml, 12.5 mg) and fentanyl (0.5 ml, 25 micrograms) in a single 3 ml syringe.In Group S, patients received hyperbaricbupivacaine (2.5 ml, 12.5 mg) in a 3 ml syringe, followed by fentanyl (0.5 ml, 25 micrograms) in a separate 3ml syringe.

Pre-anesthetic check-ups were conducted for all patients before they were transferred to the operating room. The drug codes, sealed in envelopes numbered 1-60, were opened by a designated consultant who was unaware of the study design and group allocation. The drugs were prepared using sterile techniques according to the assigned group and provided to the attending anaesthesiologist. The subarachnoid block was administered using a 26-gauge Quincke spinal needle in sitting position later kept in supine position with 5 degree head low. Sensory block onset was assessed by applying a sterile pin prick every 2 minutes until 20 minutes had elapsed. Onset was defined as the loss of sensation at the T10 dermatome. The time to onset of motor block was defined as the time taken to reach a Modified Bromage score of 3 [7].Modified Bromage Score: 0=Patient able to move knee, hip and ankle; 1=unable to move hip but able to move knee and ankle; 2=unable to move hip and knee but able to move ankle; 3=unable to move hip, knee and ankle. The regression of sensory and motor blocks was assessed from the maximal block height attained to the regression of two dermatomal levels and from a Modified Bromage score of 3 to a score of 0, respectively. Vital parameters, including blood pressure, heart rate, respiratory rate, and arterial oxygen saturation, were periodically measured throughout the procedure. Hypotension was defined as a decrease in systolic blood pressure to 80% of the baseline or less and was treated with intravenous ephedrine. Bradycardia, defined as a heart rate less than 60 beats per minute, was corrected using intravenous atropine sulfate. The need for postoperative analgesia in the form of diclofenac or a rescue dose of fentanyl was also recorded. Incidences of complications such as nausea, vomiting, and sedation were graded using respective scales.[8,9]

The primary outcome of this study was to evaluate the onset and duration of sensory and motor blocks in minutes. Additionally, secondary outcomes included variations in mean arterial pressure (MAP), heart rate (HR), time of first rescue analgesia request, sedation score and advwrse effects.

To determine the appropriate sample size, a Sample Power calculation was performed according to Kraemer and Theimann[10], utilizing the proposed figure. The calculations indicated that to achieve 80% power, each group would require a sample size greater than 25, while 85% power would require a sample size of 28 per group, and 90% power would require a sample size of 30 per group. Hence, considering a power of 90% and using the results of a previous study where the onset of sensory block was the primary outcomell, we determined a sample size of 30 patients per group. This sample size ensured a power of 0.90, an effect size of 0.961, a 10% chance of error with a = 0.05, B = 0.20, and a confidence interval of 95%.

The blind was lifted at the end of the study to evaluate the clinical efficacy of the treatment given to the patients. Data analysis was conducted using various statistical measures, including mean ± standard deviation (±SD), median, frequencies (number of cases), and percentages. Quantitative variables between the study groups were compared using the analysis of variance (ANOVA) test with LSD post-hoc analysis for parametric data and the Kruskal-Wallis H test for non-parametric data. Categorical data were compared using the Chi-square (X2) test, and the exact test was used when the expected frequency was less than 5. A probability value (P value) less than 0.05 was considered statistically significant. All statistical calculations were performed using the SPSS 21 version (Statistical Package for the Social Science) statistical program for Microsoft Windows.

**RESULTS**

Figure 1: The flow diagram illustrating the study's consort

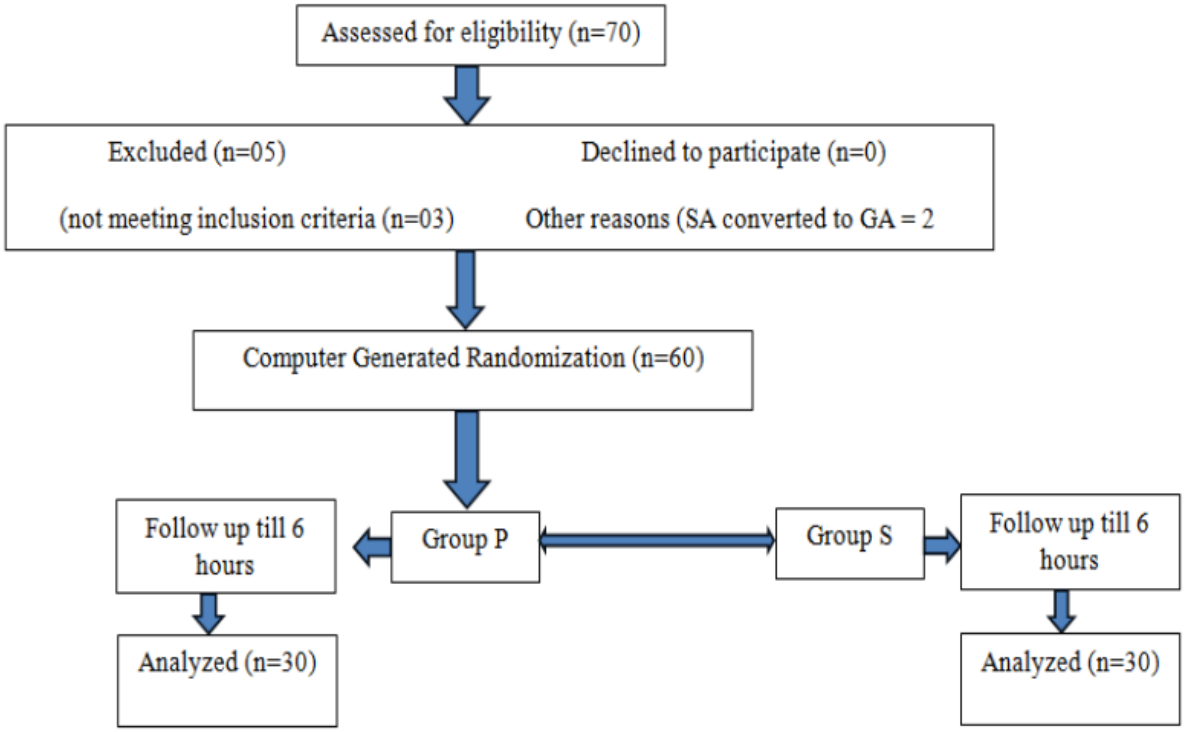


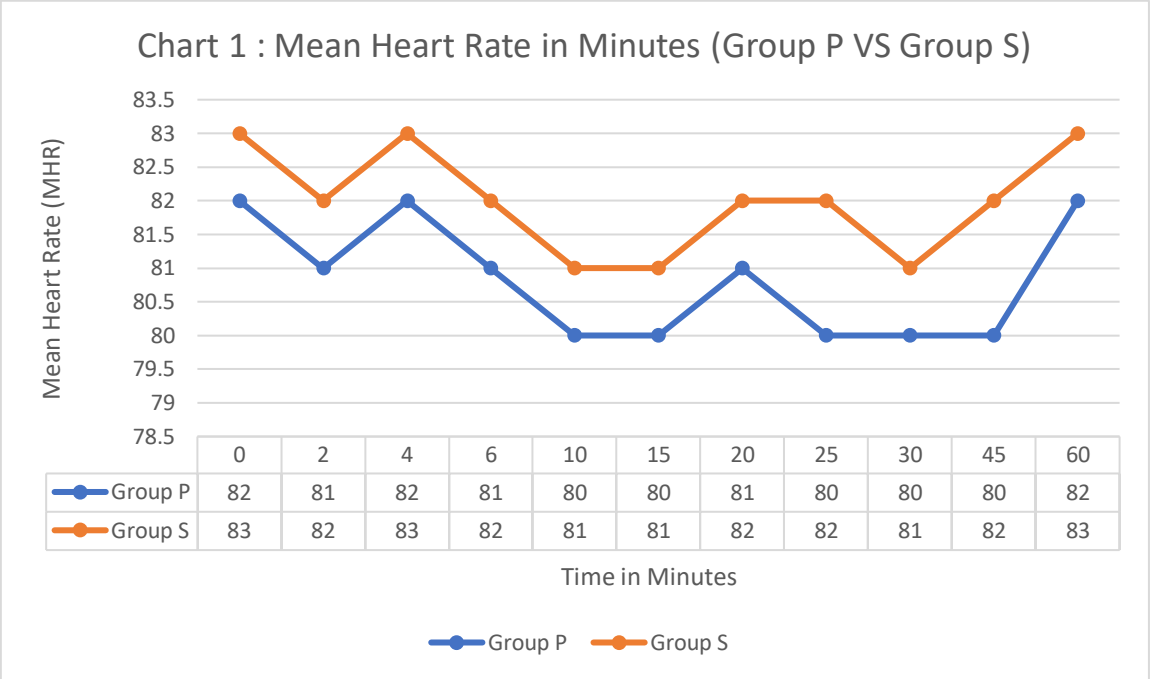

Table 1: The demographic characteristics of the participants were similar across all three groups, as shown in.

| | Mean±SD | | |
|---|---|---|---|
| | **Group P** | **Group S** | ***P value*** |
| **Age (years)** | 48.45±12.54 | 47.57±13.72 | 0.7993 |
| **Height (cm)** | 163.26±5.45 | 161.48±4.61 | 0.1773 |
| **Weight (kg)** | 62.63±8.74 | 64.25±7.08 | 0.4057 |
| **Female** | 12 | 14 | |
| **ASA I/II** | 18/12 | 17/13 | |
| **Duration of surgery (mins)** | 134.53±15.56 | 138.64±13.72 | 0.2823 |

Table 2 provides an overview of the differences in block characteristics among the three groups

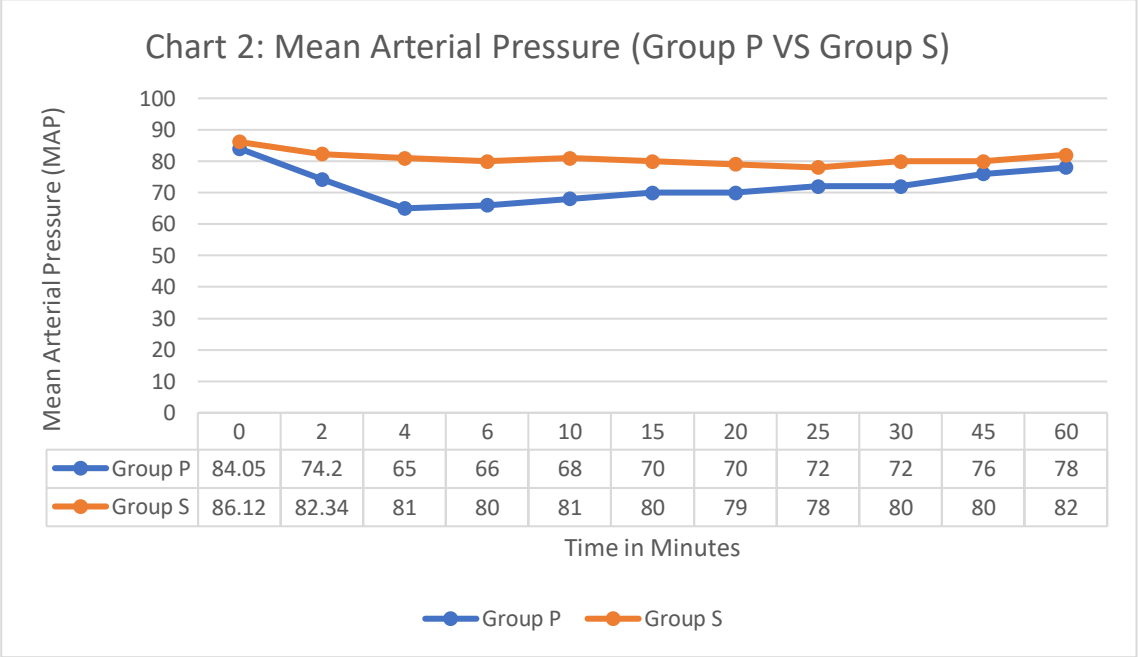
| | Mean±SD | | P value |
|---|---|---|---|
| | **Group P** | **Group S** | |
| **Sensory onset (T10) (mins)** | 4.6±1.1 | 2.8±1.3 | <0.0001 |
| **Motor onset (mins)** | 6.2±1.3 | 5.1±1.2 | 0.0012 |
| **Highest Level Achieved** | T8 | T6 | |
| **Two segment regression of sensory level (min)** | 104.23±4.45 | 108.6±5.57 | 0.0014 |
| **Regression of modified Bromage score to 0 (min)** | 248.38±12.05 | 256.56±10.84 | 0.0076 |
| **Time to first analgesic requirement (mins)** | 274.54±18.38 | 293.70±15.53 | 0.0001 |

Figure 2 shows Comparison of Mean Heart Rate of Group P VS Group S




| | 0 | 2 | 4 | 6 | 10 | 15 | 20 | 25 | 30 | 45 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Group P | 82 | 81 | 82 | 81 | 80 | 80 | 81 | 80 | 80 | 80 | 82 |
| Group S | 83 | 82 | 83 | 82 | 81 | 81 | 82 | 82 | 81 | 82 | 83 |

Figure 3 shows comparison of Mean Arterial Pressure of Group P VS Group S




| | 0 | 2 | 4 | 6 | 10 | 15 | 20 | 25 | 30 | 45 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Group P | 84.05 | 74.2 | 65 | 66 | 68 | 70 | 70 | 72 | 72 | 76 | 78 |
| Group S | 86.12 | 82.34 | 81 | 80 | 81 | 80 | 79 | 78 | 80 | 80 | 82 |

Comparing the groups, the highest sensory level achieved was T6in group S, whereas in group P, it was T8, which demonstrated statistical significance.

Intergroup comparison of heart rate (HR) revealed no significant differences at any time interval, as depicted in Figure 2. Baseline systolic blood pressure (SBP) was similar between groups P and S. The mean arterial pressure (MAP)in group P was low for initial 30 minutes compared to S group which was statistically significant ($p<0.05$) as illustrated in Figure 3. Bradycardia occurred in four patients in group P and three patients in group S, but the difference was not statistically significant. Nausea and vomiting was reported by three patients Group P and one patient in Group S, but the difference was not statistically significant. The time to first rescue analgesia was 274.54±18.38 mins in Group P, was less compared to Group S 293.70±15.53 mins which was statistically highly significant ($p<0.0001$). Sedation level was assessed with Ramay Sedation Score ( value 1 in both groups) which did not show any significant level of sedation in both groups.Nausea and Vomiting was observed in 3 patients in premixed group and 1 patient in sequential group which was not clinically significant.

## DISCUSSION

This study was conducted to compare the premixed and sequential intrathecal 0.5% hyperbaric bupivacaine and fentanyl with the primary objective of time for first rescue analgesia and effect on sensory and motor block onset, effect on intraoperative haemodynamics like MAP and MHR ,sensory and motor block regression time and side effects like nausea, vomiting, pruritus , sedation and shivering in lower limb orthopaedic surgeries.

The main findings of our study were early onset of sensory (2.8±1.3min vs 4.6±1.1min) and motor block(in 5.1±1.2min vs 6.2±1.3min ) in group S, compared to group P respectively, which was statistically significant ($p < 0.001$). Two segment regression of sensory block was early in group P compared to group S (104.23±4.45min Vs 108.6±5.57min respectively), which was statistically significant ( $P < 0.001$). Motor block regression was significantly delayed in sequential group compared to premixed group (256.56±10.84 Vs 248.38±12.05min respectively). Time for the first rescue analgesia was significantly prolonged in sequential group compared to premixed group (293.70±15.53min vs 274.54±18.38min ), which was statistically highly significant ( $P < 0.0001$).The highest sensory level achieved was T6 in group S, whereas in group P, it was T8, which demonstrated statistical significance.

This study examined the differences in sensory and motor block levels and the degree of hypotension when hyperbaric bupivacaine and fentanyl were administered during subarachnoid block, a common anesthesia technique for lower limb surgeries, either in a single syringe or separate syringes.

For operations below the umbilicus, the well-established subarachnoid block approach provides simplicity and benefits over general anesthetic. Local anesthetic (LA) has been used with a number of additives, with varied degrees of success, to enhance the quality of the block and postoperative analgesia, including fentanyl,[11], clonidine,[12], and dexmedetomidine,[13,14].Kiruthika B et al.[15] and Keera A AI et al.[16] in their study found that achievement of sensory and motor block were earlier in sequential group compared to premixed group. They also found prolonged duration of block in sequential compared to premixed which is consistent with our result. Similar to the findings of Bansal N et al.[18] and Chaudhry G et al.[2], the premixed group had a considerably longer duration until the commencement of modified Bromage score 3 than the control group. These results can be explained by intrathecal drug distribution mechanisms. A hyperbaric solution spreads under the influence of gravity along the curvature of the lumbar spine after the medication is injected into the subarachnoid space in the lumbar area and then patient is changed from sitting to supine position. Hyperbaric bupivacaine which is denser compared to hypobaric fentanyl when given separately tend to settle down, spread up slowly and produce delayed effect.

In contrast, a mixed solution produces an unpredictably high level of block because it mixes freely in the cerebrospinal fluid (CSF) and does not rely on gravity for dissemination. According to Bansal N. et al.[18] and Gaddam M. et al.[19], regression of block took longer in the sequential administration group compared to premixed group which supports our study finding.This can be explained as on administering Fentanyl separately,results in more spread in the CSF, binding strongly with opioid receptors in the spinal cordleading to prolonged and denser block.Similar to the findings of Sachan et al., the request for firstrescue analgesia was more in sequential compared to premixed group which is consistent with our study finding [3].The premixed group had a higher incidence of hypotension, which is in line with the findings of Keera et al. and Noopur et al. We believe that because hyperbaric bupivacaine is more dense compared to hypobaric fentanyl when given seperately than the premixed drug, it goes down more slowly and takes longer to reach the desired level. This delay in the beginning of the sympathetic block enables compensatory mechanisms to prevent early hypotension. Due to a higher prevalence of hypotension, which decreased cerebral blood flow and activated the vomiting center in the medulla oblongata, patients in group P reported increased nausea and vomiting. Our study has a few flaws that are important to point up. The numerous orthopedic operations our patients underwent had an impact on the duration of block. In order to forecast the spread of the medication relative to CSF, we also did not measure the specific gravity of the medicines and CSF. The sample size for this study is also less.

**Financial Disclosure**: Nil

**Conflict of Interest**: Nil

## CONCLUSION

In conclusion, our study findings suggest that the administration of hyperbaric bupivacaine followed by fentanyl (i.e., succedent) results in an early and higher level of sensory and motor block with prolonged duration of sensory block. Furthermore, the incidence of hypotension was significantly lower in the sequential administration groupcompared to the premixed group. The premixed group showed the earliest time to the first requirement of analgesia in the postoperative period, compared to sequential group.

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