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ANAESTHETIC EFFICACY OF LOW DOSE BUPIVACAINE WITH FENTANYL FOR CAESAREAN SECTION - A RANDOMISED CONTROL TRIAL

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ABSTRACT

Background : A 'good quality block' for Caesarean section should combine adequate intraoperative anaesthesia with minimal side effects .Low dose bupivacaine has been advocated to reduce incidence of hypotension but has raised concerns of poor anaesthetic efficacy .With its rapid onset of action ,intrathecal fentanyl could augment quality of anaesthesia in the intraoperative period .In this randomised controlled study we evaluated the anaesthetic efficacy of combining optimal hemodynamic dose of 7.5 mg hyperbaric bupivacaine with the intrathecal fentanyl as compared to the conventional dose of 12.5mg of bupivacaine.

Methods: 100 singleton parturients scheduled for elective caesarean section were randomly allocated into two groups. The study group received a combination of 25 µg fentanyl, 0.5ml saline and 7.5 mg of hyperbaric bupivacaine, whereas the control group received 12.5 mg of hyperbaric bupivacaine. Intraoperative patient comfort, adequacy of sensory and motor block, hemodynamics, side effects, duration of blockade and analgesia and the Apgar score of the new-born were compared between the groups.

Results: Anaesthetic efficacy was better in the Fentanyl group with only 4.1% patients requiring intraoperative supplementation as compared to 16.3% in the control group. Also 14.3% patients in control group had nausea vomiting but none in the fentanyl group. Hypotensive episodes and need for ephedrine was less in fentanyl group (18.4%) versus control group (46.9%).

Conclusion: Intrathecal low dose bupivacaine with fentanyl in Caesarean section provides good intraoperative anaesthesia, stable hemodynamics and a satisfied pain free mother in the postoperative period.

KEYWORDS : Low dose Bupivacaine; Intrathecal fentanyl; Caesarean section, Spinal Anaesthesia

INTRODUCTION:

Though spinal anaesthesia is the preferred anaesthetic technique for Caesarean section, associated hypotension is a common problem with reported incidence upto 71% [1].Intraoperative hypotension accentuates maternal discomfort, nausea, vomiting and can lead to uteroplacental hypoperfusion causing fetal acidosis[2].

Left uterine displacement, fluid loading and vasopressor therapy are some of the techniques used to reduce hypotension, yet we have not still reached a consensus on the optimal preventive management [3,4].The degree of hypotension is proportional to height of blockade which in turn is related to dosage of local anaesthetic .The recommended dose of Bupivacaine for LSCS is between 10-15 mg which gives a predicted spread between T4-T8[5].However, the use of this dose range has been associated with a high incidence of maternal arterial hypotension. Various studies have examined reducing the dose of Bupivacaine, use of less than 10mg alone or 8mg with an opioid is considered a low dose [6,7]..But this could lead to poor quality of anaesthesia with need for intraoperative anaesthetic supplementation or conversion to GA with its associated mortality risks [8,9].A recent meta-analysis by Arzola et.al evaluated effects of low dose bupivacaine in caesarean delivery and surmised that though low dose spinal produced less maternal side effects it could compromise anaesthetic efficacy[10].Pain during caesarean section could lead to a dissatisfied mother and possible medico legal litigation.

Use of intrathecal opioids opened new horizons in pain management. Intrathecal opiates engages an endogenous system comprising of opiate receptors and opiate like substances that function as neurotransmitters and neuromodulators. The addition of opioids may allow the reduction of local anesthetic dose with equivalent success rate and fewer side effects. This is because intrathecal opioids act synergistically and intensify sensory blockade without increasing sympathetic and motor block. Abboud reported use of intrathecal morphine for post caesarean pain, but its slower onset of action decreases its utility for enhancement of intraoperative analgesia[11]. Fentanyl, a short acting synthetic opioid is lipophilic, so has more rapid onset of action thereby making it preferable for intraoperative analgesia.Belzarena etal surmised that most effects of fentanyl occur in the intraoperative period thus enchancing intraoperative analgesia while allowing a lower dose of local anaesthetic[12].Choi etal commented that while 12 mg Bupivacaine was the optimal dose of hyperbaric bupivacaine, addition of 10µg fentanyl reduced the dose to 8mg which was sufficient for surgical anaesthesia[13].

So we hypothesized that combining intrathecal fentanyl with the optimal hemodynamic dose of 7.5 mg bupivacaine would provide good intraoperative surgical conditions and patient comfort with preservation of maternal hemodynamics as compared to the conventional dose of 12.5mg of bupivacaine.

MATERIALS AND METHODS:

This prospective randomised double blind controlled study was performed in a single tertiary care hospital on 100 pregnant patients scheduled for elective Caesarean section. The study protocol was approved by the hospital ethics committee and written informed consent was taken from all the patients.

Patients included for the study belonged to American society of Anaesthesiologist (ASA) grading I and II with uncomplicated pregnancy coming for elective Caesarean section .Patients in acute foetal distress, with maternal complications like pregnancy induced hypertension, any contraindications to regional anaesthesia or patients who refused regional anaesthesia were excluded from the study.

Patients were randomly allocated to control (C) or fentanyl groups(F) using a computer generated random number table and sealed envelope technique .The intrathecal solutions were prepared prior to performing the spinal injection under strict aseptic technique by an anaesthetist who had no further involvement with the patient. The solution was prepared using a 3 ml syringe with both groups having a volume of 2.5ml. Thus the anaesthetist injecting the drug and monitoring the patient was unaware of the solution administered .All patients received 2.5 ml of drug. The control group C received 2.5 ml (12.5 mg)of Heavy 0.5 % Bupivacaine .The Fentanyl group F received 25 ug (0.5 ml) fentanyl plus 1.5 ml (7.5 mg) heavy bupivacaine plus 0.5 ml 0.9% Normal saline to make a total volume of 2.5 ml.

All patients were premeditated with ranitidine 150 mg per oral and metoclopramide 10 mg per oral, one hour prior to surgery .In the operating room, standard monitoring such as electrocardiography, pulse oximetry and noninvasive blood pressure were attached and baseline values taken.Intravenous access was secured and 15 ml /kg Lactated ringers was transfused. Subarachnoid block was performed in lateral position in either L3/4 or L4/5 interspace using 25 or 27 G Quincke needle.

On completion of spinal injection, patient was placed in supine position with 15 ° Right lateral tilt. Pinprick testing every 2 minutes

was used to establish time to peak level of sensory block. Surgical incision was allowed when sensory block to T6 was achieved .Motor blockade was assessed by the Bromage scale : 0- No paralysis ,1- inability to raise extended leg , 2- inability to flex knee , 3- inability to flex ankle (complete motor block)[14].Time to complete motor blockade was noted.

Quality of surgical conditions offered was judged on a 3 point ordinal Comfort scale [12].

1. Poor - need conversion to GA
2. Good - Minimal pain relieved by small dose of intravenous fentanyl
3. Excellent - No complaints from patient/surgeon at any time of surgery

Heart rate and Spo2 were monitored continuously while Blood pressure was monitored every 2nd minute for 10 minutes, followed by 5 minute intervals till end of surgery .Hypotension was defined as decrease in systolic blood pressure by 20 % of the baseline or systolic blood pressure of < 90 mmHg .Each hypotensive episode was treated with 6 mg bolus of Ephedrine .In addition to the loading, the patient received additional 500-800 ml of Lactated Ringer's till the remainder of the surgery.

All episodes of nausea, vomiting , shivering and pruritus were judged on a 4 point ordinal scale,0-no symptoms 1- mild symptoms, not requesting treatment.2- moderate symptoms, treatment given.3- symptoms persist despite treatment .Nausea was treated with Ondansetron 4mg iv, Shivering with Tramadol 25mg iv and pruritus with Chlorpheniramine 12.5mg iv.

Sedation was assessed by a 4 point scale: 1-awake and anxious, 2- awake and calm, 3- sleepy and easily arousable, 4- sleepy, difficult to arouse. Any request for sedation by patient noted.Respiratory rate was monitored and <10/min was noted as depression.

After delivery of the neonate and clamping of the umbilical cord, Syntocinon 10 mg IV was given. APGAR scores at 1 and 5 mins after delivery was noted. All patients received Diclofenac 100 mg suppository at end of surgery. Urinary catheter was left in situ for 24 hours. Total duration of surgery, spinal to incision and spinal to delivery time were noted.

Postoperatively hourly vitals, time to sensory regression to L1 and motor regression to Bromage 0 were noted. Pain was evaluated using a standard 10 cm Visual Analogue Scale. Duration of Total analgesia time i.e. time from subarachnoid injection to 1st pain (VAS >0) and Effective analgesia i.e. time from subarachnoid injection to 1st dose of rescue analgesia (VAS >4) was noted.

Sample size determination and statistical analysis:
Sample size was calculated by using the formula:

$$n = \left(\frac{Z_{1-\alpha/2}}{\varepsilon}\right)^2$$

where,
n is the required sample size
Z = 1.96 at 0.05 level of significance
is the specified relative precision (i.e. 24%)

The required minimum sample size was calculated as 47 in each group and rounded off to 50 per group.The data was collected and entered in Microsoft Excel 2010. Different statistical analysis was performed using SPSS software version 22. The one-sample Kolmogorov –Smirnov Test was employed to determine whether the datasets followed normal distribution or not.

Descriptive statistics like mean and standard deviation were calculated for quantitative variables. Frequency along with percentage was calculated for qualitative /categorical variables. The given data set followed normal distribution. So, we applied parametric test for comparing the mean in both the groups of study. Independent sample t-test/Unpaired t-test was used to compare the mean with quantitative variables like SBP, DBP, RR etc. in both the groups .A p-value of less than 0.05 was considered significant.

RESULTS:
Two patients ,one in each group were converted to general anaesthesia. One patient in the control group did not achieve adequate level 10 minutes after the injection, due to lack of free flow in 27 gauge needle and one patient in the fentanyl group developed atonic PPH due to previously undetected uterine fibroid. Results are for 49 cases in each group.

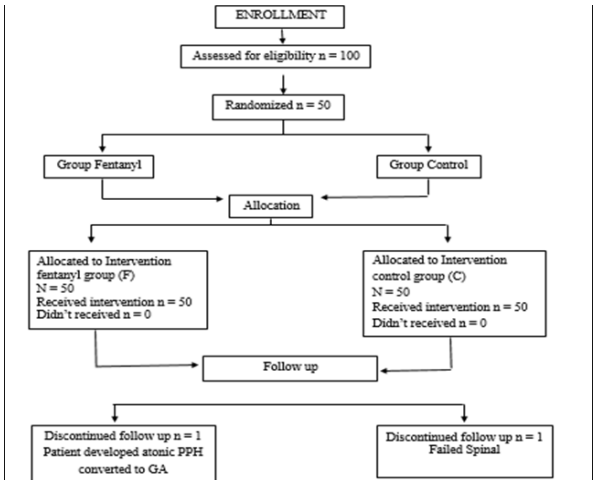
Demographic characteristics were similar in both groups (Table 1) .Though onset of sensory and motor blockade was slower in the fentanyl group (Table 2), the spinal to delivery time was not significantly different in both groups, indicating that this difference was not clinically relevant.

95.97% of patients in the fentanyl group had excellent surgical anaesthesia compared to 83.7% in the control group. 7 patients in group C and 2 patients in group F required a small intravenous dose of fentanyl during traction and exteriorisation of uterus.Patients were sleepy but easily arousable in the treated group while 20.4% patients in the control group needed sedation to allay anxiety.

Systolic and diastolic pressure were higher in group F than group C while the mean heart rate was lower in group fentanyl at all time periods .The number of hypotensive readings needing treatment were higher in group C(46.9%) compared to group F(18.4%).Also total requirement of ephedrine was increased in group C (p-0.019) . No patient in the treatment group required antiemetics as compared to 14.3% in the control group. Though 16.3% of patients in the fentanyl group complained of pruritus, it was generally mild and self-limiting with only 2% of patients requiring treatment with antipruritic. Regression of sensory and motor block took longer in the control group compared to the fentanyl group (Table 2), yet the onset of postoperative pain was delayed in the fentanyl group. (5.4 +/- 1.8 hrs in study vs 3.6+/- 1.2 hrs in the control group, p-0.001).

Neonatal condition was similar in both groups with Apgar scores above 7 at 1 minute and above 8 at 5 minutes.

Consort Diagram:



DISCUSSION:
One of the concerns with reducing the dose of local anaesthetic for subarachnoid block is that there could be inadequate intraoperative anaesthesia. This could lead to possible conversion to General Anesthesia with its associated risks and also mar the overall anaesthetic experience for the patient. In a review on low dose spinal for Caesarean delivery, Roofthooft and Van de Velde concluded that though spinal bupivacaine between 5 and 7 mg are sufficient to provide effective anaesthesia; complete motor block is seldom achieved, and adequate anaesthesia is limited in time [15].Vercauteren et al. and Choi et al. found excellent anaesthetic conditions with bupivacaine between 6 and 7 mg combined with opioids , but they had used the CSE technique and could supplement with epidural top ups if necessary [16-17]. Even with high doses of hyperbaric bupivacaine, incomplete analgesia has been reported .Shende etal reported 33% incidence of visceral pain with 12.5 mg bupivacaine[18].In a study by Belzarena etal, 13% patients reported pain despite 15 mg intrathecal bupivacaine[12].So the ideal anaesthetic dose for a simple subarachnoid block still remains elusive .The aim of this study was to evaluate the anaesthetic efficacy of 7.5 mg bupivacaine with 25 ug fentanyl for caesarean delivery.

Hunt etal reported a more rapid onset of spinal block when subarachnoid fentanyl was added to bupivacaine for caesarean delivery[19]. Subsequent studies by Ngiam etal, Dahlgren etal did not demonstrate this enhancement while Bogra etal reported slower onset in fentanyl group [20-22]. In our study, both groups attained a T4 level within 10 minutes of intrathecal injection showing no significant difference.

In our study we found that fewer patients in the low dose group reported intraoperative discomfort as compared to the traditional dose .Good operating conditions and better comfort scores were obtained in 96 % of low dose group as compared to 84% in traditional dose group collaborating the "bupivacaine sparing effect" of intrathecal fentanyl.These results were similar to those obtained by Ngiam et al and Mebzaa etal who reported no intraoperative pain in patients who received low dose bupivacaine with fentanyl[20,23].

Sedation can be considered an advantageous side effect, since it allows a calm intraoperative course. None of the patients in the fentanyl group reported intraoperative anxiety vis a vis 20.4 % patients in the control group who needed sedatives further adding to the intraoperative comfort .Further, the sedation did not produce profound drowsiness.

One of the major side effects of spinal anaesthesia in parturients is frequent hypotension .This hypotension is caused by decrease in symphathetic efferent activity and is related to the dose of bupivacaine. Multiple studies have demonstrated better intraoperative hemodynamics with low dose bupivacaine[16,18,24-26]. Ben David etal opined that due to synergistic action of opioid with local anaesthetics, it may be possible to achieve spinal anesthesia with less hypotension by combining low dose local anaesthetic with fentanyl[24].Our study showed significant decrease in the incidence of hypotension from 46.9% in the control to 18.9 % in the fentanyl group highlighting that the combination maintained cardiac stability with reduced need for vasopressors.

Intraoperative nausea and vomiting adds to the perioperative discomfort of the patients and is commonly noted in obstetric patients posted for spinal anaesthesia.It is multifactorial;opioids, hypotension, peritoneal traction and exterioration of uterus are all commonly implicated[3].In our study only the control group exhibited nausea (14.3%).The absence of nausea in the fentanyl group seems suprising since nausea is generally considered a side effect of opioids. But other studies have also shown similar results[20-25].Ngan Kee etal reported decreased incidence of nausea vomiting in patients whose systolic blood pressure was maintained at baselinewhich correlated with our findings [24].

Pruritus is a troublesome side effect associated with subarachnoid opioid administration .Although we observed a significant number of cases (16.3%), majority were self-limiting and only one patient requested treatment, which were comparable to results reported to results obtained by Shende etal[17].

Though urinary retention has been reported with intrathecal opioids, we were unable to evaluate this since all our patients were catheterized for 24 hours.

On analyzing the regression of sensory and motor blockade, we found that a significant number of patients recovered early from blockade in the fentanyl group. Though the recovery from spinal block was quick, the reporting of pain and requirement of opioids in the early postoperative period was delayed in the fentanyl group by 51/2 hours compared to 31/2 hours in the control. This facilitates early mobilization of the mother , allowing for faster bonding with the baby and greater maternal satisfaction . This finding of delayed onset of pain despite early block regression in the immediate postoperative period is similar to observations made by Choi etal, Sk Ngiam, Shende et al and Belzarena et al[12,13,17,19].

Intrathecal Fentanyl and bupivacaine for caesarean delivery have been shown to have an excellent safety record when neonatal Apgar scores, umbilical blood gases and neuro behavioral assessment were made. The present study supports the established safety of adding fentanyl to bupivacaine in finding no significant differences in Apgar scores of neonates in both groups[27].

CONCLUSION:

The principal findings of our study was that the combination of 25ug Fentanyl with 7.5mg Bupivacaine provided good intraoperative conditions for caesarean section with significantly less hypotension and nausea than 12.5 mg bupivacaine . It was also associated with delayed onset of postoperative pain despite early sensory and motor regression.

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Table: 1 Demographic characteristics

	Control	Fentanyl	P value
Age (years)	27.2±4.3	28.2±4.3	0.234
BMI	26.5±4.8	27.7±4.2	0.104
Gravida (n)	2.1±1.2	1.7±0.9	0.238

All values are in Mean ± 1 SD

Table : 2 Characteristics of sensory, motor block and postoperative analgesia

	Control Group (N= 49) Mean ± Std	Fentanyl Group (N=49) Mean ± Std
Time to sensory level T4(min)	4.14±0.88	4.132±0.75
Time to onset of motor block(min)	4.32±1.08	5.14±1.59
Spinal to Delivery time (min)	9.35±2.87	9.37±3.06
Total surgery time (min)	54±9.62	55.2±9.5
Effective Analgesia time (hrs)	3.6±1.2	5.4±1.8
Complete Analgesia time(hrs)	2.7±0.7	4.5±1.7

All values are in Mean±1SD

Table : 3 Quality of Anaesthesia and Sedation

Variable	Variable Category	Control Group (N= 49) Freq (%)	Fentanyl Group (N=49) Freq (%)
Comfort Score	**Excellent**	41 (83.7%)	47 (95.9%)
	Good	8 (16.3%)	2 (4.1%)
	Poor	0	0
Sedation	**Awake anxious**	10 (20.4%)	0
	Awake Calm	38 (77.6%)	42 (85.7%)
	Sleepy but arousable	1 (2.0%)	7 (14.3%)
	Sleepy non-arousable	0	0

All values are in Frequency (%)

Table : 4 Hemodynamics

Hemodynamic Variables	Groups	Mean ± Std	P-Value
Lowest Systolic BP recorded(mm Hg)	Control	90.6 ± 12.1	0.002
	Fentanyl	99.0 ± 13.9	
Lowest Diastolic BP recorded (mm Hg)	Control	43.3 ± 10.7	0.324
	Fentanyl	45.8 ± 13.6	
Total ephedrine used (mg)	Control	12.0 ± 4.0	0.005
	Fentanyl	8.0 ± 4.2	
Number of patients with hypotensive episodes (n)		Freq (%)	
	Control	23 (46.9%)	
	Fentanyl	9 (18.4%)	

All values are in Mean±1SD

Table : 5 Side effects

Variable		Control Group (N= 49) Freq (%)	Fentanyl Group (N=49) Freq (%)
Shivering	**no symptoms**	39 (79.6%)	41 (83.7%)
	mild, no treatment	1 (2.0%)	4 (8.2%)
	moderate, treatment given	9 (18.4%)	4 (8.2%)
Pruritus	**no symptoms**	48 (100%)	41 (83.7%)
	mild, no treatment	0	7 (14.3%)

	moderate, treatment given	0	1 (2%)
Nausea vomiting	**no**	42 (85.7%)	49 (100%)
	mild , no treatment	0 (0%)	0 (0%)
	moderate , treatment given	7 (14.3%)	0 (0%)
	symptoms persist despite treatment	0 (0%)	0 (0%)

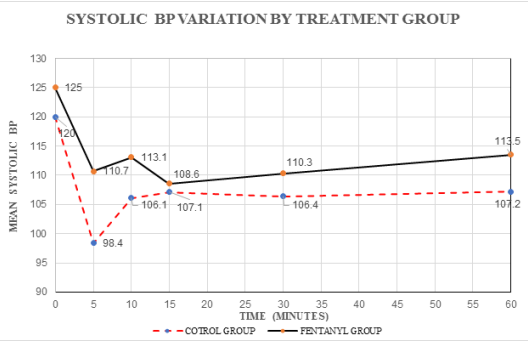

Figure 1:Systolic Blood pressure variation

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