Original research article

COMPARATIVE EVALUATION OF INTRATHECAL FENTANYL AND MIDAZOLAM AS AN ADJUVANT WITH HYPERBARIC BUPIVACAINE IN CAESAREAN SECTION

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Abstract

Background The study was done to compare and evaluate the effects of intrathecal fentanyl and midazolam as an adjuvant with hyperbaric bupivacaine.

Material and methods This study was conducted on 90 adult female patients aged 18-35 years and ASA grade I/II undergoing elective or emergency caesarean section. The patients were randomly divided into three groups having 30 patients in each group.Group A received 1.5ml 0.5% Bupivacaine plus 0.5ml NS, Group B received 1.5ml 0.5% Bupivacaine with 0.5ml(25 mcg) Fentanyl, Group C received 1.5ml 0.5% Bupivacaine with 0.5ml (2.5 mg) Midazolam.

Results There was no significant difference in the demographic data and surgical characteristics in the three groups.Regression to sensory level S2 was significantly prolonged in Group B(257.87±11.95 min) and Group C(252.87±8.66min) as compared to Group A(151.80±8.0min). However, the duration of motor blockade was comparable between Group A, Group B and Group C (P value>0.05). Duration of complete and effective analgesia was significantly prolonged in the Group B and Group C as compared to Group A ($p<0.0001$).

ConclusionPresent study demonstrated that addition of fentanyl (25µg) and Midazolam (2.5 mg) to low dose bupivacaine (7.5 mg) intrathecally in patients undergoing caesarean section improves the quality of anaesthesia and post-operative analgesia with hemodynamic stability and without compromising neonatal outcome.

Key words: **INTRATHECAL FENTANYL, MIDAZOLAM ,HYPERBARIC BUPIVACAINE ,CAESAREAN SECTION**

INTRODUCTION

Spinal anaesthesia is the preferred technique for caesarean section, being simple to perform, economical and produces rapid onset of anaesthesia and complete muscle relaxation. It carries high efficiency, involves less drug doses, minimal neonatal depression, awake mother and lesser incidences of aspiration pneumonitis. However it has some disadvantages including higher incidence of hypotension and a definite duration of anaesthesia. (1, 2) Bupivacaine is the most popular local anesthetic for subarachnoid blockade in parturients undergoing caesarean section. However, intrathecal bupivacaine alone may be insufficient to provide prolonged post operative analgesia, even with high sensory block. For that intrathecal opioids have been recommended for parturients undergoing caesarean section under spinal anaesthesia.(3) Various intrathecal adjuvants have been tried for post operative analgesia in caesarean section such as opioids, ketamine, clonidine, midazolam and neostigmine. Adding adjunct (opioid or non opioid) allows reduction in dose of bupivacaine and provides post operative analgesia with cardiovascular stability. (4) Fentanyl, a lipophilic opioid, after intrathecal administration it diffuses into epidural space and subsequently into the plasma, suggesting that it acts not only through spinal opioid receptors but also systemically. Fentanyl added to low dose bupivacaine intrathecally provides better surgical anaesthesia and increased reliability of block than intrathecal bupivacaine alone.(5) In the quest for a newer, safer local anaesthetic additive, researchers have found that benzodiazepines lead to segmental block of nociception without any adverse effect on cardiovascular and respiratory system. There are benzodiazepine receptors throughout the nervous system, including the spinal cord, which show connections with gamma-aminobutyric acid (GABA) receptors. Intrathecal midazolam by binding to benzodiazepine receptors in the spinal cord increases the threshold for pain. (6, 7) So far the literature reviewed several clinical studies have been conducted on intrathecal use of fentanyl and midazolam in various lower limb and abdominal surgery, but studies with intrathecal use of midazolam in caesarean section were less found. We conducted this study to compare the intrathecal fentanyl and midazolam as an adjuvant to low dose hyperbaric bupivacaine for quality of anesthesia and post operative analgesia in patients undergoing caesarean section.

MATERIAL AND METHODS

After taking hospital ethical committee approval, the present study was conducted on 90 adult female patients aged 18-35 years and ASA grade I/II undergoing elective or emergency caesarean section, after taking written informed consent. After doing a thorough preoperative evaluation, patientswere explained about the procedure of lumbar punctureand their participation in the study. They were also explained about visual analog scale (VAS) scale, which they would be shown in the postoperative period. The patients were randomly divided into three groups. Group A Inj.Bupivacaine 0.5% (heavy) 1.5 ml (7.5 mg) +0.5 ml Normal saline (NS). Group B Inj. Bupivacaine 0.5% (heavy) 1.5 ml (7.5mg)+ Inj. Fentanyl 0.5ml (25µg).Group C Inj. Bupivacaine 0.5% (heavy) 1.5 ml(7.5mg) + Inj Midazolam 0.5 ml (2.5 mg). In the operation theatre, pulse oximeter, NIBP monitor, and ECG were attached and baseline readings were recorded. IV line was taken and all patients were preloaded with Inj. Ringer Lactate 10ml/kg. Patients were premedicated with inj. ondansetron 4mg IV. Under all aseptic precautions, with patient in left lateral/sitting positionlumber puncture was performed through midline approach with 25gauge Quinke's spinal needle in suitable intervertebral space (L3-4/ L4-5).After confirming free flow of clear CSF selected drug was injected.After completion of procedure, patient was immediately

turned to supine position. All patients received supplementation of oxygen (4 liters per minute by venti mask). The time to attain sensory level up to T10 and time to attain motor block up to Bromage grade-3 were recorded. Intraoperative pulse, BP, SpO2 and RR were monitored every 2 min before delivery then every 5 min till the end of surgery and every 30 min post operatively. Bradycardia was defined as pulse rate less than 60 beats/min and was treated with inj. Atropine 0.6 mg IV. Hypotension was defined as fall in blood pressure more than 20% of baseline value and was treated with i.v. fluids, manual uterine displacement to left and injection ephedrine 6 mg IV if required. Apgar scores were recorded at 1 min and 5 min after delivery of baby. Post operative pain was evaluated using a standard 10 cm linear visualanalogue scale with 0 corresponding to no pain and 10 to the worst possible pain. Pain was evaluated every hourly for 24 hrs post-operatively. Duration of analgesia (time from subarachnoid injection to first feeling of pain) was recorded. Time of recovery from the sensory block, as defined by regression of block up to S2 level, was recorded. Furthermore, time of recovery from motor block to Bromage scale-0 was also recorded.Patients were observed for 24 hours postoperatively for any neurological deficit. Intraoperative and postoperative adverse events such as hypotension,bradycardia, nausea, vomiting, shivering, respiratory depression, sedation and neurological deficit were monitored and documented. Complications like hypotension, bradycardia, respiratory depression(SpO2 <92%, RR<10/min), pruritus, nausea, vomiting, shivering were noted and treated accordingly. Statistical analysis was done by using unpaired t-test and chisquare test. Medcalc softweare - version 12.6.1.0. was used. Data were expressed as mean ± standard deviation or numbers and percentages. Analysis of data p valueless than 0.05 was considered as significant.

Results

Table 1 DEMOGAPHIC DATA (mean ± SD):

VARIABLES	GROUP A	GROUP B	GROUP C
Age (years)	24±3.6	25.2±3.6	25.6±4.8
Height(cm)	162.9±4.5	163.5±5.5	162.4±5.4
Weight(kg)	52.1±4.6	54.5±7.1	53.4±5.08
ASA I:II	19:11	19:11	21:9
Duration of surgery	60±9.06	58±9.99	60±9.06

Demographic data of all the three Groups were comparable.

TABLE-2: MEAN ONSET TIME OF SENSORY AND MOTOR BLOCKADE.

TIME	GROUP A (mean±SD)	GROUP B (mean±SD)	GROUP C (mean±SD)	p value
Time to T_{10} sensory level (sec)	86.47±5.92	83.50±7.78	86.30±6.99	A Vs B - 0.10 A Vs C - 0.91 B Vs C - 0.14
Time to modified Bromage grade 3(sec)	280.47±8.77	282.43±9.45	281.13±8.39	A Vs B - 0.40 A Vs C - 0.76 B Vs C - 0.57

Time of sensory onset was comparable among the three groups. (p value >0.05) and time of motor onset was also comparable among the three groups (p value >0.05)

TABLE-3: DURATION OF SENSORY AND MOTOR BLOCKADE.

TIME	GROUP A (mean±SD)	GROUP B (mean±SD)	GROUP C (mean±SD)	p value
Sensory regression to S_2 from highest sensory level (min)	151.80±8.00	257.87±11.95	252.73±8.66	A Vs B<0.0001 A Vs C<0.0001 B Vs C - 0.06
Time for Bromage grade 0 (min)	148.40±5.94	146.07±10.85	145.73±8.66	A Vs B – 0.76 A Vs C – 0.86 B Vs C – 0.89

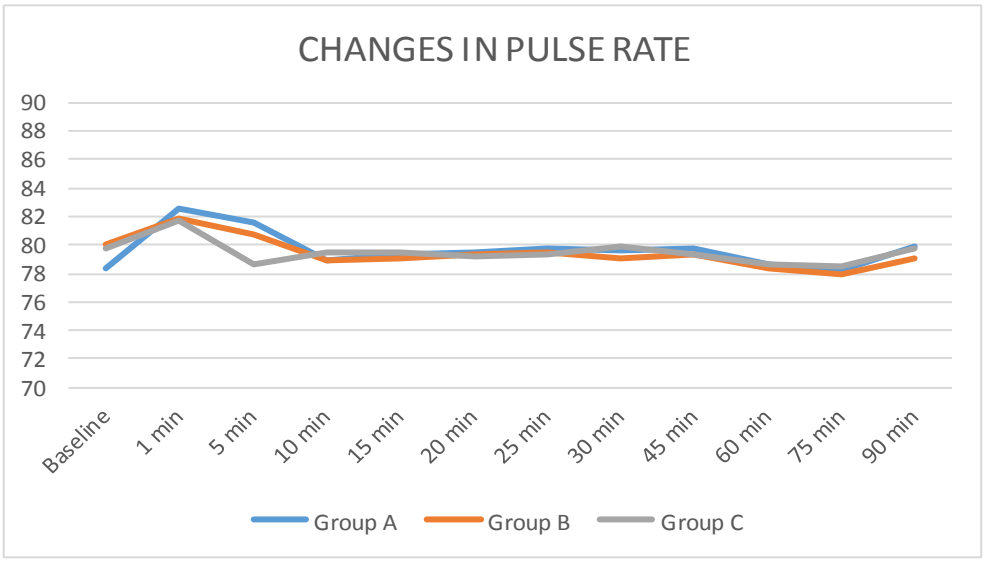
The regression of sensory blockade to S2 was significantly prolonged in Group B and Group C as compared to Group A (P value < 0.0001). However, the duration motor blockade to Bromage grade 0 was comparable between Group A, Group B and Group C (P value>0.05).

TABLE - 4: DURATION OF ANALGESIA.

PARAMETERS	GROUP A (mean±SD)	GROUP B (mean±SD)	GROUP C (mean±SD)	p value
Duration of complete analgesia (min)	119.20±8.91	244.13±9.23	243.80±8.24	A Vs B<0.0001 A Vs C<0.0001 B Vs C - 0.88
Duration of effective analgesia(min)	152.40±7.29	293.67±11.23	293.33±9.91	A Vs B<0.0001 A Vs C<0.001 B Vs C - 0.90

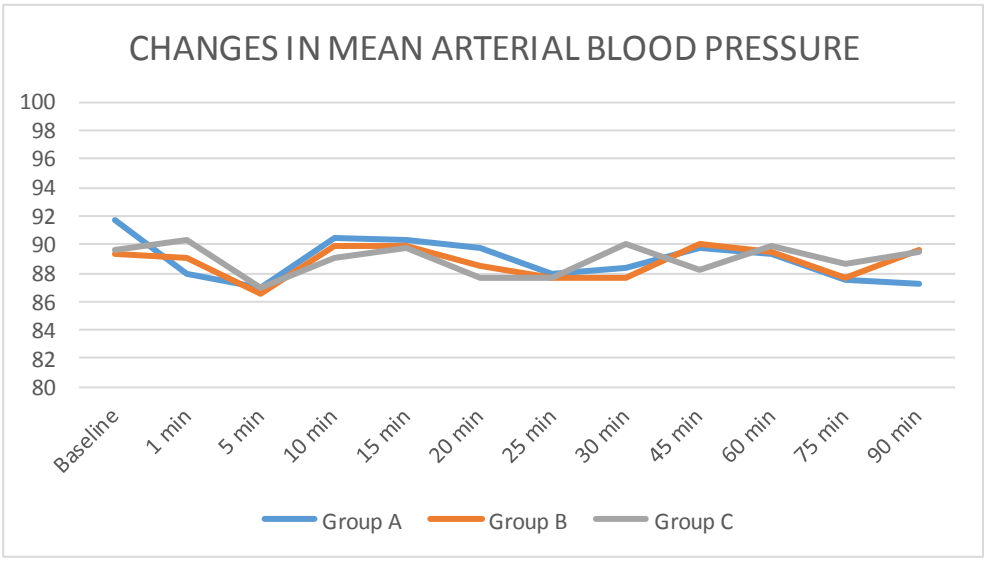
Duration of complete and effective analgesia was significantly prolonged in the Group B and Group C as compared to Group A (p<0.0001). However, there was no significant difference between Group B and Group C (p value >0.05).

Chart no 1: CHANGES IN PULSE RATE PER MINUTE.



As illustrated in the chart above, there was no statistically significant difference in pulse rate among all the three groups.

Chart no 2: CHANGES IN MEAN ARTERIAL BLOOD PRESSURE (mmHg).



Mean arterial pressures of all the three groups were comparable.

TABLE NO – 5: VAS AT FIRST RESCUE ANALGESIC.

	Group A (mean±SD)	Group B (mean±SD)	Group C (mean±SD)	p Value
VAS (1-10cm)	4.53±1.55	3.10±1.12	3.07±1.12	A Vs B -0.0001 A Vs B -0.0001 B Vs C -0.9

Visual analog scale in Group B and Group C were significantly lower than Group B.(P<0.0001)

Quality of VAS was better in Group B and Group C as compared to Group A.

- No complications such as hypotension, bradycardia, nausea and vomiting, pruritus, shivering in mother and respiratory depression, sedation, neurological deficit, in babies were observed in any of the patients among three groups
- There was no statistically significant difference in hemodynamics postoperatively among all the three groups.

DISCUSSION

Regional anesthesia is highly popular for cesarean deliveries because of the high morbidity and mortality associated with general anaesthesia. However, the main drawback of spinal anaesthesia, particularly in parturients, is hypotension caused by blockade of sympathetic output. Decreasing the dose of local anesthetic decreases the magnitude of hypotension but compromises upon the quality of anesthesia with limited duration of post operative analgesia.(6)

In 'augmentation strategies' wide variety of opioids and nonopioids are used as an adjunct to subarachnoid block to improve quality of block, quality of anesthesia and prolongation of analgesia in postoperative period.(4)

The present study was carried out in 90 adult female patients of ASA grade I and II undergoing lower segment caesarean section under spinal anesthesia. Demographic data regarding age, height, weight and duration of surgery were comparable in all the three groups.

In the present study, Sensory onset was comparable in Group A (86.47±5.92sec), Group B (83.50±7.78 sec) and Group C (86.30±6.99sec).

Onset of motor blockade was also comparable among Group A(280.47±8.77sec), Group B(282.43±9.45sec) and Group C (281.13±8.39sec). Manoj K. Sanwal et al and Dr B. N. Biswas et al had studied the intrathecal fentanyl and midazolam as an adjuvant to heavy bupivacaine in LSCS respectively and found that onset of sensory and motor block were not enhanced by adding adjuvants.(6,17)

Time of sensory regression to S2 was prolonged in Group B(257.87±11.95 min) and Group C(252.87±8.66min) as compared to Group A(151.80±8.0min). and this difference was statistically significant ($P<0.05$). As per DR B.N.Biswas et al study, the time for sensory regression to L1 was 151±7.33 min in fentanyl group. This findings differ with present study as our dose of fentanyl is higher than their study.

Duration of motor blockade to grade 0 was comparable in Group A (148.40±5.94min), Group B (146.07±10.85min) and Group C (145.73±8.66min) in our study. Our findings are consistant with study of Neerja Bharti et al.(10)

Few studies have reported prolongation of motor blockade after intrathecal midazolam.(18,25) But a meta-analysis aiming to evaluate the effectiveness and side-effects of intrathecal midazolam in the perioperative setting reported that intrathecal midazolam did not affect the duration of motor blockade.(26) Total time of motor blockade are not prolonged, which is beneficial to the patients for early mobilization in post operative period and also decreases the chances of DVT.(12)

In our study we found that, duration of complete analgesia in Group B

(244.13±9.23min) and Group C(243.80±8.24min) was significantly prolonged as compared to Group A(119.20±8.90min). Duration of effective analgesia was also prolonged significantly in Group B(293.67±11.23min) and Group C(293.33±9.91min) as compared to Group A(152.40±7.29min). Difference in duration of complete and effective analgesia was not clinically significant between Group B and Group C. our findings are consistant with the study of Dr. B. N. Biswas et al and Akannmu et al.(17,11)

A preclinical study has demonstrated the role of spinal benzodiazepine receptors in segmental nociceptive action of intrathecal midazolam.(27) This is said to be mediated via benzodiazepine/GABA-A receptor complex which are abundant in the lamina II of dorsal horn ganglia as well as release of endogenous opioid acting at spinal delta and kappa receptors.(28)

Quality of intraoperative anesthesia and post operative analgesia were better in patients Group B and Group C than Group A in present study. Visual analog scale at the time of first post-operative analgesic dose in Group B (3.10±1.12) and Group C(3.07±1.12) was significantly less than Group A(4.53±1.55) ($P<0.05$). This findings are similar to the study of Akanmu ON et al and P.R Dhumal et al. (11, 12)

Postoperative pain intensity is less in patients receiving intrathecal fentanyl and midazolam as adjuvant to bupivacaine. This is possibaly due to residual analgesic effect of the midazolam and fentanyl that became manifest after the sensory block due to the effect of the low dose intrathecal local anesthetic had been dissipated.(11)

This study revealed that either fentanyl or Midazolam intrathecally had no adverse impact on neonatal condition when assessed by Apgar Scoring. This findings are similar with the study of Dr.PallabRudra et al. (2)

SUMMARY AND CONCLUSION

Present study was conducted on 90 adult female patients aged 18-35 years and ASA grade I/II undergoing elective/emergency caesarean section under spinalanesthesia. Written informed consent was taken from each patient after proper preoperative evaluation.

Patients were randomly divided into three groups. Each group was having 30 patients.

Group A (Bupivacaine + NS): Inj. Hyperbaric Bupivacaine 0.5% 1.5 ml(7.5 mg) + inj. normal saline 0.5 ml .

Group B (Bupivacaine + Fentanyl): Inj. Hyperbaric Bupivacine 0.5% 1.5 ml (7.5mg) + Inj. Fentanyl 0.5ml (25µg).

Group C (Bupivacaine + Midazolam) : Inj. Hyperbaric Bupivacaine 0.5% 1.5 ml (7.5mg) + Inj Midazolam 0.5 ml(2.5 mg).

- Data were analysed with Medcalcsoftwere version-12.6.1.0.
- The age, sex, weight, height, duration of surgery and ASA grade were comparable in all the three groups.
- Hemodynamic changes were comparable in all the three groups.
- There was no significant change in RR and SPO2.
- Mean time of sensory and motor onset was comparable in all the three groups.

- Regression to sensory level S2 was significantly prolonged in Group B (257.87 ± 11.95 min) and Group C (252.87 ± 8.66min) as compared to Group A (151.80 ± 8.0min). There was no significant difference between Group B and Group C.
- Duration of motor blockade to Bromage score 0 was comparable among all the three groups.
- Duration of complete analgesia in Group B (244.13 ± 9.23min) and Group C (243.80 ± 8.24min) was significantly prolonged as compared to Group A (119.20±8.90min). There was no significant difference between Group B and Group C.
- Duration of effective analgesia was prolonged significantly in Group B (293.67 ± 11.23min) and Group C (293.33 ± 9.91min) as compared to Group A (152.40 ± 7.29min). Difference between Group B and Group C was not significant.
- Quality of anesthesia and quality of analgesia (postoperative VAS) were better in Group B and Group C as compared to Group A.

Present study demonstrated that addition of fentanyl (25µg) and Midazolam (2.5 mg) to low dose bupivacaine(7.5 mg) intrathecally in patients undergoing caesarean section improves the quality of anesthesia and post operative analgesia with hemodynamic stability and minimal side effects, without compromising neonatal outcome.

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Conflict of Interest : NIL