COMPARATIVE STUDY OF BUPIVACAINE WITH FENTANYL VS BUPIVACAINE WITH FENTANYL PLUS MORPHINE IN SPINAL ANAESTHESIA FOR LOWER SEGMENT CAESAREAN SECTIONS

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ABSTRACT

BACKGROUND

Anaesthesiologists all over the world are facing challenges to manage increasing number of caesarean deliveries. Central neuraxial techniques of subarachnoid blockade with 0.5% Bupivacaine heavy solutions in different doses are generally employed.

MATERIALS AND METHODS

Sixty parturients coming for non-urgent caesarean deliveries were randomized into 2 groups of 30 each; Group I receiving 7.5 mg Bupivacaine heavy plus 16 µg Fentanyl and Group II receiving 7.5 mg Bupivacaine heavy plus Fentanyl 16 µg & Morphine 125 µg, the volume of solutions being 2 ml in both the groups.

RESULTS

Demographic data, pre-operative, intra-operative & post-operative vitals, characteristics of motor blockade and complications were comparable in both the groups. However sensory blockade (analgesia) in Group II was much longer and post-operative analgesic consumption in the first 24 hours were much lesser in Group II.

CONCLUSION

It has been concluded that addition of Fentanyl 16 µg and Morphine 125 µg to Bupivacaine 7.5 mg is a very good option for non-urgent Caesarean deliveries.

KEY WORDS

Intrathecal Morphine; Fentanyl; Bupivacaine; LSCS.

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BACKGROUND

In the last few decades, number of caesarean birth has increased dramatically in both the developed and developing countries especially in countries like India where the actual incidence has been reported to have crossed even 40% of all deliveries in some centres.^{1,2} The brunt of the problem falls more on the anaesthesiologists providing anaesthesia to an apparently healthy pregnant woman whose anatomy and physiology are stretched to the maximum to provide the need for the foetus, which is in the fastest phase of human growth.³ Regional anaesthesia employing central neuraxial blockade through lumbar subarachnoid block by injecting preservative free Bupivacaine heavy 0.5% is the most popular anaesthesia technique.⁴

The dose of the local anaesthetic (LA) decides the extent and duration of the block - too little dose will cause untimely

wearing away of the block, visceral pain on exteriorization of uterus & handling of other abdominal contents, whereas too large a dose might result in an intensive block with the resultant hypotension, bradycardia and sometimes even cardiac arrest.

With a view to lower the dose of LA and to improve the quality & duration of the sub-arachnoid block (SAB) at the same time, adjuvants like clonidine, dexmedetomidine, morphine, fentanyl etc. are added to the LA. The adjuvants like clonidine, dexmedetomidine etc. improve the quality and prolong the duration of block but the incidence of hypotension, bradycardia are still of concern.^{5, 6} Fentanyl, a synthetic opioid, improves the quality and duration of block but at doses like 25 µg, the incidence of pruritus is high,⁷ and the duration of block to provide adequate postoperative analgesia is not satisfactory. Morphine, a hydrophilic opioid, when given intrathecally has a slower onset of action but prolonged analgesic effect with incidence of post-operative respiratory depression at higher doses.^{8,9}

A hypothesis was made that addition of fentanyl to a lower dose of Bupivacaine will enhance the onset of a smooth subarachnoid block and morphine with its slower but sustained action in the central neuraxial blockade will provide a prolonged post-operative analgesia. This clinical study was undertaken to compare the effects of 7.5 mg of Bupivacaine heavy with a low dose of Fentanyl (16 µg) alone

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on one end and addition of 125 µg of Morphine to this mixture on the other end, comparing the hemodynamic parameters, maternal and foetal side-effects and duration of post-operative analgesia.

MATERIALS AND METHODS

We used a double blind randomized controlled trial. Randomization in a ratio of 1:1 was carried out using a computer-generated random process with concealment. Whenever a patient came in, the allocation was informed to the investigator by a third party from the Community Medicine Department of the institute. The drugs in both intervention as well as controlled arms were similar in physical characteristics, volume and were prepared by another person, who was not involved in the study. The assessors (investigators) were also blinded.

The sample size of 60 patients for the study was taken for convenience. All term (>36 weeks) singleton pregnant women opted for elective caesarean section were included in the study. Pregnant women with contraindication to sub-arachnoid block (SAB) with the study drugs, with morbid and comorbid conditions like PIH, eclampsia, multiple pregnancy, placenta praevia and, other systemic diseases with physical status ASA III and above were excluded. All eligible willing participants were recruited and numbered consecutively. Pregnant women posted for elective caesarean section in the Department of Anaesthesiology, between July 2018 and September 2018 had been recruited.

Parturients were cannulated with 18G canula and ringer lactate solution started. After connecting to a standard monitor to record ECG, SpO₂ & NIBP and with aseptic and antiseptic measures, the primary investigator located and punctured the dura at L3-4 level with a 25G Quincke needle while the subject was lying in right lateral decubitus position. After confirmation of free flow of CSF, the blinded primary investigator gave a mixture of the following solutions intrathecally: 1.5 ml (7.5 mg) of preservative free Bupivacaine heavy + 16 µg of Fentanyl in Group I and 1.5 ml (7.5 mg) of preservative free Bupivacaine heavy + 16 µg Fentanyl + 125 µg Morphine in Group II. The volume of the mixture in both the groups was made 2 ml by preparing the adjuvants in normal saline. After successful intrathecal injection, parturients were returned to supine position with a wedge under the right hip. Bladder catheterization and co-loading with Ringer lactate solution 500 ml over 5-10 minutes were initiated. Oxygen with face mask at 4 L/min was given to all parturients till the delivery of the baby. Extent of sensory block was assessed by perception of temperature with cold propyl alcohol at 15 seconds interval. Skin incision started when the sensory block is above T₆ and after the parturient did not respond to painful stimuli by the operating obstetrician. Modified Bromage scale at 15 minutes post SAB in each subject were recorded and thereafter at every 15 minutes intervals till Modified Bromage scale 6 was achieved.

Modified Bromage Scale

Score	Criteria
1	Complete block (Unable to move feet to Knee)
2	Almost complete block (Able to move feet only)
3	Partial block (Just able to move Knees)
4	Detectable weakness of hip flexion while supine (Full flexion of knees)
5	No detectable weakness of hip flexion while supine
6	Able to perform partial knee bend

Intraoperative vitals were recorded at every 5 minutes interval and episodes of hypotension (mean arterial pressure <60 mm Hg was treated by intravenous (IV) mephentermine, in 3 mg aliquots and bradycardia < 50/min associated with fall of mean arterial pressure < 60 mmHg, by 0.2 mg glycopyrrolate IV. Intraoperative complaints of visceral pain were recorded and treated by judicious use of IV midazolam (0.5 to 1 mg).

Intramuscular (IM) Inj. Oxytocin 10 mg was given just before delivery of the baby and inj. Methylergometrine 0.2 mg IM was given as and when asked by the obstetricians. The baby's Apgar Scores at 5 min of delivery were recorded and compared.

Post-operatively subjects were followed up to the first 24 hours, the time to request the first analgesic was recorded and Inj. Diclofenac Sodium 75 mg IM was given as rescue analgesic and total doses of diclofenac in the first 24 hours were recorded. Side-effects such as nausea & vomiting and pruritus were recorded and symptomatic treatment with ondansetron and antihistaminics were prescribed whenever required. Serious side-effect of respiratory depression was closely observed, and Injection Naloxone was kept ready for any eventuality. Since all of the subjects were catheterized for the first 24 hours urinary retention as a side effect of intrathecal opioids could not be assessed.

Data were summarized using mean (SD), frequency and proportions. Proportions were compared using Chi square and continuous variables were compared using independent 't' test. Data were entered in Microsoft Excel and analysed using IBM SPSS version 21. A p-value of less than 0.05 was considered statistically significant.

Institutional Ethics Committee approved the study. Written informed consent was obtained from each participant. Data were accessible only to the investigators and analysis team.

RESULTS

Demographic data like age, weight and height of the subjects and base line haemodynamic parameters are expressed as mean ± standard deviation (SD) & are shown in Table 1. There was no statistically significant difference.

	Group I (n=30)	Group II (n=30)	P value
Age mean ± SD in years	30.03 ± 6.04	30.8 ± 5.53	0.61
Weight mean ± SD in kg	68.96 ± 4.07	67.3 ± 3.65	0.1
Height mean ± SD in cm	152.6 ± 3.14	152.57 ± 2.71	0.96
Pulse Rate ± SD (per min)	79.6 ± 9.49	79.26 ± 10.01	0.89
Systolic BP ± SD mmHg	123.23 ± 7.36	124.23 ± 6.56	0.58
Diastolic BP ± SD mmHg	78.13 ± 5.69	78.86 ± 5.11	0.60

Table 1. Demographic Profile & Baseline Vitals of the Participants in Study Groups

Apgar Score (AS) of the newborns, Intra-operative pulse rates, mean arterial pressure, use of vasopressors and anticholinergics in both the group were comparable and reproduced in Table 2. The median of the AS was 8; none of

the new born had AS less than 7 at 5 minutes. Two subjects in Group I and 1 subject in Group II had discomfort on exteriorization of uterus and successfully treated with 1 mg Inj. Midazolam IV. There was no statistically significant difference in any of the observations/parameters.

	Group I (n=30)	Group II (n= 30)	P value
Pulse Rate $\pm$ SD (per min)	85 $\pm$ 4.2	84 $\pm$ 3.4	0.7
Mean arterial pressure $\pm$ SD mmHg	80.52 $\pm$ 3.58	81.46 $\pm$ 4.68	0.39
Doses of Mephentermine	10	11	0.82
Doses of Glycopyrrolate	0	1	0.32
Intra-operative discomfort	2	1	0.47
Apgar Score at 5 minutes (Median)	8	8	0.14
Table 2. Intra-Operative Vitals, Use of Vasopressors & Glycopyrrolate			

The time to reach T6 level of sensory blockade, Modified Bromage Scale (MBS) at 15 minutes post spinal injection & the time to reach MBS 6 were noted (Table 3). There was no statistically significant difference in these parameters. The time to request first analgesic and total doses of rescue analgesics in the first twenty-four hours were recorded and showed clinically as well as statistically significant difference; parturients in Group II having much longer pain free period and much lesser doses of rescue analgesic injections.

	Group I	Group II	P value	Statistical Significance
Time to reach sensory block to T6 (sec)	120.5 $\pm$ 19.16	114.67 $\pm$ 24.08	0.31	NS
Modified Bromage Score (MBS) at 15 min (Median)	1	1	0.75	NS
Time to First analgesic (Minutes)	250 $\pm$ 51.58	1022 $\pm$ 278.63	<0.0001	significant
Time to MBS 6 (Minutes)	125 $\pm$ 11.83	121.83 $\pm$ 24.40	0.53	NS
Total doses of analgesic in first 24 hr	32	3	<0.0001	significant
Table 3. Characteristics of Sensory and Motor Blockade & Analgesic Use				

The incidence of side effects like nausea & vomiting, pruritus and respiratory depression were observed up to the first 24 hours (Table 4). Seven subjects in Group I and 6 subjects in Group II had pruritus. There was no incidence of life-threatening side-effects like respiratory depression in both the groups.

Complications	Group I		Group II		p	Significance
	No.	%	No.	%		
Nausea & Vomiting	6	20	4	13.3	0.49	NS
Pruritus	7	23.3	6	20	0.76	NS
Respiratory depression	0	0	0	0		NS
Table 4. Side Effects						

DISCUSSION

This randomized study was conducted to show the beneficial effects of intrathecal fentanyl and morphine combined with

low dose Bupivacaine in caesarean deliveries, utilizing the faster action of intrathecal fentanyl and prolonged analgesic efficacy of intrathecal morphine. There are a number of studies where Fentanyl added to Bupivacaine heavy had shown beneficial effects in terms of rapid onset, smooth maintenance & extended duration of post-operative analgesia.¹⁰ Most of the study had employed Fentanyl in the dose of 25 μ g. Intrathecal morphine was first described in 1801 and since the publication on it by Wang JK, et al, in 1979, the popularity of the intrathecal morphine has overgrown tremendously.¹¹ There is no evidence that administration of intrathecal morphine in single, repeated or as continuous infusion causes neurotoxicity. In one case report where accidentally 510 mg (34 ml) of morphine was injected intrathecally; naloxone infusion, blood pressure and seizure control led to complete neurological recovery indicating that morphine does not have any neurotoxicity.¹² In a meta-analysis based on studies on spinal anaesthesia with morphine as an adjuvant of a local anaesthetic, it was documented that with the use of intrathecal morphine at doses < 0.3 mg, episodes of respiratory depression was not high as compared to the placebo group who received systemic opioids.¹³

Dhumal PR, et al,¹⁴ In their study on intrathecal Fentanyl and Bupivacaine combination for caesarean section concluded that addition of low dose preservative free Fentanyl (25 μ g) to 0.5% hyperbaric Bupivacaine for spinal anaesthesia causes faster onset and satisfactory intraoperative sensory and motor blockade, hemodynamic stability, less side effects and effective postoperative analgesia. Level of sensory blockade and onset of motor blockade were almost similar in all pregnant women in all groups with average T4 [T3-T6] in all groups. In their study they didn't report a high incidence of pruritus. But other studies and meta-analysis of use of intrathecal fentanyl at a dose of 25 μ g in caesarean sections, the incidence of pruritus was very high ranging from 20 to 100%.¹⁵

Bogra J et al,¹⁶ studied intrathecal Bupivacaine in doses of 8 mg, 10 mg, and 12.5 mg alone or in combination with 12.5 μ g of fentanyl for Caesarean sections and observed that the onset of sensory block to T6 occurred faster either with increasing Bupivacaine doses or with Bupivacaine-Fentanyl combination groups but with more incidences of hypotension and bradycardia occurring in higher doses of Bupivacaine. But the post-operative analgesia didn't last beyond 80 minutes to 150 minutes post intrathecal injection. However, the incidences of side-effects like nausea & vomiting and pruritus were very low with the dose of intrathecal Fentanyl.

Kiran S et al,¹⁷ also studied three doses of Bupivacaine 7.5 mg, 8.75 mg & 10 mg intrathecal doses for caesarean section and observed that increasing Bupivacaine dose increases the time for two segment sensory regression and also the duration of analgesia. But the incidence of hypotension was increased with increasing doses of bupivacaine. In Low dose bupivacaine group women could be made ambulatory at the earliest and also had better hemodynamic stability.

C Sibilla et al¹⁸ studied combination of 12-14 mg Bupivacaine with Fentanyl 25 μ g alone or in combination with Morphine 100 μ g for caesarean sections and could not demonstrate any benefit of combination of both opioids.

Likewise, Karaman S et al,¹⁹ concluded in their study that addition of intrathecal fentanyl 25 µg plus intrathecal morphine 100 µg to 10 mg bupivacaine for caesarean sections did not show any advantage of the combination and analgesia with only intrathecal morphine and bupivacaine was much superior. In these two studies, they had used a much larger dose of Bupivacaine which alone was more than enough for the procedure and which had masked the rapid onset of subarachnoid blockade initiated by intrathecal fentanyl. Weigl et al²⁰ in a similar study, concluded that combination of Morphine 100 µg and 25 µg Fentanyl to different doses of Bupivacaine, shortens the incision time and much improved the perioperative analgesia. With intrathecal fentanyl, pain relief is obtained within 10 minutes while intrathecal morphine takes about 60 minutes for onset of its analgesic action.²¹

In our study, we have fully utilized the synergistic effect of intrathecal fentanyl on rapid onset of analgesic sensory blockade and prolonged analgesic effect of intrathecal morphine with reduced dose of Bupivacaine and Fentanyl. A dose of Morphine which is not too high is selected to avoid high incidence of side-effects, to enable early ambulation but to obtain a prolonged pain free post-operative period.

CONCLUSION

Addition of Fentanyl 16 µg and Morphine 125 µg to 0.5% hyperbaric Bupivacaine 7.5 mg was effective for spinal anaesthesia in caesarean section surgeries, with minimal side effects, enabling early ambulation and prolonged analgesia.

Combinations of 7.5 mg 0.5% Bupivacaine with Fentanyl 16 µg were also beneficial in caesarean section surgeries, with moderate prolongation of analgesia. Addition of opioids such as fentanyl and morphine did not produce any adverse effects either in the mother or the neonate.

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