Journal of Cardiovascular Disease Research

ISSN:0975-3583,0976-2833 VOL14,ISSUE05,2023

Comparison of Premixed vs Sequential Administration of Fentanyl as an Adjuvant to low dose Intrathecal Hyperbaric Bupivacaine in Lower Segment Caesarean Section

Ashay Jain[1], Rohit Kumar Varshney[2], Mukesh Kumar Prasad[3], Pallavi Ahluwalia[4], Payal Jain[5], Pratiksha Gogia[6]

[1]Resident, Department of Anaesthesia, Teerthanker Mahavir Medical College and Research Centre, Moradabad, Uttar Pradesh, India
[2]Professor and Head, Department of Emergency Medicine, Teerthanker Mahavir Medical College and Research Centre, Moradabad, Uttar Pradesh, India
[3]Professor and Head, Department of Department of Anaesthesia, Teerthanker Mahavir Medical College and Research Centre, Moradabad, Uttar Pradesh, India
[4]Professor, Department of Anaesthesia, Teerthanker Mahavir Medical College and Research Centre, Moradabad, Uttar Pradesh, India
[5]Associate Professor, Department of Anaesthesia, Teerthanker Mahavir Medical College and Research Centre, Moradabad, Uttar Pradesh, India
[6]Assistant Professor, Department of Anaesthesia, Teerthanker Mahavir Medical College and Research Centre, Moradabad, Uttar Pradesh, India

Abstract
Background: Neuraxial block is the recommended method for caesarean section as general anaesthesia carries higher chances of maternal and foetal morbidity/mortality.The current study comparesintrathecal administration of premixed vs serial injection of fentanyl as an adjuvant drug to low dosage heavy bupivacaine in lower segment caesarean section. **Material and Methods:** The research involved 70 patients consisting of Group P (35 patients) who received neuraxial block using premixture of 7.5mg(1.5ml) of 0.50% heavy bupivacaine with 25 mcg injection fentanyl in same syringe. However, in Group S (35 patients) the same drug was administered using one syringe without barbotage and 25mcg of fentanyl from other syringe. Block characteristics, hemodynamic parameters, VAS (visual analogue scale), APGAR score and any complications or side effects were noted. **Results:** On comparing the groups, there was no statistical significance found among hemodynamic parameters. The average duration of sensory blockade was considerably shorter in group S (1.91±0.28) than in group P. (2.63±0.49) (p=0.001). Similar statistically significant results were obtained on comparing onset of sensory block between the groups. Moreover, on comparing onset/duration of motor block statistically significant results were obtained($p<0.05$). The results were comparable on comparing VAS and APGAR scores between the groups. **Conclusion:** Serial injection of fentanyl as an addon drug to low dosage heavy bupivacaine is helpful in quicker onset and extended period of sensory and motor blockade with stable hemodynamic parameters.
Keywords: Bupivacaine, Cesarean Section, Fentanyl.

Corresponding Author: Dr. Rohit Kumar Varshney, Professor and Head, Department of Emergency Medicine, Teerthanker Mahavir Medical College and Research Centre, Moradabad, Uttar Pradesh, India

INTRODUCTION

Neuraxial block is recommended method for caesarean sections since general anaesthesia is associated with airway associated negative consequences like risk of aspiration, and greater atonic uterus which leads to more loss of blood.[1] Despite the fact that caesarean sections are more common and safer than any other type of surgery, they are nevertheless linked to considerable maternal as well as neonatal morbidity/mortality.[2,3]

Spinal induced hypotension (SIH) is a common occurrence particularly in parturients scheduled for caesarean section. This is due to paradoxical activation of cardioinhibitory receptors as well as arterio-venous vasodilatation brought due to sympathetic blockade.[4,5]

The prevention of SIH is of utmost priority as it may lead to worrisome complications to the mother and fetus. Many techniques and adjuvant drugs in spinal anaesthesia were used to decrease the chances of spinal induced hypotension but none had proven to be completely effective.

In previous studies, researchers have compared premixed vs consecutive administration of fentanyl as an add on drugto intrathecal bupivacaine in orthopaedic lower limb surgeries and other abdominal surgeries. They

ISSN:0975-3583,0976-2833 VOL14,ISSUE05,2023

observed that when giving sequential administration of fentanyl in lower limb surgeries, there were less incidence of hypotension. Moreover, they observed that sequential administration of fentanyl was statistically more effective in prompt onset and longperiod of sensory/motor blockade than other group.[6]

Extensive medline search revealed that very few studies were found comparing premixed vs sequentially injecting of fentanyl as an add on drug to low dose intrathecal heavy bupivacaine in parturients. Therefore, The current study's goal was to compare the effectiveness of premixed vs serially administering of fentanyl as an adjuvant/add on drug to low dose heavy bupivacaine intrathecally in parturients posted for cesarean delivery.

The null hypothesis [H0] of present study was that premixed and succedent administration of fentanyl as an adjunct to low dose intrathecal heavy bupivacaine would be equally effective in parturients posted for lower segment cesarean section. However, the alternative hypothesis [H1] was that the sequential administration of fentanyl would be more effective as its premixed administration together with low dose intrathecal heavy bupivacaine in parturients.

METHODOLOGY

After receiving written and informed consent and clearance from Institutional Ethical Committee (IEC), the present study was planned in Department of Anaesthesiology, Teerthanker Mahaveer Medical College and Research Centre (TMMC & RC), Moradabad from July 2021 to June 2022.The present study was also registered under Clinical Trial Registry of India (CTRI/2021/09/036325 dated 08/09/2021).

The parturient aged from 18 to 40 years having ASA (American Society of Anaesthesiologists) physical Grade I/II posted for caesarean section were taken in the research. However, the patients having any contraindication for subarachnoid block, less than 150 cms in height, with known fetal anomaly, intrauterine deaths (IUD), serious pregnancy induced hypertension (PIH), or any known allergy to medications or with associated liver/kidney/cardiac/pulmonary disease were not taken in the study.

The sample size calculation was made using onset of sensory blockade as the parameter and after assuring 90% of an effect.[6] After taking Type I error as 0.05 and Type II error as 0.20, the final sample size estimated was 35 patients per group at power of 0.90.

Randomization was performed using chit and box method and thereby 35 patients in each group was assigned. Group P received neuraxial block using premixture of 7.5mg (1.5ml) of 0.50% heavy bupivacaine with 25 mcg injection fentanyl in single syringe. Group S received neuraxial block using two separate syringes, first one was 7.5mg(1.5ml) 0.50% heavy bupivacaine without barbotage and second was 25mcg of fentanyl.

Pre anaesthetic evaluation was done in every patient before procedure. In the operating room, after attaching the standard monitors, the heart rate, meanarterial pressure, electrocardiogram and oxygen saturation (SpO_2) was continuously monitored. Surgery was commenced once the patient attained sensory block level till T6. Haemodynamic parameters were noted at every five minutes for the first thirty minutes of the surgery and thereafter every ten minutes till its completion. Pain was analyzed using Visual Analog Score (VAS) that characterizes as well as measure pain between 0-10. If VAS observed to be equal or more than 4, then patient was given intramuscular injection of Diclofenac 75mg as rescue analgesic. APGAR scores were measured at 1st and 5thminutes after the birth of baby by a paediatrician who was unaware of the study. Hypotension was defined as SBP < 90 MM Hg or fall of blood pressure to more than 30%. Inj. Mephentermine 6mg iv and additional 100 ml bolus of Ringer Lactate was used to treat hypotension. Bradycardia, defined as HR <60 beats/min or >30% fall from baseline were managed with Inj. Atropine 0.50 mg intravenously. All adverse reactions of spinal anaesthesia like emesis and shivering, were noted and handled symptomatically.

Statistical analysis

"IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp." was used for all statistical analyses. The parametric data was evaluated using Student's t-test whereas Fisher's exact test or Chi-square test for non-parametric data. Statistical significance was noted when p value falls less than 0.05.

RESULTS

The current study enrolled 70 patients and one patient ingroup P was eliminated from study due to change in anaesthesia plan [Figure 1]. On comparing demographic characteristics, the mean age in Group P was 27.54±4.35 years and in Group S was 28.40±4.28 years (p=0.41) [Table 1]. Moreover, on comparing body mass index and ASA grade between the groups the results were statistically insignificant [Table 1].

Table 1: Demographic Data.

Variables	Group P (n=34)	Group S (n=35)	P value
Age (years)	27.54±4.35	28.40±4.28	0.41
Height (cms)	162.83±6.82	162.05±7.33	0.65
Weight (kgs)	56.46±6.27	56.97±6.91	0.75

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BMI (kg/m2)		21.32±2.33	21.78±2.88	0.47
ASA grade (I and II)	I II	25(71%) 10(29%)	21(60%) 14(40%)	0.45

Table 2: Block Characteristics

Block Characteristics	Group P (n=34)	Group S (n=35)	P value
Onset of sensory block (minutes)	2.63±0.49	1.91±0.28	0.001*
Duration of sensory block (minutes)	64.94±4.94	68.23±4.37	0.004*
Onset of motor block (minutes)	3.17±0.38	2.89±0.32	0.001*
Duration of motor block (minutes)	100.31±3.69	111.06±4.90	0.001*

*P<0.05

[Table 2] depicts that the onset of mean sensory block was 2.63± 0.49 mins in Group P and 1.91±0.28 mins in Group S (p=0.001). The duration of sensory blockade was 64.94± 4.94 min in group P and 68.23±4.37 min in group S (p=0.004) (Table 2). Similarly, statistical significance was observed on comparing the time period of onset and duration of mean motor blockade between the two groups (p<0.05) [Table 2].

On comparing the hemodynamic parameters (heart rate and mean arterial pressure), no statistical significance was found between the groups from baseline till the completion of surgery [Table 3,4].

The Mean VAS Score between premixed and sequential Groups at baseline was 0.57±0.50 and 0.63±0.49 (p=0.63) [Table 5]. Similarly, the mean VAS scores at 2nd, 4th and 6th hour revealed no significant results(p>0.05) [Table 5]. The comparison of mean APGAR score at 1st and 5th minutes between the two groups had insignificant results (p>0.05) [Table 6]. Shivering was observed in 5.8% and 8.6% of cases in Group P and Group S respectively (p=0.64) [Table 7]. Hypotension was encountered in 8 and 5 patients of premixed and sequential groups respectively (p=0.73). However, none of the patients experienced respiratory depression, arrhythmia or pruritus [Table 7].

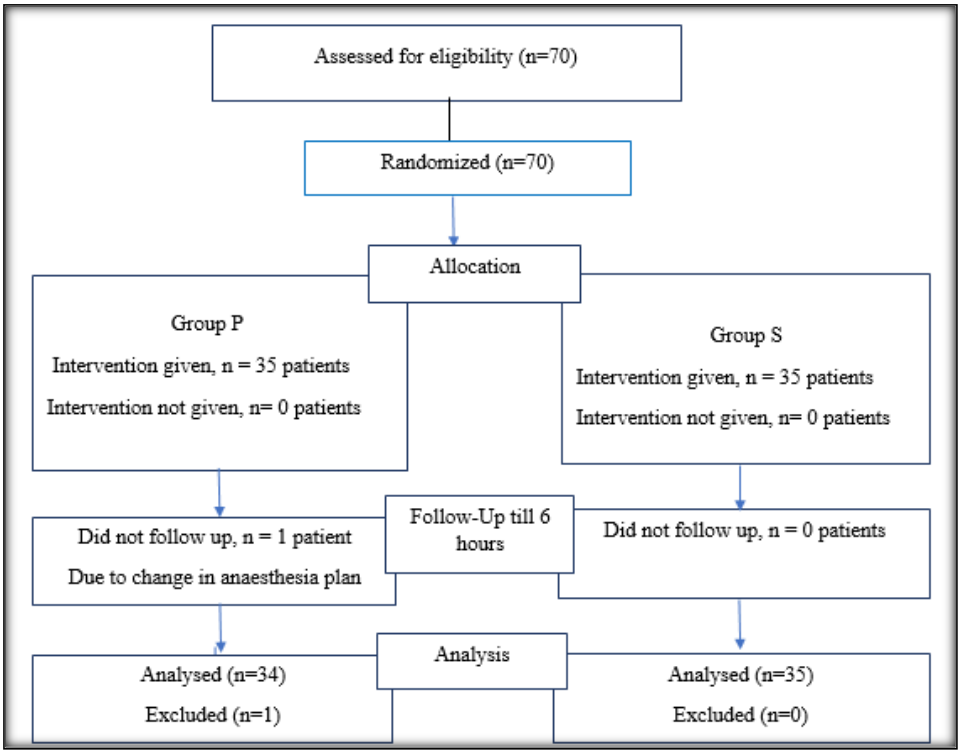

Figure 1: Consort flow diagram

Table 3: Comparison of mean heart rate

Heart Rate (in minutes)	Group P (n=34)	Group S (n=35)	P value
Baseline	88.06±6.57	86.57±17.35	0.63
5	99.06±9.68	95.66±29.14	0.51
10	95.06±17.06	88.4±20.6	0.14
15	98.46±16.54	90.14±24.77	0.10

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20	95.97±16.03	98.77±10.2	0.38
25	94.63±14.2	97.14±10.12	0.39
30	89.46±13.74	94.71±11.74	0.09
40	95.57±12.64	98.71±12	0.29
50	90.6±12.48	97.03±12.98	0.83
60	95.34±17.69	96.26±13.93	0.81
70	89.66±19.7	87.37±19.68	0.62
80	86.69±11.6	87.54±13.5	0.77

Table 4: Comparison of mean arterial pressure

Mean Arterial Pressure	Group P (n=34)	Group S (n=35)	P value
Baseline	95.87±4.94	95.47±5.5	0.75
5	88.89±10.4	90.51±7.12	0.45
10	85.89±6.05	85.74±5.9	0.92
15	84.86±12.0	86.84±7.39	0.41
20	93.58±10.7	92.98±11.02	0.81
25	93.22±10.0	92.9±10.32	0.89
30	92.85±6.94	92.22±9.09	0.74
40	87.39±9.47	88.25±11.14	0.73
50	89.92±7.71	90.54±7.73	0.73
60	90.98±6.96	91.8±6.56	0.61
70	90.61±5.53	89.36±3.81	0.27
80	88.68±6.81	88.94±4.26	0.84

Table 5: Mean VAS score

VAS score	Group P (n=34)	Group S (n=35)	P value
0 hrs.	0.57±0.50	0.63±0.49	0.63
2 hrs.	2.94±0.24	3.03±0.17	0.08
4 hrs.	4.11±0.32	4.17±0.57	0.60
6 hrs.	2.97±0.17	3.03±0.17	0.16

Table 6: APGAR score

APGAR score	Group P (n=34)	Group S (n=35)	P value
At 1 min	7.17±0.70	7.06±0.68	0.49
At 5 min	8.71±0.45	8.83±0.38	0.26

Table 7: Complications/Adverse effects

Complication	Group P (n=34)	Group S (n=35)	P value
Shivering	2(5.8%)	3 (8.6%)	0.64
Nausea and Vomiting	4 (11.5%)	3 (8.6%)	0.69
Pruritus	0	0	NA
Respiratory distress	0	0	NA
Arrhythmias	0	0	NA
Hypotension	8 (22.9%)	5 (14.3%)	0.73

DISCUSSION

Spinal anaesthesia is the choice of technique for emergency or elective LSCS and provides advantage in enabling early detection of complications. However, it can contribute to significant hemodynamic instability especially in pregnant patients. Lot of measures had been undertaken to minimise the chances of SIH (Spinal induced hypotension) among parturients but none has proved to be perfect.

Gomaa et al performed a study evaluating nalbuphinevs fentanyl when combined to bupivacaine intrathecally for relief of post-operative painafter caesarean section. They observed that both the adjuvants were equally effective in providing good relief from intra-op and early post-op pain.[7] A research performed by Routray et al on heavy bupivacaine along with clonidine and fentanyl as adjunct in neuraxial block for orthopaedic lower limb surgery and noted that clonidine causedextended time period of pain reliefin addition to more sedation than intrathecal fentanyl.[8] However, a study performed by Malhotra et al on use of fentanyl as premixed versus succedent administration in intrathecal block for lower limb surgeries and concluded that sequential administration of fentanyl after injecting bupivacaine in intrathecal space provides quicker onset and increased

ISSN:0975-3583,0976-2833 VOL14,ISSUE05,2023

time period of sensory/motor blockade.[6] Therefore, we used fentanyl as adjuvant in our study in premixed and sequential administration with bupivacaine among patients posted for lower segment caesarean section.

Ebrie et al studied the analgesic as well as hemodynamic effects of fentanyl and heavy bupivacaine (8 mg) intrathecally in individuals having caesarean delivery and they observed that lower bupivacaine dosage is linked to a quicker recovery and reduced risk of hypotension. In spinal anaesthesia for caesarean sections, combining fentanyl with a lower dosage of bupivacaine might provide equivalent anaesthesia with less chances of hypotension and extended postoperative analgesia.[9]. Jahanara et al did a similar study using 9mg hyperbaric bupivacaine and morphine as an adjuvant. They found that premixed and sequentially administered intrathecal morphine and hyperbaric bupivacaine revealed no differences in quality of neuraxial block, maternal hemodynamic and neonatal consequences.[10] Nagata et al in japanese parturients performed a research comparing effects of 8 mg and 10 mg doses of heavy bupivacaine during neuraxialblock. They observed that the use of lower dosage of bupivacaine in neuraxial block for cesarean sections had beneficial effect in providing pain relief and haemodynamics.[11] Another research was conducted by Venkata et al where they comparedlow dosage bupivacaine (7.5mg) and fentanyl premixture to ausual dose of bupivacaine heavy (10mg) for cesarean section. They observed that duration of analgesia during caesarean section is longer and hemodynamically stable when low dosage bupivacaine and fentanyl are combined instead of bupivacaine alone.[12]

In the current study, intrathecal succedent injection of fentanyl as an additive to heavy bupivacaine had statistical significance for duration/onset of sensory as well as motor blockade compared to premixed administration of the adjuvant. Our results were similar to the research performed by Chekole et al using fentanyl as an adjuvant in sequential versus premixed mixture with heavy bupivacaine for patients scheduled for caesarean section.[13] They observed that sequential administration of fentanyl provides quicker onset of sensory blockade with extended time period of motor blockade. Jahanara et al,[10] performed similar research with morphine as an adjunct in neuraxial block for caesarean section. They noted that there was no discernible change in block characteristics between premixed and sequential groups. Sachan et al conducted a study on effectiveness of premixture clonidine vs serial clonidine injection as an adjunct to intrathecal heavy bupivacaine in caesarean section. They observed that administering clonidine sequentially leads to quicker sensory/motor block onset and also markedly lengthened relief from post-operative pain. [14]

In the current research, there was no statistically significant difference among the two groups when evaluating the hemodynamic variables. However, Chekole et al observed a statistically significant change in average arterial blood pressure at 5 minutes, 10 minutes, and 15 minutes[13]. The findings may be attributed due to higher doses of hyperbaric bupivacaine used in their study. Moreover, in a study conducted by Singam et al, hypotension was recorded in 52% patients in premixed category as compared to 12% in sequential category.[15] This can be explained from the same fact that the researchers had used a much higher dosage of hyperbaric bupivacaine (15 mg) in their study.

In the present study, VAS Scores was comparable at baseline, 2 hours, 4 hours, and 6 hours after spinal anaesthesia. Similar to our study, El Kenany conducted a study on lower limb orthopaedic surgical patients and observed no statistically significant change in the median VAS score at the fourth, fifth, and sixth hours.[16] Chekole et al. observed that after the caesarean delivery, the sequential group had considerably lower median pain score than the premixed group. at 4, 5 and 6 hours.[13]

The present study also compares neonatal outcome by using APGAR scores. We observed no statistically significant difference between the groups. The results of Chekole et al simulates with our findings and they discovered no discernible difference among the two categories.[13]

The authors of the present study reported 8 and 5 patients of hypotension in Group P and S respectively. However, all cases of hypotension were successfully managed by fluids and intermittent doses of intravenous Mephenteramine 6 mg. Nausea/vomiting was recorded in 4 patients belonging to Group P and 3 cases of Group S. No cases of pruritus, respiratory depression and arrhythmia was observed in any of our patients. Our observations were similar to research done by several authors and they also observed insignificant adverse events between the premixed and sequential groups.[15,16] On contrary to our findings, the study by A.T. Chekole et al. reported that hypotension was noted in 11 cases of Group M and 3 cases of Group S.[13] Also, research conducted by Keera et al. on 60 Birthing woman who had a spinal anaesthesia for an elective caesarean section revealed that hypotension was more common in group M (51.6%) than category S (29%). The findings of high incidence of hypotension among other researchers is because of the use of higher doses of hyperbaric bupivacaine in their studies.

The present study carries some limitations. The results would be better if the speed of intrathecal drug administration would have been recorded. Moreover, the study can be conducted on a bigger sample size to have a better precision of the observations. The VAS score may be recorded for 24 hours to have a better idea on about post-operative analgesia. The outcome of neonates can be better predicted if arterial blood gas analysis of neonatal cord blood had been done.

ISSN:0975-3583,0976-2833 VOL14,ISSUE05,2023

CONCLUSION

Our study's findings reveal sequential administration of fentanyl as an adjuvant to local anaesthetic for lower segment caesarean deliveries carries better outcome of the parturients as compared to premixed. Although both the techniques carry stable hemodynamics but in view of sensory/motor blockade sequential administration of fentanyl is advocated. The sequential administration of fentanyl provides better postoperative pain relief, good neonatal outcome with lesser side effects.

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