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Original Research Article

EFFICACY OF PREMIXED VERSUS SEQUENTIAL INTRATHECAL ADMINISTRATION OF BUPRENORPHINE AS AN ADJUVANT TO HYPERBARIC BUPIVACAINE IN INFRAUMBILICAL SURGERIES: A RANDOMIZED CONTROLLED STUDY

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ABSTRACT

Background: Subarachnoid block is a widely practiced regional anaesthesia technique for infraumbilical surgeries. Opioid adjuvants such as buprenorphine are commonly added to hyperbaric bupivacaine to enhance block quality and duration. However, premixing opioids with hyperbaric local anaesthetics may alter solution density and influence intrathecal drug spread. **Objectives:** To compare the efficacy and haemodynamic effects of premixed versus sequential intrathecal administration of buprenorphine as an adjuvant to hyperbaric bupivacaine, with respect to block characteristics and adverse effects.
Materials and Methods: This prospective, randomized, double-blinded study included 105 ASA I–II patients aged 18–65 years undergoing infraumbilical surgeries under spinal anaesthesia. Patients were randomized into three groups (n=35 each): Group A received premixed hyperbaric bupivacaine with buprenorphine; Group B received buprenorphine followed by hyperbaric bupivacaine; Group C received hyperbaric bupivacaine followed by buprenorphine. Primary outcomes included onset of sensory and motor block, two-segment sensory regression time, and duration of motor block. Secondary outcomes were haemodynamic parameters and incidence of adverse effects. Statistical analysis was performed using one-way ANOVA and Chi-square test.
Results: Sequential administration significantly hastened the onset of sensory and motor blockade, with Group C showing the fastest onset ($p<0.001$). Two-segment sensory regression time and duration of motor block were significantly prolonged in sequential groups compared to the premixed group ($p<0.001$). Haemodynamic parameters remained comparable among groups. The incidence of hypotension and bradycardia was significantly higher in the premixed group ($p<0.05$).
Conclusion: Sequential intrathecal administration of buprenorphine and hyperbaric bupivacaine offers superior block characteristics with better haemodynamic stability and fewer adverse effects compared to premixed administration in infraumbilical surgeries.
Keywords: Subarachnoid block; Intrathecal buprenorphine; Hyperbaric bupivacaine; Sequential administration; Premixed spinal anaesthesia; Infraumbilical surgery; Opioid adjuvant.

INTRODUCTION

Subarachnoid block (SAB) is one of the most commonly used regional anaesthesia techniques.[1] Due to its lower cost, simpler technique and higher patient acceptance, subarachnoid block is the procedure of choice for lower limb, perineal and lower abdominal surgeries.[2] It is relatively easy to

administer, provides rapid onset of anaesthesia with good muscle relaxation and is economical with low failure rate.[2]

Buprenorphine is a long acting, highly lipophilic opioid, which has proved to be a promising analgesic, by epidural and intrathecal route.[3,4] It is about 25 times more potent than morphine and has a low level of physical dependence. It is a mixed agonist-antagonist opioid with superior affinity at both Mu and kappa receptors. It is similar to morphine in its analgesic potential. When injected intrathecally, buprenorphine is compatible with CSF and does not cause adverse reactions.[5]

The ability to predict the ultimate level of block during spinal anesthesia is essential in providing adequate anesthesia while minimizing side effects. Many factors have been identified to regulate the spread of local anesthetic solutions within the subarachnoid space, which includes patient characteristics, physical properties of CSF, injection technique and dose and properties of the local anesthetic used.[6]

Opioid densities are lower than hyperbaric and, in some cases, isobaric local anaesthetic. Mixing of opioids with local anaesthetics will decrease the final density of the mixture. It is a routine practice to mix opioids with hyperbaric bupivacaine in a single syringe before injecting the premixed solution into the subarachnoid space, thus altering the density of both the drugs and directing their spread in the subarachnoid space.[7]

The rationale behind performing this study was to see differences in block characteristics mainly onset of block and duration of block along with determining effects on haemodynamic whilst administering hyperbaric bupivacaine and buprenorphine in a single syringe or separate syringes. The effect of administering opioid prior to LA and vice versa on these parameters was also assessed.

MATERIALS AND METHODS

It was a Prospective, randomized, double blinded, single center study conducted at KMCT Medical College, – a tertiary care center at Kozhikode district from April 2021 to September 2021 among american society of anaesthesiologists physical status,[8] I and II of either gender aged 18-65 undergoing infraumbilical surgery under spinal anaesthesia.

A total of 105 patients undergoing spinal anaesthesia for infraumbilical surgeries will be divided into 3 groups of 35 each. Group A patients received premixed 0.5% hyperbaric bupivacaine 2.5ml (12.5mg) and 0.3 ml (90microgram) of buprenorphine in a single 5.0 ml syringe. Group B patients first received 0.3 ml (90 microgram) of buprenorphine in a 2.0 ml syringe followed by 0.5% hyperbaric bupivacaine 2.5ml (12.5mg) in a 5.0ml syringe and Group C received 0.5% hyperbaric bupivacaine 2.5ml (12.5mg) in a 5ml syringe followed by 0.3ml (90microgram) of buprenorphine in a 2.0ml syringe.

Sample size calculation done using formula

$$n = \frac{(Z_{\alpha/2}+Z_{1-\beta})^2 \times 2(SD)^2}{d^2}$$

SD = Standard deviation obtained from previous study = 1.5 min (Sensory onset (T10) (mins),[9]

d= accuracy of the estimate= 1 min

Zα/2 = Normal deviate for two tailed hypothesis = 1.96 Z 1-β = 0.84 (Type II Error)

n = 35

So 35 samples in each group and a total of 105 samples

Inclusion Criteria

- American society of anaesthesiologists physical status I and II
- Age 18-65
- Patients undergoing spinal anaesthesia for infraumbilical surgery
- Height 149-180 cm

Exclusion Criteria

- Patient refusal
- Any obvious spine deformity
- Pregnancy
- Psychiatric disorders
- Signs and symptoms suggestive of Increased Intracranial tension
- Diseases: significant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine or neurological diseases
- Any known allergy or contraindication for bupivacaine or buprenorphine
- Children and old age
- Pregnancy
- American society of anaesthesiologists physical status greater than II
- Failed spinal anaesthesia
- Any contraindication to spinal anaesthesia

Patients were allocated into three groups of 35 patients each according to computer generated random numbers before the commencement of study. The drug codes sealed in envelopes numbered 1–120 were opened by an anaesthesiologist just before the administration of anaesthesia and drug was prepared using sterile technique according to group allocated. The drug was then handed over in a coded form to the attending anaesthesiologist who was unaware about the study design and the study groups. Observer will not be present while subarachnoid block was administered. After obtaining institutional ethics committee clearance, 105 patients aged 18– 65 years, American Society of Anaesthesiologists (ASA) grade I and II scheduled for infraumbilical surgery (inguinal hernia, hydrocele, haemorrhoidectomy, perineal surgery, urological procedures, orthopaedic procedures like lower limb fractures, implant removals, etc.) under subarachnoid block, were enrolled in this study. After written informed consent patients were allocated into three groups of 35

patients each according to computer generated random numbers before the commencement of study.

Statistical Methods

All statistical procedures were performed using Statistical Package for Social Sciences (SPSS) 20.0. Calculations for power (80%) of study was performed before commencement of the study. All quantitative variables expressed in mean and standard Deviation. Qualitative variables were expressed in percentages. Chi square test was used for association of qualitative variable, One Way ANOVA was used for quantitative variables. Probability value ($p < 0.05$) was considered statistically significant.

RESULTS

Table 1: Comparison of ASA grade

Groups	I	II	P value
Group A	19	16	0.96
%	54.3%	45.7%	
Group B	19	16	
%	54.3%	45.7%	
Group C	18	17	
%	51.4%	48.6%	

In the above study, 19 subjects in each of group A,19 subjects in group B and 18 sujects were in ASA grade I. Similarly, 16 subjects in each of group A and group B and 17 subjects in group C were in ASA grade II. Chi square test was applied and P- Value of 0.96 was obtained. Therefore, No Significant difference found.

Table 2: Comparison of types of surgery between Group A, Group B and Group C

TYPES OF SURGERY		GROUPS A	GROUPS B	GROUPS C	Total
Appendicectomy	n	7	8	6	21
	%	33.3%	38.1%	28.6%	100.0%
Cystoscopy	n	1	3	8	12
	%	8.3%	25.0%	66.7%	100.0%
Debridement +SSG	n	2	2	4	8
	%	5.7%	5.7%	11.4%	7.6%
Fistulectomy	n	4	0	0	4
	%	11.4%	0.0%	0.0%	3.8%
Haemorrhoidectomy	n	2	0	0	2
	%	5.7%	0.0%	0.0%	1.9%
Hernioplasty	n	6	7	3	16
	%	37.5%	43.8%	18.8%	100.0%
Hydroceolectomy	n	0	2	1	3
	%	0.0%	5.7%	2.9%	2.9%
ORIF tibia	n	6	7	10	23
	%	17.2%	20.0%	28.6%	22.0%
URS	n	7	6	3	16
	%	20.0%	17.1%	8.6%	15.2%
Total	n	35	35	35	105
	%	100.0%	100.0%	100.0%	100.0%

Table 3: Comparison of ONSET OF SENSORY BLOCK

	Mean	SD	P value
Group A	$4.93^{ab\#}$	0.76	<0.001
Group B	4.12^{ac}	0.28	
Group C	3.32^{bc}	0.26	

Comparison of mean time of onset of sensory blockade (in minutes) between Group A (PREMIXED), Group B (BUPRENORPHINE FOLLOWED BY BUPIVACAINE) and Group C (BUPIVACAINE FOLLOWED BY BUPRENORPHINE) showed that mean time taken for onset of sensory blockade was 4.93 minutes for Group A, 4.12 minutes for Group B and 3.32 minutes for Group C with standard deviation of 0.76 min, 0.28 min and 0.26 minutes respectively. The difference was statistically significant with p value of <0.001. Onset of sensory blockade was faster for Group C followed by Group B and then Group A and it was statistically significant.

Table 4: Comparison of two segment regression time (min)

	Mean	SD	P value
Group A	133.34^{ab}	11.84	0.001*
Group B	141.37^{a}	10.39	
Group C	140.51^{b}	6.65	

Comparison of two segment regression time (in minutes) between Group A (PREMIXED), Group B (BUPRENORPHINE + BUIPIVACAINE) and Group C.
(BUPIVACINE + BUPRENORPHINE) using one way ANOVA showed that time taken was 133.34 minutes for Group A, 141.37 minutes for Group B and 140.51 minutes for Group C with standard deviation of 11.84 min 10.39 min and 6.65 minutes respectively. The difference was statistically significant with p value of <0.001. Sensory level in Group A subjects regressed faster than Group C and Group B. On intergroup comparison between Group B and Group C using Bonferroni post hoc analysis time taken for two segment regression of spinal was comparable between group B and Group C.

Table 5: Comparison of onset of motor block (min)

	Mean	SD	P value
Group A	7.23[ab #]	0.69	<0.001**
Group B	5.78[ac]	0.57	
Group C	5.32[bc]	0.28	

Comparison of onset of motor block (in minutes) between Group A (PREMIXED), Group B (BUPRENORPHINE + BUPIVACAINE) and Group C
(BUPIVACAINE + BUPRENORPHINE) using one way ANOVA showed that time taken was 7.23 minutes for Group A, 5.78 minutes for Group B and 5.32 minutes for Group C with standard deviation of 0.69min, 0.57min and 0.28 minutes respectively. The difference was statistically significant with p value of <0.001. Onset of motor block was faster in group C followed by Group B and then Group A.

Table 6: Comparison of duration of motor block (min)

	Mean	SD	P value
Group A	154.28[ab #]	6.98	<0.001**
Group B	164.48[a]	4.42	
Group C	163.65[b]	3.08	

Comparison of duration of motor block between Group A(PREMIXED), Group B (BUPRENORPHINE + BUPIVACAINE) and Group C (BUPIVACAINE + BUPRENORPHINE) using one way ANOVA showed that duration was 154.28 minutes for Group A, 164.48 minutes for Group B and 163.65 minutes for Group C with standard deviation of 6.98 min 4.92 min and 3.08 minutes respectively. The difference was statistically significant with p value of <0.001. Motor blockade lasted more in Group B followed by Group C and then Group A.

Table 7: Comparison of mean heart rate at various time intervals between the groups

Heart rate BPM	Group A Mean (SD)	Group B Mean (SD)	Group C Mean (SD)	P value
Baseline	82.6 (9.61)	81.85 (7.92)	81.01 (6.51)	0.12
3	81.71 (10.53)	80.57 (6.34)	80.28 (5.10)	0.08
6	78.42 (9.78)	77.25(6.20)	76.78 (5.98)	0.21
9	75.10 (6.71)	75.97(3.89)	74.14 (4.68)	0.23
12	75.61 (6.66)	74.37 (4.91)	74.18 (3.27)	0.77
15	73.17 (6.98)	73.05 (3.38)	72.48 (4.89)	0.66
20	70.14 (6.37)	70.91 (3.11)	70.15 (3.04)	0.13
25	70.62 (3.84)	69.88 (3.34)	68.14 (3.63)	0.25
30	70.10 (3.01)	69.71 (3.37)	69.28 (3.25)	0.16
45	70.80 (3.94)	69.40 (3.37)	69.12 (2.92)	0.66
60	70.74 (3.84)	69.82 (4.51)	69.62 (4.16)	0.31
90	71.45 (4.47)	71.11 (5.08)	70.14(4.18)	0.09
120	72 (4.15)	73.18 (4.11)	72.91(4.08)	0.08
150	72 (4.16)	73.14 (3.74)	72.40(4.42)	0.14
180	72.28 (9.55)	73.74 (4.74)	72.71(4.86)	0.12

The table suggests that there is no statistically significant difference between mean heart rate of Group A(PREMIXED), Group B (BUPRENORPHINE + BUPIVACAINE) and Group C (BUPIVACAINE + BUPRENORPHINE).Hence were comparable during most of the observations(P>0.05).

Table 8: Comparison of Hypotension

Groups	No	Yes	P value
Group A	20	15	0.001**
%	57.1%	42.9%	
Group B	31	4	
%	88.6%	11.4%	
Group C	33	2	
%	94.3%	5.7%	

Comparing the incidence of hypotension between group A, Group B and Group C using chi square test hypotension was more in Group A (42.90%) compared to Group B(11.40%) and Group C(5.70%) which was statistically significant (P value 0.001).

Table 9: Comparison of Bradycardia

Groups	No	Yes	P value
Group A	31	4	0.02*
%	88.6%	11.4%	
Group B	35	0	
%	100.0%	0.0%	
Group C	35	0	
%	100.0%	0.0%	

Comparing the incidence of bradycardia between Group A (PREMIXED) Group B (BUPRENORPHINE + BUPIVACAINE) and Group C (BUPIVACAINE + BUPRENORPHINE) using Chi square test bradycardia was found in 4 (11.4%) subjects of Group A and none in Groups B and Group C. This was statistically significant with P value 0.02.

DISCUSSION

Subarachnoid block is an old age technique which is relatively simple and advantageous as compared to general anesthesia for surgeries below umbilicus. A number of factors affect the spread of drug in the CSF.

Comparison of mean time of onset of sensory blockade between Group A (premixed), Group B (buprenorphine followed by bupivacaine) and Group C (bupivacaine followed by buprenorphine) showed that mean time taken for onset of sensory blockade was 4.93±0.76 minutes for Group A, 4.12±0.28 minutes for Group B and 3.32±0.26 minutes for Group C. The difference was statistically significant with p value of <0.001. Onset of sensory blockade was faster for Group C followed by Group B and Group A.

Malhotra A et al9 in their randomized control trial to One hundred and twenty patients were randomly allocated into three groups of 40 each: Group A received premixed 0.5% heavy bupivacaine 2.5 ml (12.5mg) and 0.5 ml (25□g) of fentanyl in a single syringe, Group B received 0.5 ml (25□g) of fentanyl in a syringe followed by 0.5% heavy bupivacaine 2.5 ml (12.5 mg) in a syringe, Group C received 0.5% heavy bupivacaine 2.5 ml (12.5 mg) in another syringe followed by 0.5 ml (25□g) fentanyl in another syringe. The mean time for onset of sensory and motor block was least in group C followed by group B.

Sachan P et al,[10] in their study in premixed versus sequential administration of clonidine as an adjuvant to hyperbaric bupivacaine intrathecally in cesarean section, the onset time of sensory block and the time to reach maximum sensory block height was less in sequential group and It was more in mixed group. This may be because of the fact that baricity of both drugs was better maintained when given sequentially. Mixing of the drugs alters the density and distribution of drugs and thus reduces their effect.

Gunjan Chaudhry et al11 study in lower limb surgery also supports our finding in which time to achieve T10 sensory level was significantly less in group S(separate) (4.467 ± 0.973 min) compared with group P (premixed) (5.5 ± 1.167 min) (p-value 0.0004).Study in lower limb surgery supports our finding in which patients in group S (separate) achieved maximum sensory block earlier than those in premixed group (10.37 ± 1.474 min vs. 11.17 ± 1.56 min, (p-value 0.0454) which was statistically significant. Comparison of two segment regression time between Group A (PREMIXED), Group B (BUPRENORPHINE FOLLOWED BY BUPIVACINE) and Group C (BUPIVACAINE FOLLOWED BY BUPRENORPHINE) showed that time taken was 133.34±11.84 minutes for Group A, 141.37±10.39 minutes for Group B and 140.51±6.65 minutes for Group C.

The difference was statistically significant with p value of <0.001. Sensory level in Group A subjects regressed faster than Group C and Group B. In Gunjan Chaudhry et al,[11] study in lower limb surgery, time for two-segment regression of sensory block was significantly longer in group S (separate) (131±14.937 min) than premixed group (119 ± 17.291 min) (p-value 0.0056). This is similar to our results. Archana Shivashankar et al,[12] also reports that time required for regression of the sensory block was significantly lower in mixed group.

Comparison of onset of motor block between Group A, Group B and Group C showed that time taken was 7.23±0.69 minutes for Group A (PREMIXED), 5.78±0.57 minutes for Group B

(BUPRENORPHINE FOLLOWED BY BUPIVACINE) and 5.32±0.28 minutes for Group C (BUPIVACAINE FOLLOWED BY BUPRENORPHINE). The difference was statistically significant with p value of <0.001. Onset of motor block was faster in group C followed by Group B and then Group A. In comparative study conducted by Noopur et al,[13] Premixed versus sequential administration of intrathecal Fentanyl and Bupivacaine in elective caesarean section- The mean (± SD) time for onset of motor block was in separate group was 3.1(± 0.3) minutes and 7.23 (± 1.07) minutes in premixed group which was also statistically significant.

Chaudhry G et al,[11] in sixty orthopaedic patients scheduled for elective lower limb surgery time to regression of motor block to modified bromage I was also significantly more in group S (separate) 145 ± 9.783 minutes than in group P (Premixed) 129.67 ± 18.473 minutes. Malhotra, et al,[9] study on Premixed versus succedent administration of fentanyl and bupivacaine also found that motor block duration to be more in separate injection group.

The study suggests that there is no statistically significant difference in mean heart rate. According to Chaudhry G et al,[11] the difference in HR was statistically insignificant at all-time intervals. Similar results were found by Archana Shivashankar et al,[12] Noopur et al.[13]

The incidence of hypotension was more in Group A (42.90%) compared to Group B (11.40%) and Group C (5.70%) which was statistically significant (P value 0.001). Archana Shivashankar et al,[13] in their study noted hypotension in 58.3% of patients in Group M (Mixed) and 21.7% of patients in Group S (Separate) which was statistically significant. Vasopressor requirement was also higher in Group M. This could be explained on the basis of the fact that the level of the block was higher in the mixed group which resulted in greater sympathetic block and hence a greater fall in the blood pressure.

The incidence of bradycardia in our study was found to be 4 (11.4%) subjects of Group A and none in Groups B and Group C. This was statistically significant with P value 0.02. In the study by Malhotra A et al9 Group A patients received premixed 0.5% hyperbaric bupivacaine and fentanyl. Group B patients first received fentanyl followed by 0.5% hyperbaric bupivacaine and Group C received 0.5% hyperbaric bupivacaine 2.5 ml followed by fentanyl bradycardia was seen in only 4 patients in group A, none in group B and 3 patients in group C and was statistically insignificant.

Limitations of the study

1. Even though duration of motor block and 2 segment regression of sensory block was noted, total duration of sensory blockade was not compared between the two groups.
2. Type of surgery was not standardized. We took all infraumbilical procedures. So we could not compare the time for first request of analgesic which may vary with the type of procedures.
3. In the study we measured the densities of solutions in vitro but, we could not measure the densities when injected into the CSF. Hence, we could not assess what actually happens to the drug densities intrathecally and also the temperature of the drugs injected was not measured as it can affect the spread of the drugs in the CSF.
4. The patients included in this study were all healthy individuals (ASA 1 or 2). Thus the effect of intrathecal buprenorphine sequential and premixed on patients with significant cardiovascular problems remains to be studied.
5. Sequential administration is spillage of drugs while changing the syringes which was minimized by reducing the time of change over.
6. There are very less studies of addition of buprenorphine to bupivacaine sequentially and premixed with less number of variable studied, which made comparison of our study with previous studies difficult.

CONCLUSION

We conclude that administering buprenorphine as sequential injection after hyperbaric bupivacaine intrathecally enhances onset of sensory and motor blockade in infraumbilical surgeries. Two segment sensory regression time and duration of motor block was more in sequential group in which hyperbaric bupivacaine was administered after buprenorphine. Hemodynamic parameters where comparable between the groups. The incidence of side effects like bradycardia, hypotension observed more when hyperbaric bupivacaine and buprenorphine were mixed and given intrathecally.

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