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Comparison of Characteristics of Mixed Versus Sequential Administration of Levobupivacaine and Fentanyl in Subarachnoid Block for Lower Limb Surgeries: A Randomized Control Study

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Abstract: ***Aim: To evaluate differences in characteristic of subarachnoid block administered by giving levobupivacaine and fentanyl as a mixture or individually in a varying sequence for lower limb surgeries. Methods: From January 2021 to June 2022 a prospective randomized single blind controlled study on a total of 120adult patients allocated into three groups of 40 patients each according to computer generated random numbers before the commencement of study. Group A patients will receive mixed 0.5% isobaric levobupivacaine 3 ml (15 mg) and 0.5 ml (25 microgram) of fentanyl in a single 5.0 ml syringe. Group B patients will receive 0.5 ml (25 microgram) of fentanyl in a 3.0 ml syringe followed by 3 ml of 0.5% isobaric levobupivacaine in a 5 ml syringe and Group C will receive 3ml of 0.5% isobaric levobupivacaine in a 5ml syringe followed by 0.5 ml (25 microgram) of fentanyl in a 3 ml syringe. Result: Sequential administration levobupivacaine followed by fentanyl resulted in a faster onset of both sensory and motor blocks, a shorter time to achieve the highest sensory level, and a more prolonged time until the need for the first rescue analgesia with a comparable adverse effects profile. Conclusion: Administering levobupivacaine first followed by fentanyl i.e., sequentially leads to an early onset and prolonged duration of sensory and motor block.***

Keywords: Levobupivacaine, Fentanyl, Subarachanoid Block

1. Introduction

In patients requiring lower abdomen and lower limb procedures, a subarachnoid block is a popular anaesthetic technique. The use of the right type and dose of local anaesthetic in the subarachnoid space result in a faster onset of effective sensory and motor blockade and a higher success rate.

Levobupivacaine is amino-amide local anaesthetic drug that belongs to amino-amide class of group. It is the pure S (-) enantiomer of bupivacaine. Bupivacaine and levobupivacaine are both effective, but levobupivacaine has a better pharmacokinetic profile. In clinical studies, both bolus and continuous post-operative infusions of levobupivacaine have been found to be well tolerated in regional anaesthesia procedures. [1]

Fentanyl is a lipophilic synthetic phenylpiperidine opioid agonist that has analgesic and anaesthetic characteristics. After intrathecal injection, it exhibits a quick onset of effect. Fentanyl binds to the mu-receptor in the central nervous system (CNS) and activates it, simulating the actions of endogenous opiates. When medications are mixed, their physiochemical properties change, and their intrathecal distribution may differ. Opioids have the second impact, which increases mean spread and delays regression regardless of the method of administration.[2]

It's customary to combine opioids and hyperbaric bupivacaine in a single syringe before injecting the mixture intrathecally. The density of the hyperbaric solution may be altered by mixing these medicines, altering the dissemination of local anaesthetic and opioid. Fentanyl and morphine mixed with hyperbaric bupivacaine produce a higher amount of sensory block than bupivacaine followed by opioid, which may be linked to a higher postoperative opioid demand.[3]

When bupivacaine and fentanyl were given together or separately and in varied sequences, differences in time of onset of sensory and motor block, length of sensory and motor blocks, and haemodynamics were found. When hyperbaric bupivacaine is given initially, followed by fentanyl, sensory and motor block occur quickly and last a long time. [4]

The effects of combining levobupivacaine and fentanyl, as well as giving them separately in different sequences was investigated in this study with the aim to evaluate differences in characteristic of subarachnoid block

2. Materials and Methods

Study Design and Setting:
After obtaining approval from the institutional ethics committee, this randomized, controlled trial was undertaken in Department of Anaesthesiology, School Of Medical Sciences & Research, Greater Noida, UP

Study Duration: From January 2021 to June 2022

Study Design: Prospective randomized single blind controlled study.

Patient Population: A total of 120adult patients of either sex

Inclusion Criteria:
- Patients of age between 18-65 years.
- American Society of Anaesthesiologists (ASA) grade I&II
- Scheduled for lower limb surgeries under subarachnoid block

Exclusion Criteria:
- Patient refusal to participate in the study.
- Any history of allergy to the study medications.
- Any history of clotting or bleeding disorder.
- Infection at the site of lumbar puncture.
- Patients with pre-existing neurological deficit
- Any history of psychiatric illness
- Pregnant patients

3. Methodology

After written informed consent patients will be allocated into three groups of 40 patients each according to computer generated random numbers before the commencement of study.

Group A patients will receive mixed 0.5% isobaric levobupivacaine 3 ml (15 mg) and 0.5 ml (25 microgram) of fentanyl in a single 5.0 ml syringe.

Group B patients will receive 0.5 ml (25 microgram) of fentanyl in a 3.0 ml syringe followed by 3 ml of 0.5% isobaric levobupivacaine in a 5 ml syringe and Group C will receive 3ml of 0.5% isobaric levobupivacaine in a 5ml syringe followed by 0.5 ml (25 microgram) of fentanyl in a 3 ml syringe.

After shifting patient to operation theatre and base line heart rate; blood pressure and oxygen saturation was recorded. Drugs were injected through Quincke spinal needle, 25-gauge, inserted in the L3-4 interspace. Sensory block was assessed by a sterile pin prick every 2 min till 20 min and then after every 10 min till the highest level was achieved. Onset was defined as the loss of sensation at T10 dermatome. The time to onset of motor block was defined as time taken to reach Modified Bromage score of 4.

I — no block with full flexion possible at knees and feet
II — partial block, with patient just able to flex knees with full flexion possible at feet;
III — almost complete, with patient unable to flex knees but flexion of feet possible; and
IV — complete block, i.e., inability to move legs and feet.

Time of sensory block regression was assessed from maximal block height attained to regression till two dermatomal level. Time of regression of motor block was assessed as time to reduce to from maximum attained Modified Bromage score to score of 0.

Statistical Analysis

Comparison of quantitative variables between the study groups will be done using ANOVA test with LSD post-hoc analysis and Kruskal–Wallis H test for parametric and nan-parametric data respectively.

For comparing categorical data, Chi-square (X2) test will be performed and exact test will be 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 done using Microsoft excel and SPSS 21 version (Statistical Package for the Social Science) statistical program for Microsoft Windows.

4. Results

Among group A 30% patient block height was till T5 dermatome, 15% in T6 dermatome, 20% T7 dermatome and 35% T9 dermatome. Among group B 17.5% in T5 dermatome, 37.5% in T6 dermatome, 20% t& dermatome and 25% in T9 dermatome. Among Group C 25% in T4 dermatome, 22.5% in T5 dermatome, 20% in T6 dermatome and 32.5% in T7 dermatome.

Table 1: Distribution of highest level of block dermatome (N=120)

S. no	Highest level of block dermatome	Group A	Group B	Group C
1	T4	0 (0)	0 (0)	10 (25)
2	T5	12 (30)	7 (17.5)	9 (22.5)
3	T6	6 (15.0)	15 (37.5)	8 (20)
4	T7	8 (20)	8 (20)	13 (32.5)
5	T9	14 (35)	10 (25)	0 (0)

X^2=40.70, df(8),p=<0.001

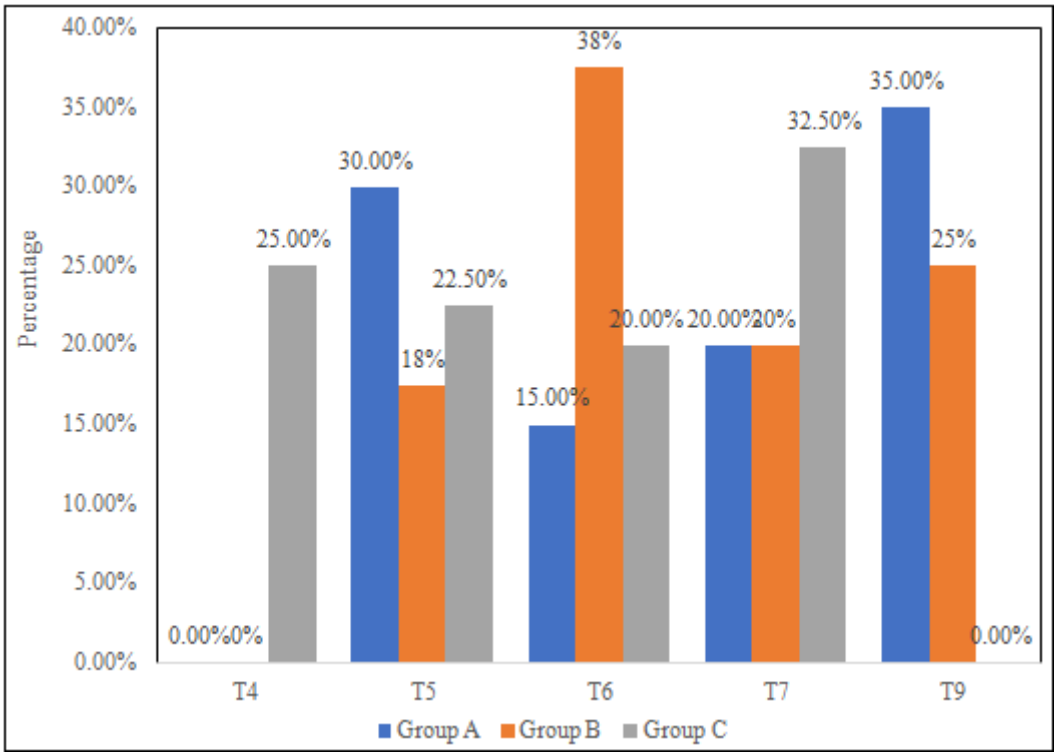

Figure 1: Distribution of highest level of block dermatome (N=120)

Mean onset time to T10 dermatome in minutes among Group A is 4.98±1.57min, among group B 5.28±1.35min and among group C 3.88±0.91min.

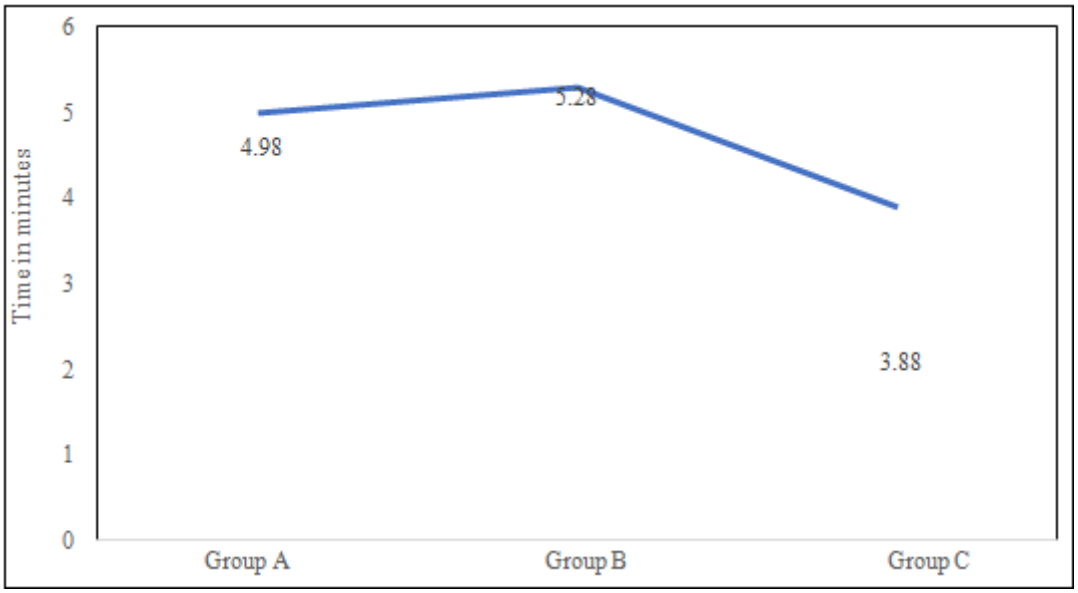

Figure 2: Mean Time to attain block till T10 dermatome in minutes (N=120)

Mean time to attain T6 level block in minutes among Group A is 6.48±1.88 min, among group B 7.02±1.65min and among group C 4.90±0.98min.

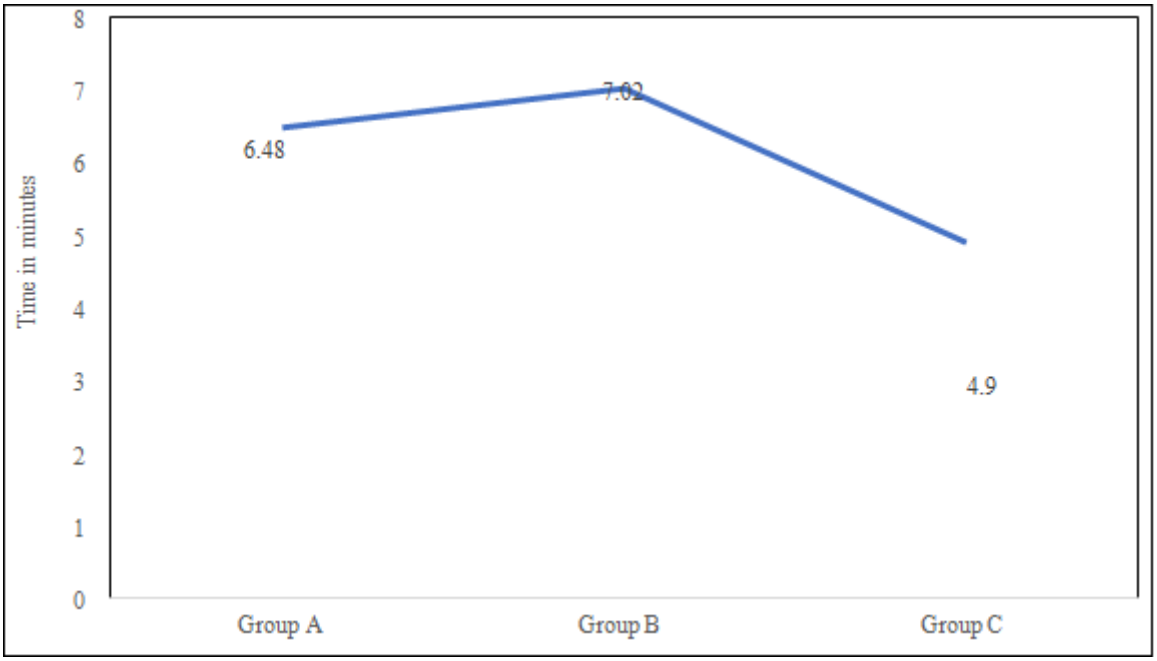

Figure 3: Mean Time to Attain T6 level block in minutes (N=120)

Mean block in minutes among Group A is 125.88±7.84 min, among group B 126.12±7.61 min and among group C 109.63±11.57 min.

Table 2: Mean duration of block in minutes (N=120)

S no	Group	Mean±SD (Minutes)	p value (<0.05-statistically significant)
1	Group A	125.88±7.84	<0.001
2	Group B	126.12±7.61	
3	Group C	109.63±11.57	

Mean onset time to bromage grade IV in minutes among Group A is 10.53±1.62 min, among group B 10.30±1.54 min and among group C 5.40±1.05 min.

Table 3: Mean Onset Time to Attain Modified Bromage Grade IV Block in min (N=120)

S. no	Group	Mean ± SD (Minutes)	p value (<0.05-statistically significant)
1	Group A	10.53±1.62	<0.001
2	Group B	10.30±1.54	
3	Group C	5.40±1.05	

Mean duration of analgesia among Group A is 159.33±7.86 min, among group B 159.80±7.00 min and among group C 172.55±7.69 min.

Table 4: Mean duration of Analgesia in min (N=120)

S No	Group	Mean ± SD (Minutes)	p value (<0.05-statistically significant)
1	Group A	159.33±7.86	<0.001
2	Group B	159.80±7.00	
3	Group C	172.55±7.69	

5. Discussion

The results of the current prospective, controlled, randomised, and single-blind trial have shown that the sequential administration levobupivacaine followed by fentanyl resulted in a faster onset of both sensory and motor blocks, a shorter time to achieve the highest sensory level, and a more prolonged time until the need for the first rescue analgesia with a comparable adverse effects profile.

In our study mean age of the study participants among Group A is 45.85±12.73 years, among group B 41.75±14.32 years and among group C 40.68±14.41 years. In our study there were about 32.5% females and 67.5% males among Group A. There were about 40% females and 60% males among Group B. There were about 57.5% females and 42.5% males among Group C. In our study there were about 32.5% in ASA I and 67.5% in ASA II among Group A. There was about 37.5% ASA I and 62.5% ASA II among Group B. There was about 42.5% ASA I and 57.5% ASA II among Group C. In our study mean duration of surgery in minutes of the study participants among Group A is 50.48±4.72 min, among group B 49.95±4.90 min and among group C 52.63±4.54 min.

In a study by El kenany S et al[5],patients in the group sequential experienced a statistically significant faster onset of both sensory and motor block (4.58±1.5versus 5. 40±1.8 min, p = 0.02), a shorter time to achieve the highest sensory level (6.12±1.96 min versus 8.77±2.5min, p =0.00), and a longer time till the first postoperative rescue analgesic need (252.26±39.3 min versus 234.70±40.2 min, However, patients in group P where drugs were given as premixed solution reached a statistically significant greater level of sensory blockade (T 6 (T3 -T6) vs T 5 (T4- T7), p = 0.04) and demonstrated a longer duration of sensory blockage (216.30±30.8 vs 199.44±23.8, p = 0.003).

In our study the mean onset time to T10 dermatome in minutes among Group A is 4.98±1.57min, among group B 5.28±1.35min and among group C was 3.88±0.91min which was minimum of all the three groups. Mean time to highest level (T6) in minutes among Group A is 6.48±1.88 min, among group B 7.02±1.65min and among group C 4.90±0.98min; Similar results were seen in study by Chaudhry G et al[7]which showed time to achieve T10 spinal

level was significantly less in sequential group (5.5 ± 1.167 min) (Group S) as compared to group P which was premixed with hyperbaric bupivacaine 12.5 mg and dexmedetomidine 10 µg (4.467 ± 0.973 min).

The lower concentration of levobupivacaine that results from mixing it with opioid may be responsible for the increased amount of sensory block that was observed in this investigation when the pre-mixed solution was utilised. It has been discovered that when levobupivacaine is delivered in the sitting posture, hypobaric levobupivacaine achieves a higher block level in comparison to plain or hyperbaric levobupivacaine. The therapeutic significance of this observation in the current investigation could be called into question due to the fact that the sensory level is only greater by one dermatome and that there were no variations in hemodynamics found between the twogroups.[8]It is possible that the preferential cephalad distribution of fentanyl upon injecting it individually accounts for the shorter amount of time needed to reach the greatest sensory level when sequentially administering medications, as was shown in this investigation. The level of block in Group B and Group C has been observed to be higher when fentanyl was given alone without mixing with levobupivacaine as compared to Group A when fentanyl and levobupivacaine was premixed. This observation is supported by the findings of other researchers who reported similar results when they administered morphine and fentanyl separately during spinal anaesthesia in parturient undergoing caesarean section rather than using these opioids mixed with bupivacaine. This observation is supported by the findings of other researchers who reported similar results.[9]

Duration of block achieved by sequential administration of levobupivacaine and fentanyl was observed to be dependent on the sequence of administration of drugs. In Group C when levobupivacaine was administered before fentanyl the duration of analgesia was found to be longer than when fentanyl was given before levobupivacaine. The sequential administration of levobupivacaine with fentanyl and in this trial resulted in more prolonged duration of analgesia and therefore formation of firmer opioid receptor bonds giving denser and more prolonged block in contrast to the less profound block induced by the diluted mixture of fentanyl and levobupivacaine. In a similar vein, Gray et al. discovered that the intrathecal administration of hypobaric morphine (in normal saline) resulted in a longer duration of post thoracotomy analgesia in comparison to the administration of hyperbaric morphine (combined with dextrose). This was because the distribution of the hypobaric morphine changed when it was combined with the dextrose.[10]

In our study time to attain Modified Bromage grade IV in min was attained fastest in group C (5.40±1.05 min) and thus our result is comparable to study done by Chaudhry G et al[7] Time for two segment regression of sensory level observed in our study was maximum in group C i.e., 111.00±0.81mins while it was 107.00±2.24 mins in Group A and 108.57±2.36 in Group B. KanwariyaAetal[6] also found similar result in their study.

Time to complete recovery from motor block was more in group C 130.85±1.09 mins in our study as compared to group A and B. Similar result were found by Sachan et al[11] In study by Malhotra A et al regression of Modified Bromage grade 0 was more in sequential group as compared to premixed group.In our study the need of first analgesic dose needed at 159.33±7.86mins in Group A,159.80±7.00mins in Group B while the effect lasted longer in group C which was 172.55±7.69 mins. In study by Malhotra A et al found that time for first requirement of analgesia was longer in sequential group i.e group C 4.0±0.8 hours as compared to premixed group (Group A) 3.3±0.6hours.[4]

6. Conclusion

We conclude that administering levobupivacaine first followed by fentanyl i.e., sequentially leads to an early onset and prolonged duration of sensory and motor block.

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