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Comparison of Intrathecal Fentanyl and Midazolam as an Adjuvants to Hyperbaric Bupivacaine in Parturients undergoing Elective Cesarean Sections

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Abstract

Aims: The aim of this study was to evaluate and compare the efficacy and safety of fentanyl and midazolam given intrathecally with hyperbaric 0.5% bupivacaine in patients undergoing elective caesarean sections. *Materials and Methods*: A total of 180 women undergoing elective cesarean section were included in a prospective, double-blind, controlled trial. Patients were divided in three groups of 60 each and randomly assigned to receive spinal anesthesia with 2 mL 0.5% hyperbaric bupivacaine with 0.4ml of normal saline (Group C) , 2 mL 0.5% hyperbaric bupivacaine with 12.5 µg fentanyl (Group F) and 2 mL 0.5% hyperbaric bupivacaine with 2mg midazolam (Group M). Each group had a total volume of 2.4ml made by addition of normal saline. Onset and duration of sensory and motor block, duration of postoperative analgesia, hemodynamic effects and adverse effects due to study drugs were recorded and Statistical analysis was done. *Results:* Duration of analgesia was significantly prolonged in fentanyl group (254.83±14.84 mins.) compared to midazolam group(211.16±15.02 mins) and bupivacaine group (143.16±13.08 mins.) Hemodynamic parameters were comparable in the three groups. Side effects in all three groups were minimal. Apgar score did not differ in 3 groups. *Conclusion:* 12.5 µg fentanyl seems to be a better alternative to 2 mg midazolam as an adjuvant to bupivacaine in patients undergoing elective cesarean section as it prolongs the duration of analgesia without any deleterious effects on the mother and baby .

Keywords: Fentanyl; Midazolam; Cesarean Section; Spinal Anesthesia.

Introduction

Spinal anesthesia is commonly used for cesarean section.Spinal anesthesia avoids the risks of general anesthesia such as aspiration of gastric contents, difficulty with airway management, infant respiratory distress, and mothers awareness during operation [1,2]. The main limitations of spinal anaesthesia are its short duration of action and do not provide prolonged postoperative analgesia when it is performed only with local anaesthetics [3]. It has become a popular practice to add opioids to spinal solutions to enhance and prolong intra operative and postoperative analgesia [4]. Fentanyl, a phenylpiperidine derivative, is asynthetic µ-opioid receptor agonist. It is preferred as an adjuvant in spinal anaesthesia because of its rapid onset and short duration of action of about 3-4 hrs with lesser incidence of respiratory depression. Fentanyl and bupivacaine co-administration has a synergistic inhibitory action on the A δ and C- fiber conduction causing improved perioperative analgesia [5].

The benzodiazepines are used primarily for anxiolysis, amnesia and sedation. Midazolam is a water soluble non-opiate benzodiazepine has been used for potentiating the analgesic effect of local anaesthetic induced neuro-axial blockade as it is potent short acting drug. Intrathecal midazolam reduces excitatory GABA-mediated neurotransmission

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in inter neurons, leading to a decrease in the excitability of spinal dorsal horn neurons. Its antinociceptive effect is mediated via spinal δ opiate receptors [6].

In this study we have compared intrathecal fentanyl with midazolam in regard to their efficacy and safety as an adjuvant to intrathecal bupivacaine for spinal anaesthesia by comparing onset and duration of sensory and motor block, duration postoperative analgesia, hemodynamic effects and adverse effects in patients undergoing elective caesarian section.

Material and Methods

A prospective, randomized, double blind study was conducted in the Department Of Anaesthesiology, Acharya Vinoba Bhave Rural Hospital, Sawangi (M), Wardha from Aug 2013 to Dec 2016. The protocol was approved by the medical ethics committee. Informed consent was obtained from 180 healthy women based on American Society of Anesthesiologists classification system (ASA Physical status I and II) scheduled for elective term cesarean section under spinal anesthesia. Parturients with contraindication to spinal anesthesia, allergy to the local anesthetics, fentanyl or midazolam were excluded. Parturients were randomly divided by a random number table, to receive intrathecally one of the three medications according to the group they belongs.

Group C : (n=60) patients receiving 2 ml of hyperbaric inj. bupivacaine (0.5%) plus 0.4 ml of normal saline intrathecally.

Group F: (n=60) patients receiving 2 ml of hyperbaric inj. bupivacaine (0.5%) plus 12.5 μg (0.25 ml) of inj. fentanyl intrathecally.

Group M: (n=60) patients receiving 2 ml of hyperbaric inj. bupivacaine (0.5%) plus 2 mg(0.4ml) of inj. midazolam intrathecally.

Sedatives and hypnotics were avoided in premedication, as well as intraoperatively. Patients were preloaded with Ringer Lactate (RL) 20 ml/ kg. Pre-operative parameters like pulse rate, oxygen saturation and blood pressure were recorded. Spinal anaesthesia was given with 25G Quincke needle in left lateral position with aseptic precautions. Depending upon the groups, respective agents were injected intrathecally. Each group had a total volume of 2.4ml made by addition of normal saline. Both the patient and anaesthesiologist were blinded to the study solutions. After injection of the study solution, the patients were turned to the supine position with a 15^0 wedge under the right hip for left uterine displacement. Oxygen (3 L/min) [1] was administered via facemask. Cardio respiratory parameters were monitored continuously and recordings were made every 5 minute till the end of surgery. Postoperatively 30 minutes interval up to 6 hour in recovery room. Intraoperatively and postoperatively incidence of bradycardia (heart rate<50 beats per minute) was treated with 0.6 mg iv injection atropine. Hypotension, defined as a decrease of systolic blood pressure by more than 30% from baseline or a fall below 90 mmHg, was treated with increasing the rate of intravenous fluid administration, and by inj. mephentermine 3 to 6 mg iv.

The sensory block level was assessed by a pin prick test. Onset time was defined from the time of injection of drugs into the intrathecal space to the peak of sensory block and the duration of sensory block was defined from peak of sensory block up to 4 sensory level regressions. The motor blockade was assessed by Bromage scale [7] (0-No motor block; 1 -Inability to raise extended leg, able to move knees and feet; 2- Inability to raise extended leg and move knee, able to move feet; 3-Complete motor block of limb). Onset of motor block was defined as time taken from the completion of injection of study drug till patient attains Bromage Grade 3 and duration of motor blockade was defined as the time taken from injection of drug till the patient attains Bromage Grade 1. After the end of sensory block, pain level was measured with respect to Visual Analogue Scale (VAS) [8] (0=no pain, 10=the most severe pain the individual has suffered). If the postoperative VAS was higher than 4, it was treated by inj.diclofenac 75 mg i.m. Analgesia duration was defined as the interval between injection of intrathecal drug and the time when inj. diclofenac was injected.

Ten IU of inj oxytocin was given i.v. after delivery of the baby and clamping of the umbilical cord. Apgar score of all the babies at 1 and 5 minutes were recorded. The details of any other adverse events in mother due to study drugs such as hypotension, sedation, shivering, pruritus, nausea-vomiting and respiratory depression were recorded. Statistical analysis was done by using descriptive and inferential statistics using chi square test, one way ANOVA and Multiple Comparison Tukey Test and software used in the analysis were SPSS 17.0 version, Graph Pad Prism 6.0 version and EPI-INFO 6.0 version and $p<0.05$ is considered as level of significance.

Observations and Results

Table 1: Demographic Data

	Group C	Group F	Group M	P value
Age (Years)	24.13±3.09	24.56±2.44	24.51±03.27	>0.05, NS
Height (cm)	157.06±2.88	154.40±3.36	155.23±3.68	>0.05, NS
Weight (Kg)	61.88±5.98	59.40±5.18	60.38±05.91	>0.05, NS
ASA Status I/II (n=60)	28/32	29/31	27/33	>0.05, NS
Primi/Multi Gravida (n=60)	32/28	34/26	35/25	>0.05, NS
Duration of Surgery (min)	47.00±6.07	48.4±5.56	50.3±3.42	>0.05, NS

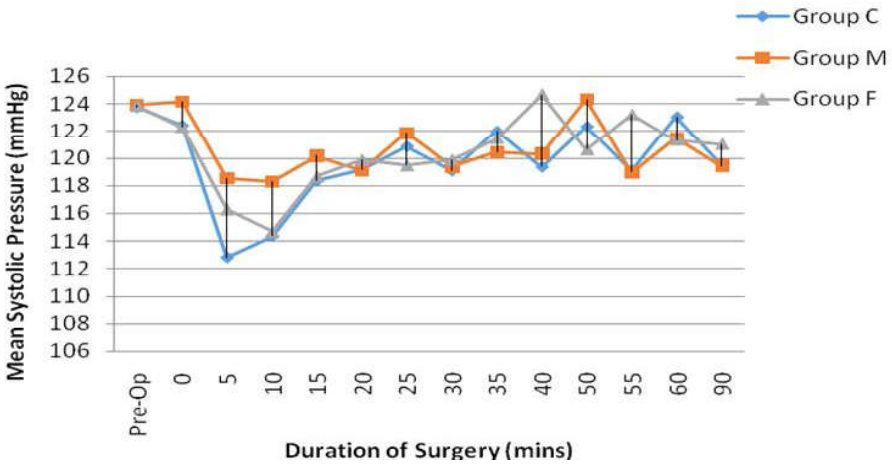
Table 2: Block characteristics and postoperative analgesia

	Group C	Group F	Group M	P value
Onset of sensory block(mins)	5.59±0.53	5.50±0.54	5.40±0.46	0.797,NS
Onset of motor block(mins)	4.19±0.39	4.40±0.64	4.20±0.47	0.653,NS
Duration of sensory block (mins)	108.80±12.82	166.10±12.75*,#	148.25±11.15*	0.0001,S
Duration of motor block (mins)	98.56±10.12	140.20±10.45*	130.35±09.51*	0.0001,S
Duration of Analgesia(mins)	143.16±13.08	254.83±14.84*,#	211.16±15.02*	0.0001,S

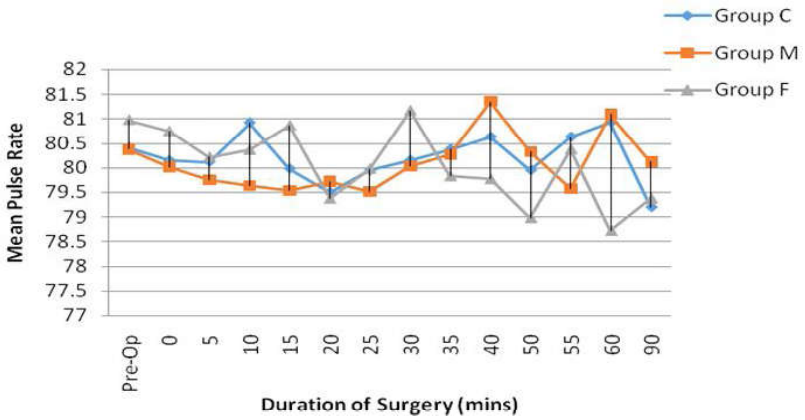
*p <0.05- compared to group C, # p<0.05- compared to group M
p by using using one-way ANOVA. Post-hoc analysis for inter group comparison.

Table 3: Mean first and fifth minuets Apgar score in the three groups

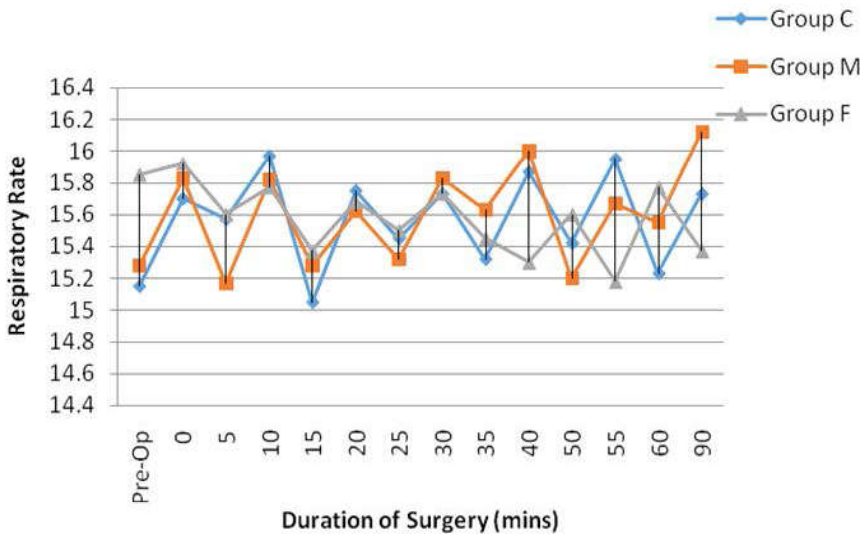
Apgar score	Group C	Group F	Group M	F-value
1 min	8.08±0.27	8.03±0.18	8.06±0.25	0.50 p=0.68,NS
5 min	9.93±0.25	9.91±0.27	9.93±0.25	0.20 p=0.89,NS



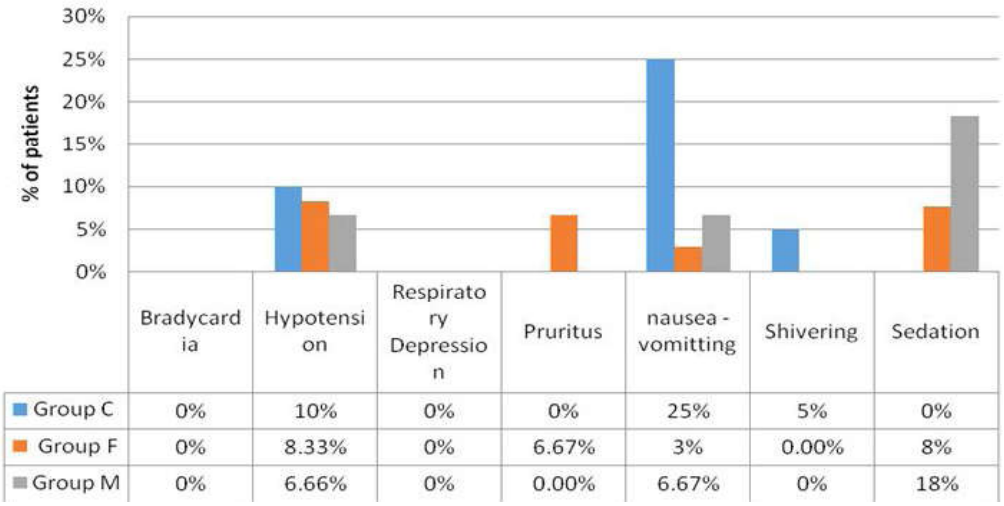
Graph 1: Variations in Systolic Blood Pressure in Group C, Group F and Group M.



Graph 2: Variations in Mean Pulse Rate in Group C, Group F and Group M.



Graph 3: Variations in Respiratory Rate in Group C, Group F and Group M.



	Bradycardia	Hypotension	Respiratory Depression	Pruritus	nausea - vomitting	Shivering	Sedation
Group C	0%	10%	0%	0%	25%	5%	0%
Group F	0%	8.33%	0%	6.67%	3%	0.00%	8%
Group M	0%	6.66%	0%	0.00%	6.67%	0%	18%

Graph 4: Comparison of Adverse Effects in Group C, Group F and Group M.

Discussion

Various doses of fentanyl ranging from 6.25 μg upto 60 μg have been studied for intrathecal administration to improve the quality of block and postoperative analgesia. The dose of fentanyl used in our study was 12.5 μg as this dose was recommended by previous studies [9,10]. Intrathecal midazolam used in human and the doses of 1 mg, 2 mg have been described to provide pain relief without any side effects [11]. In the present study, the effects of addition of fentanyl and midazolam to bupivacaine was observed to find out the best additive among them by weighing effects versus side effects.

A total of 180 patients were enrolled, 60 in each group. The three groups were comparable with respect to age, weight, height, ASA grading and gravid status. The duration of surgery was also similar (Table 1).

Our study demonstrated prolonged duration of sensory as well as motor blockade after subarachnoid injection of midazolam or fentanyl to hyperbaric 0.5% bupivacaine in patients undergoing cesarean section. Duration of sensory block in fentanyl group was 166.10±12.75 mins. this was in accordance with the study by Biswas et al [9] used fentanyl as an adjuvant and found that duration of sensory block was 151±7.33min. Duration of sensory block in midazolam group was

148.25±11.15mins. Boules & Botros [12] with intrathecal midazolam (1 mg) noticed the duration of sensory block was 115.3±6.60 min. Many researchers reported increase in duration of motor block after addition of intrathecal fentanyl or midazolam [11,13]. In our study we noticed that fentanyl increases the duration of sensory blockade significantly when compared to midazolam ($p<0.05$) (Table 2).

Duration of postoperative analgesia was significantly prolonged in fentanyl and midazolam group as compared to plain bupivacaine group. When fentanyl and midazolam groups were compared statistically significant difference was noticed. Duration of analgesia with miadazolam was 211.16±15.02 mins. as in line with earlier study by Sen et al [14] 2 mg intrathecal midazolam produced analgesia that lasted for 196.5±3.3 minutes.

Immediate postoperative analgesia was better with fentanyl as observed by a significant delay in the first request for analgesia (254.83±14.84 mins) and lower VAS score in this group. 12.5 μg intrathecal fentanyl produced analgesia that lasted for 248±11 minutes in a study by Biswas et al [9] and 214±20 mins in a study by Islam et al [15], these results supports findings of our study. Fentanyl significantly increases the duration of postoperative analgesia when compared with midazolam (Table 2).

Comparable Apgar score in all the groups at 1and 5 minutes signifies that Fentanyl and Midazolam have no deleterious effect on the neonates and mothers (Table 3). Further, there is very little information, and no evidence that any anaesthetic agent given in a single dose, is secreted in clinically significant amounts in breast milk. (Rolbin & Morgan) [16].

Hypotension and bradycardia are common side effects of spinal anesthesia, and they represent normal physiologic responses to anesthetized spinal sympathetic nerve fibers. In this study preoperative hemodynamic variables (systolic pressure, pulse rate and respiratory rate) were similar in the three groups. In all groups, Systolic BP decreased 5-15 min after spinal anesthesia, with no difference between them .

The incidence of hypotension were comparable in all the groups ($p=0.59$). Systolic blood pressure were comparable through-out the operation. Total intra-operative consumption of mephentermine was similar all the groups (Group C- 9.0±2.26 mg, Group M- 10±0.5 mg and Group F- 8.66±2.34 mg). None of the patients required vasopressors postoperatively. There were no episodes of bradycardia and none of the patients needed inj. atropine. No patient in our study had respiratory depression (Graph 1,2 and 3).

Visceral pain is a common problem in the casarean section under spinal anesthesia, it is experienced when the uterus is exteriorized and peritoneum is stretched. It is often associated with autonomic activity causing nausea, vomiting. Significant less incidences of nausea and vomiting was noticed in midazolam and fentanyl groups than plain bupivacaine group.

Rudra & Rudra [10] reported similar findings. Pruritus in 4(6.67%) was seen only in fentanyl group. 3(5%) patients had shivering in control group as compared to none in group M & F. 11(18.33%) patients in midazolam group and 5(8.33%) patients in fentanyl group had sedation (Graph 4). None of the patient in the study groups demonstrated any signs of neurological deficit which was at par with the findings of Bhure et al [17].

Conclusion

The present study demonstrated that addition of fentanyl and midazolam to bupivacaine significantly improves the duration of sensory and motor block with relative hemodynamic stability and prolongs the duration of analgesia in comparison to bupivacaine alone . From findings of our study, 12.5 μg fentanyl seems to be a better alternative to 2 mg midazolam as an adjuvant to bupivacaine. It is effective and safe for improving the duration of postoperative analgesia without any deleterious effects on the mother and baby.

Limitations

Since pain is a subjective phenomenon associated with a wide variability of responses among the individuals, it is difficult to standardize the variables. What may be tolerable for one person may be intolerable for another person. Urinary retention, which is a known complication of neuraxial opioids could not be assessed, all patients were catheterized preoperatively with Foley's catheter and the catheter was kept for 24 hrs postoperatively. Neuro-behavioral examination, neurologic and adaptive capacity score, umbilical blood gas analysis and acid base evaluation of neonatal outcome was not done.

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