European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 09, Issue 02, 2022

Comparative study of low dose subarachnoid bupivacaine (9 mg) with different dose combinations of fentanyl versus standard dose bupivacaine (12 mg) in parturients undergoing caesarean section

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Received on: 15 April 2022, **Reviewed on**: 10 May 2022, **Published on**: 23 May 2022

Abstract

Background: Opioids and local anaesthetics act synergistically and it's a popular technique to combine bupivacaine and fentanyl in spinal anaesthesia for caesarean delivery. The aim of the study was to find out optimal dose combination of bupivacaine and fentanyl for spinal anaesthesia for better quality of perioperative analgesia and reduction of feto-maternal adverse outcome during caesarean section.
Methods: Three hundred and four parturients scheduled for caesarean delivery were randomly allocated to four groups of 76 each. Data of 298 parturients (Gp I=73, Gp II=75, Gp III=75 and GP IV=75) was included in the primary outcome analysis. The control group received 12 mg of 0.5% hyperbaric bupivacaine for spinal anaesthesia. Fentanyl 15, 20 or 25 µg was added to each study group who received 9 mg of 0.5% hyperbaric bupivacaine in spinal anaesthesia. Onset and duration of spinal anaesthesia, hemodynamic parameters, intraoperative nausea & vomiting (IONV), failed block, APGAR score and other side effects were noted.
Results: The duration of effective and complete analgesia was significantly longer in all fentanyl groups. However, increasing the dose of fentanyl from 15 to 25 µg had little effect on further prolongation of analgesia. Duration of motor blockade was significantly prolonged in control group. The incidence of hypotension and IONV episodes were significantly low in the study groups.
Conclusion: Bupivacaine and fentanyl have super additive effect in spinal block. However, strict drug dose calculation is required in spinal anaesthesia to minimize adverse outcomes during caesarean delivery. Spinal anaesthesia with fentanyl 15 µg and 0.5% hyperbaric bupivacaine, 9 mg provides optimal surgical conditions for caesarean delivery with negligible side effects as compared to other dose combinations.

Keywords: Caesarean, analgesia, bupivacaine, fentanyl, spinal, anaesthesia, subarachnoid

ISSN 2515-8260 Volume 09, Issue 02, 2022

Introduction

Worldwide caesarean delivery is the most common surgery performed with an estimation of 29.7 million per year, at the rate of 21.1% of total births as on 2015[1].With the development of smaller gauge needles and newer bevel designs, single shot spinal anaesthesia has established itself globally as the most preferred technique for caesarean section. Spinal anaesthesia is superior to general anaesthesia (GA) due to its simplicity, reliability, rapid onset and minimal fetal drug exposure. However, its major drawback is sympathetic block induced maternal hypotension which is primarily related to the dose of local anaesthetic injected into the subarachnoid space.

An extensive literature based on clinical and experimental studies has established that intrathecal opioids can reversibly modulate the ascending noxious stimuli by binding to the pre-and post-synaptic opioid receptors at the dorsal horn of spinal cord[2]. However, when used alone neuraxial opioids are ineffective in producing adequate depth of analgesia required for surgery. Due to different mechanisms of action, addition of opioids to local anesthetics for spinal anaesthesia has synergistic effect which can decrease the undesirable side effects by reducing the doses of individual drugs.

Several clinical trials have studied the potential effects of various doses of intrathecal fentanyl and bupivacaine, still the ideal dose combination is controversial and lacks clarity. Variable dose range of fentanyl starting from 2.5 µg to 60 µg has been used intrathecally but most of these studies had smaller sample size and lacked adequate power[3, 4].Similarly, the meta-analysis by Arzola C *et al*. demonstrated that low dose (<8 mg) intrathecal bupivacaine compromises anaesthetic efficacy despite reduced maternal side-effects[5].

This study was conducted with the primary objective to find out suitable dose combination of intrathecal bupivacaine and fentanyl for better quality perioperative analgesia (duration of analgesia and motor block) and secondary objective to observe the incidences of feto-maternal adverse events among the groups.

Methods

This was a prospective, randomized, double-blinded, parallel group and comparative effectiveness trial conducted at a teaching hospital in central India after approval from Institutional Ethics Committee. Parturients scheduled for elective/urgent caesarean delivery with American Society of Anaesthesiologists grade II physical status were included in the study. Patient's refusal, infection at injection site, allergy to opioids & local anaesthetics, demyelinating disease, fixed cardiac output status, coagulopathy, sepsis and immunocompromised patients were excluded from the study. Written informed consent was obtained from all patients fulfilling the inclusion criteria.

Pre-anaesthesia check-up was conducted for all the elective cases and rapid clinical assessment was performed for all urgent caesarean deliveries. Elective patients were kept fasting for at least 10 h prior to surgery and urgent cases were premedicated with inj. metoclopramide, 10 mg and inj. pantoprazole, 40 mg intravenously (IV) ninety minutes prior to surgery. Baseline hemodynamic parameters and fetal heart rate were checked before shifting the patient to operation theatre (OT). Prior to surgery, enrolled patients were explained about the methods of assessment pain & lower limb movement.

The parturients (N=304) were randomly allocated to four groups of 76 each. Randomization was done by using computer generated random numbers, which were kept in a sealed envelope by an operation theatre (OT) assistant. Specific syringe with the relevant study solution was provided by the OT assistant who only knew the allocation group. Patient and the staff (anaesthesiologist, obstetrician, paediatrician and nurses) performing the procedure and making observations were blinded throughout the study.

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Patients were categorized into following four groups with seventy-six patients in each group based on dose combinations of intrathecal bupivacaine and fentanyl:
Group I: Bupivacaine 0.5% heavy, 12 mg (B12).
Group II: Bupivacaine 0.5% heavy, 9 mg plus fentanyl, 25µg (B9F25).
Group III: Bupivacaine 0.5% heavy, 9 mg plus fentanyl, 20µg (B9F20).
Group IV: Bupivacaine 0.5% heavy, 9 mg plus fentanyl, 15µg (B9F15).

Inside the operating room vital parameters were again noted and patient was co-loaded with Ringer's lactate @ 15ml/kg. Under strict aseptic conditions, the desired drug combination was injected into subarachnoid space with 25G/26G/27G Quincke's spinal needle in L3-L4 or L4-L5 lumbar intervertebral space by midline approach in sitting position after free flow of clear CSF. The patient was turned back immediately to supine position with fifteen degree left tilt of the OT table and connected to a multi parameter monitor. Supplemental oxygen @ 5 litres per minute was given till the delivery of baby. In our setting, we measured the heart rate (HR), blood pressure (BP), ECG and SPO_2 at three minutes interval during the whole intra operative period. Time of onset for abolition of pinprick sensation to T4 dermatome level was checked bilaterally at midclavicular line every 30 seconds. Bromage scale (BS) was used to assess the motor block (BS grade I = unable to move feet or knees, II = able to move feet only, III = just able to move knees and IV = full flexion of knees & feet). Time for onset of BS (grade II) motor block and time of regression of motor block to BS (grade IV) was noted. After the clamping of umbilical cord, inj. Oxytocin, 5 IU IV bolus followed by 20 IU in 500 ml of normal saline infusion @ 20-40 drops per minute was administered. Newborn babies were evaluated by paediatrician and neonatal APGAR score at 5 minutes was noted. Spinal injection to skin incision time, incision to delivery time and total duration of surgery also was recorded.
Post operatively vital signs were recorded one hourly for first 4 hour then every six hourly for the next 24 hours. Complete analgesia duration and effective analgesia duration were noted. Ten point numeric visual analog scale (VAS) score was used to assess the severity of pain at 30 minutes interval from skin incision till the appearance of pain (VAS score-1) postoperatively.
Code breaking or unblinding was planned while making standard operating procedure to manage severe expected/unexpected adverse events. Intraoperative breakthrough pain, if any was managed with multimodal IV analgesia or conversion to general anaesthesia. Maternal side effects like hypotension, bradycardia, respiratory depression, IONV, pruritus and shivering were noted and managed with appropriate measures. Unblinding was done at the end of the study to evaluate the clinical effectiveness of treatment given to the patient.

Operational definitions

Hypotension was defined as decrease in BP of more than 30% from the baseline and was managed with rapid infusion of normal saline and 3 mg aliquots of inj. mephentermine intravenously. Bradycardia was defined as heart rate <50/min. Respiratory depression was defined as respiratory rate <10/min. Complete analgesia duration was defined as time of onset of sensory analgesia to T4 till the first appearance of pain with VAS score-1. Effective analgesia duration was defined as the time of first request for post-operative analgesia.

Sample size calculation

The statistical power analysis suggested that a sample size of 64 patients/group was required to achieve a power of 80%, α=0.05, effect size of 0.5 [effect size conventions=0.5 (medium)], allocation ratio of 1:1 as input parameter, to be able to detect significant difference of

ISSN 2515-8260 Volume 09, Issue 02, 2022

analgesia between the control (bupivacaine alone) and test group (bupivacaine + fentanyl group) by using G*Power software**,** version 3.1.9.4 (Franz Faul, Christian-Albrechts-Universität Kiel, Germany) (with non-centric parameter δ=2.828, critical t=1.978, degree of freedom (DF)=126 as output parameters). So considering 20% of loss to follow up or of incomplete data, sample size for single group was finalised as 76 per group and total sample size was 304.

Statistical analysis

The data was compiled in Microsoft excel and thoroughly analysed with the help of Statistical Package for the Social Sciences (SPSS, version 16). For qualitative characteristics, frequencies & percentages were estimated and compared with Fisher exact test among the groups. For qualitative observation, mean & standard deviation (SD) with 95% confidence interval were computed and groups were compared using one way analysis of variance (ANOVA) and Bonferroni's test. *P* value of ≤0.05 was considered statistically significant.

Results

The flow of study participants was as shown in figure 1.

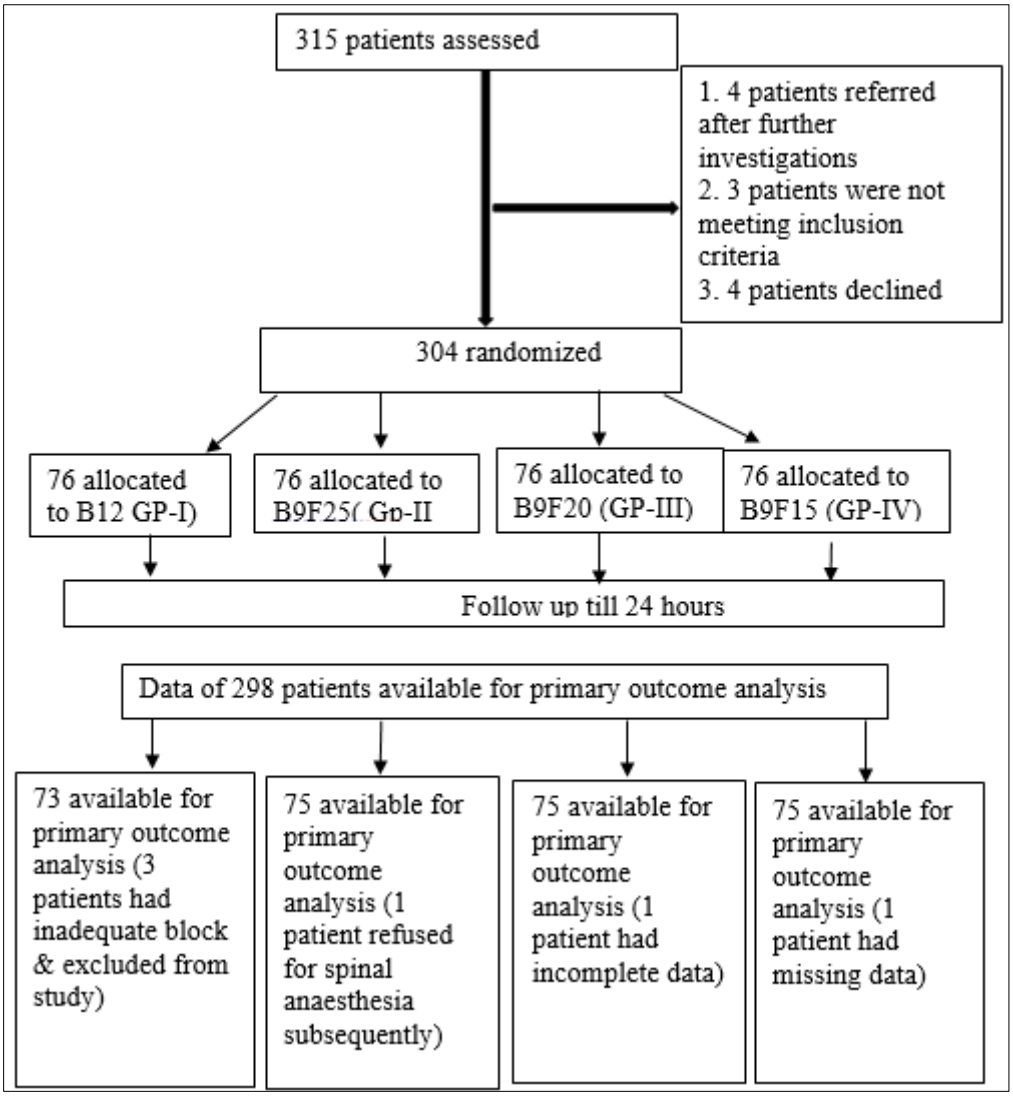

Fig 1: Flow diagram of study participants

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The age, weight, height, heart rate, systolic blood pressure and diastolic blood pressure profile among the groups were comparable and statistically insignificant as shown in table 1.

Table 1: Demographic and clinical characteristics of patients

Parameters	Group I Mean±SD	Group II Mean±SD	Group III Mean±SD	Group IV Mean±SD	P-Value
Age (yrs)	27.54±4.07	27.62±3.73	26.66±3.76	27.52±3.72	0.374
Weight (kg)	69.60±12.99	67.58±9.28	69.14±10.20	70.01±9.66	0.524
Height (cm)	155.67±2.63	155.50±2.70	155.49±2.99	156.73±3.60	0.035
Heart Rate per min	76.54±8.84	75.22±9.29	75.62±8.40	77.88±8.48	0.257
Systolic BP in mmHg	118.39±12.21	119.54±6.99	120.92±6.69	118.84±6.45	0.280
Diastolic BP in mmHg	74.67±6.57	73.70±6.76	75.34±7.12	72.49±5.94	0.051

The onset time to loss of pinprick sensation to T4 dermatome was significantly shorter in all fentanyl groups. There was statistically significant difference observed between group I vs group II (0.000), III (0.000) and IV (0.016) and no statistically significant difference was observed among study groups for loss of pinprick sensation to T4 dermatome. Onset time of BS grade II motor block was lower in study groups but not statistically significant (P=0.060). The duration of complete and effective analgesia was significantly longer in all fentanyl groups as depicted in table 2. Regression time of motor block to BS (grade IV) was significantly shorter in all fentanyl groups as compared to control group [group I (156.43±3.79), group II (148.45±5.03), group III (147.62±3.80) and group IV (148.90±4.54)]. For complete analgesia duration, effective analgesia duration and regression of motor block, no statistically significant differences were observed among study groups (group II, III and IV).

Table 2: Subarachnoid block data

Parameters	Group-I	Group-II	Group-III	Group-IV	P-Value
Time for loss of pinprick sensation to T4 (min)	3.14±.72	2.76±.40	2.80±.29	2.90±.32	0.000
Onset of BS grade II motor block (min)	4.83±.79	4.64±.52	4.62±.40	4.61±.43	0.060
Complete analgesia duration (min)	136.70±3.69	159.20±4.69	159.78±3.51	159.84±4.08	0.000
Effective analgesia duration (min)	192.23±5.40	201.41±4.69	202.41±4.91	203.41±4.55	0.000
Regression time of motor block to BS grade IV (min)	156.43±3.79	148.45±5.03	147.62±3.80	148.90±4.54	0.000

Maximum fall in BP was observed within first ten minutes of intrathecal drug administration. The severity and incidence of hypotension was significantly higher in the control group (P=0.000). Hemodynamic stability was better in the fentanyl groups with minimum fluctuation of blood pressure in B9F15 group. Intra operative nausea and vomiting (IONV) was significantly lower in all fentanyl groups (P=0.008) as mentioned in table 3. Decrease in baseline heart rate between the study groups and control group was insignificant and asymptomatic bradycardia was noticed in two patients each in group I and II. Mild self-limiting pruritus was observed in two patients receiving fentanyl 25 µg. The incidence of shivering between the study groups and control group was also not statistically significant (P=0.901). Respiratory depression was not observed in any patients.

Table 3: Maternal side effects

Adverse events	GP-I	GP-II	GP-III	GP-IV	p-value
Hypotension	12	3	1	0	0.000

Bradycardia	2	2	0	0	0.265
Respiratory depression	0	0	0	0	NA
IONV	6	2	0	0	0.008
Pruritus	0	2	0	0	0.248
Shivering	1	0	1	1	0.901

Injection to skin incision time, skin incision to delivery time, APGAR scores in new born at 5 minutes and duration of surgery were similar across all groups and not found to be statistically significant as shown in table 4.

Table 4: Surgical quality and other parameters

Characteristics	GP-I	GP-II	GP-III	GP-IV	P Value
Spinal injection to skin incision time (min)	7.83±2.11	8.36±2.35	8.16±1.86	8.03±1.82	0.460
Skin incision to delivery time (min)	8.87±2.88	8.04±2.10	8.15±2.08	8.65±2.04	0.086
APGAR score in new born at 5 min	8.85±.36	8.89±.31	8.92±.27	8.89±.31	0.548
Duration of surgery (min)	51.72±9.01	49.29±10.07	46.69±8.94	49.89±8.61	0.011

Discussion

In this study, the onset of sensory block was shorter in all fentanyl groups and statistically significant when compared with the control group. The rapid onset could be due to high lipid solubility of fentanyl and supported by an earlier study [6]. As evident from the results, the duration of complete and effective analgesia was significantly prolonged in all fentanyl groups. Fentanyl modulates the Aδ and C fibres without affecting the motor (Aα) nerve fibres at the spinal cord level and hence prolongs the duration of bupivacaine induced sensory block [7]. Our study showed that increasing the dose of fentanyl from 15 to 25 µg did not offer added advantage over the quality of surgical analgesia which was consistent with earlier experiments [8, 9]. In the fentanyl groups, the onset time of motor block was reduced but not statistically significant similar to a previous study [10]. Regression time of motor block to BS grade IV was longer in the control population and akin to prior studies [11, 12].Prolonged motor block in control group could be due to higher dose of bupivacaine (12 mg) used in comparison with fentanyl groups (9 mg). No patients of the study groups developed failed block, which could be due to local anaesthesia sparing effect of neuraxial fentanyl [13].

Subarachnoid block induced hypotension was more prominent and a common event in the control group. The lower incidences of hypotension in the fentanyl groups supported by the study of Cheng Wang *et al*. indicate that fentanyl do not have any measurable effect on the sympathetic efferent pathways [14]. The incidence of bradycardia noted between the study groups and the control group was not significant. During spinal anaesthesia, the complex interplay between preganglionic sympathetic block of cardiac accelerator fibres or reverse Bainbridge reflex (decrease HR) and baroreceptor activation secondary to hypotension (increase HR) causes variations in heart rate [15].

The major factors of IONV during spinal anaesthesia were hypotension, unopposed vagal over activity due to sympathetic block and visceral pain caused by surgical traction & exteriorization of uterus. Due to modulation of visceral pain pathway, minimal action on sympathetic efferent and better control of hypotension, intrathecal fentanyl reduces the intraoperative emetic episodes which was evident in our study and supported by other investigators [16-18].

Low-dose lipophilic intrathecal opioids might cause early (0-1 h) respiratory depression [19]. However, no patient in the present study developed respiratory depression. Respiratory depression after 2 h of intrathecal injection of fentanyl or sufentanyl has never been described [20]. Two incidences of self-limited pruritus were observed in this study and were related to

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the higher doses of intrathecal fentanyl (25µg). This was in contradiction with earlier reports where the incidence was high and not dose related [21]. The incidence of shivering was also negligible in our study. Crowley LJ *et al*. observed that neuraxial opioids particularly meperidine and fentanyl reduced the likelihood of shivering [22]. Similar to earlier reports, there was no adverse neonatal outcome in our trial and APGAR score was comparable amongst the groups [23].

Conclusion

In parturient undergoing caesarean section, low dose spinal bupivacaine with fentanyl was better than bupivacaine alone in reducing adverse maternal events and providing superior quality of analgesia. Fentanyl 15µg along with 1.8 ml of 0.5% bupivacaine, heavy (9 mg) was found to be an ideal dose combination for spinal anaesthesia during caesarean section.

Conflict of interest: There is no conflict of interest in the present study.

Funding source: The study received no financial aid from any funding organization or agency.

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