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Comparison of Efficacy of Midazolam and Fentanyl as Adjuvants to Intrathecal Bupivacaine in Patients Undergoing Elective Gynaecological Surgeries

Dr Anupama Gupta[1], *Dr Arun Mathur[2], Dr Shashipal Dabas[3]

[1]Associate Professor, Department of Anaesthesiology, SMS Medical College, Jaipur, India
[2]Associate Professor, Department of Anaesthesia, Pacific Medical College & Hospital, Udaipur, India
[3]Ex-Medical Officer, Municipal Corporation, New Delhi, India
Corresponding Author: *Dr Arun Mathur

Abstract: ***Background and Aims: Spinal anaesthesia is most commonly used for gynaecological surgeries, but it is often criticized due to its short action. Various adjuncts are being used to prolong the duration of analgesia. This study aims to compare analgesic efficacy of midazolam and fentanyl as an adjunct to intrathecal hyperbaric bupivacaine. We studied total duration of postoperative analgesia as primary outcome variable and thecharacteristics of the block, hemodynamic variable and adverse effects as secondary outcome variable. Material and Methods: The present prospective, randomized, double-blind study was undertaken on ninety American Society of Anaesthesiologists (ASA) I-II patients, 20–50 yrs. of age, undergoing elective lower abdominal gynaecological surgeries under spinal anaesthesia. Patients were randomized into three group of 30 each using chit in box method.In group B, patients received 15 mg hyperbaric bupivacaine 0.5% with 0.4 ml normal saline, group M, received 15 mg hyperbaric bupivacaine 0.5% with 2 mg (0.4 ml) midazolam and in group F, 15 mg hyperbaric bupivacaine 0.5% with 20 µg fentanyl (0.4ml) intrathecally. Results: Time to onset of sensory and motor block in all the three groups was comparable. However, duration of sensory block and postoperative analgesia was significantly prolonged in groups M and F in comparison to group B (P< 0.0001) and it was the longest in Group F. The duration of motor blockade was similar in all the three groups. Intra- and post-operative hemodynamic parameters, as well as side effects, were comparable. Conclusion: Addition of midazolam and fentanyl as adjuvants to intrathecal 0.5% bupivacaine prolongs postoperative pain relief without causing hemodynamic variations and adverse effects but fentanyl is superior as compared to midazolam.***

Keywords: Adjuvants, bupivacaine, fentanyl, intrathecal, midazolam

1. Introduction

Spinal anesthesia remains a well-established technique for patients undergoing lower abdominal surgeries. Bupivacaine is the most extensively used drug for spinal anaesthesia, however due to its short duration of action, various adjuvants are being used to provide long lasting pain relief as uncontrolled post-operative pain may produce a range of detrimental acute and chronic effects. Opioids like morphine and fentanyl are extensively used to potentiate analgesic effect of local anesthetics in neuraxial blockade, but adverse effects like pruritus, urinary retention, postoperative vomiting and respiratory depression limit the use of opioids.

Midazolam produces a synergistic effect on postoperative analgesia when administered intrathecally with bupivacaine. Previous reports have shown that administration of intrathecal midazolam with local anesthetics prolongs the duration of spinal anesthesia and produces longer postoperative analgesia after lower abdominal surgeries.[1, 2, 3, 4, 5]

Therefore, we designed this prospective randomized double-blind study to compare the analgesic efficacy of intrathecal midazolam with fentanyl as an adjunct to hyperbaric bupivacaine in patients undergoing lower abdominal surgeries under spinal anaesthesia. We also assessed quality of sensory-motor block and side effects.

2. Material & Methods

After approval by Institutional Ethics Committee, this prospective, randomized, double-blind, clinical study was conducted in a tertiary care centre. Ninety American Society of Anaesthesiologists (ASA) I-II patients, 20 – 50 yrs. of age, undergoing elective lower abdominal gynaecological surgeries under spinal anaesthesia. Patient's refusal for block, presence of bleeding disorders, local infection at the site of block, any history of allergy to study drugs were excluded from study. Patients in whom spinal anaesthesia failed were also excluded from the study.

All patients were explained about the procedure, advantages and risks of the procedure during the preoperative assessment done one day prior to surgery and then informed consent was obtained from the patient. Pain was assessed using a verbal numeric scale (VNS) from 0 to 10 (0 = no pain; 10 = maximum imaginable pain). The patients were randomized into three groups using chit box method.**Group B** – patients received 15 mg (3mL) hyperbaric bupivacaine 0.5% + 0.4 mL normal saline intrathecally.

Group M-patients received 15 mg (3mL) hyperbaric bupivacaine 0.5% + 2 mg (0.4 mL) midazolam, preservative free intrathecally.

Group F-patients received 15 mg (3mL) hyperbaric bupivacaine 0.5% + 20 µg fentanyl (0.4ml) intrathecally. After shifting the patient inside operation theatre, chits were opened by anaesthesiologist not involved in the study to prepare the drug solution according to randomization. The

observer who collected the peri-operative data as well as the patient was blinded to the drug solution administered.

After checking the fasting status, patients we shifted in operation theatre. Routine standard monitoring including pulse oximeter, non-invasive blood pressure and five lead electro-cardiogram was commenced and baseline parameters, i.e., heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), peripheral oxygen saturation (Spo2) were recorded. Intravenous access was established using 18G, intravenous cannula and preloading was done with 15ml/kg of inj. ringer's lactate solution.

Lumbar puncture was performed in the left lateral position using a 27-gauge Whitacre needle at L3-4 interspace using a midline approach. After free flow of cerebrospinal fluid, the premixed solution (3.4 mL) was injected over 10 seconds with the needle orifice directed cephalad according to the group assigned. Patient was then placed supine; a pillow was placed under the head and shoulder. Oxygen was supplemented at the rate of 4 litres/min to the patients with face mask.

HR, SBP, DBP and mean arterial pressure were noted at baseline, immediately after block insertion and then every 2 min for the first 30 min and every 5 min until the end of the surgery. Hypotension was defined as a fall in systolic pressure >20% below baseline and injection mephentermine 5 mg bolus was given. Bradycardia (heart rate <50/min) was treated with intravenous atropine sulphate 0.02 mg/kg.

The level of sensory block was assessed every minute by pinprick in the dermatomes T-10, T-8 and T-6, until a stable level of block was achieved at T6 level. Thereafter assessment was done at 15 min interval till one hr and then at 30 minutes interval till the patients complained of pain. Time of onset of sensory blockade was taken as the time to attain the highest level of sensory blockade. Two segment regression time was defined as time of regression of sensory level by two segments from the highest level attained. The duration of sensory block was defined as the time from intrathecal injection to regression of the sensory block to L1.

Motor block was assessed using a modified Bromage score [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]. The onset of motor blockade was taken as the time taken to achieve Bromage grade 3 blocks from the time of intrathecal injection. Duration of motor block was defined as the time elapsed from the Bromage score 3 to 0.

The duration of analgesia was defined as the period from spinal injection to the time of administration of first rescue analgesic for pain in the postoperative period. Pain was assessed using a VNS from 0 to 10 (0 = no pain; 10 = maximum imaginable pain) every 15 min after the block until the end of the surgery and 2, 4, 8, 12 h postoperatively. Postoperatively, intramuscular diclofenac 75 mg was given for rescue analgesia, whenever the pain score was >3.

Degree of sedation was assessed using a 5-point sedation score [0-none,patient alert;1-mild,patient may be sleepy but easily arousable,2-moderate,patient is drowsy but still arousable;3-severe,difficult to arouse;4-sleeping]

The incidence of side effects such as hypotension, bradycardia, sedation, pruritus, nausea and vomiting was noted every 15 min during surgery and 2, 4, 8, 12 h postoperatively. The primary outcome was duration of analgesia. The secondary outcomes were block characteristics, haemodynamic variable and side effects, if any. Perioperative monitoring of heart rate and noninvasive blood pressure was done every 5 minutes for first 30 minutes, there after every 10 minutes and any changes greater than 20 % from the baseline value were treated.

Statistical analysis

Duration of analgesia was taken as the outcome measure for sample size calculation. It was estimated that 24 subjects would be required per group in order to detect a difference of 45 min in this parameter between the groups, with 80% power and 5% probability of Type 1 error. To account for probable drop outs and block failure we included 30 patients in each group.

Quantitative data were represented as mean± standard deviation; number and percentage were used for qualitative data. Statistical analysis was done for comparing observed data by using student t-test and analysis of variance (ANOVA). *P* value of <0.05 was considered statistically significant.

3. Results

Ninety patients scheduled for elective gynaecological surgeries under spinal anaesthesia were enrolled in the study. All the patients were comparable with respect to demographic profile. (Table 1)

Characteristics of sensory and motor block are shown (Table 2)

The onset times of sensory and motor blockade were comparable in all three groups. Sensory block at T_6 level was achieved in6.17±1.57, 5.77±1.43 and 5.60±1.60 minutes, respectively in groups B, M and F (P =0.341). Mean time taken to achieve adequate motor block (Bromage score 3) was 11.03± 1.72, 11.47±1.69 and 10.63±1.22 minutes in groups B, M and F, respectively (*P* =0.120).

Mean duration of motor block was minimum in group B (119.0±17.27 minutes) and maximum in group F (127.77±16.04 min) and in group M, this time was 122.77±14.26 min. This difference was not significant statistically. Total duration of sensory block (two segment regression) was maximum in group F (139.70±29.37 min) and minimum in group B (86.73±22.15 min) and in group M, the duration was 126.47±16.33 min. (*P<0.0001*), it was statistically highly significant.

The total duration of analgesia was highest in Group F (268.97±24.35 min), followed by Group M (196.73±24.49

min) and Group B (132.33±23.48 min). This difference was highly significant statistically. (P <0.0001)

Table 1: Demographic profile of patients

Variable	Group B (n=30)	Group M (n=30)	Group F (n=30)	P –value (ANOVA)
ASA grade I/II	24/6	25/5	27/3	
Age(Yrs)	39.00±7.89	37.9±7.42	39.17±7.81	0.787 (NS)
Weight(Kg)	57.00±4.27	54.87±3.98	58.13±4.52	0.114(NS)

Data presented as mean ± SD or as number of patients, Group B-only bupivacaine; Group M- bupivacaine plus midazolam; Group F- bupivacaine plus fentanyl; p value <0.05 is considered as significant

Table 2: Block characteristics and duration of postoperative analgesia

Variable	Group B	Group M	Group F	P –value (ANOVA)
Onset of sensory block (minutes)	6.17±1.57	5.77±1.43	5.60±1.60	0.341 (NS)
Onset of motor block (minutes)	11.03± 1.72	11.47±1.69	10.63±1.22	0.120 (NS)
Time for 2 segments sensory regression (minutes)	86.73±22.15	126.47±16.33	139.70±29.37	0.000 (HS)
Duration of motor block (minutes)	119.0±17.27	122.77±14.26	127.77±16.04	0.107 (NS)
Total duration of analgesia (minutes)	132.33±23.48	196.73±24.49	268.97±24.35	0.000 (HS)

Notes: Data presented as mean ± SD, Group B- only bupivacaine; Group M- bupivacaine plus midazolam; Group F- bupivacaine plus fentanyl;Significance between groups for total duration of analgesia (Group B vs Group M-0.0001, Group B vs Group F-0.0001, Group M vs Group F-0.0001); NS- non significant; HS- highly significant.

4. Discussion

The baseline characteristics in all three group were comparable from statistical standpoint. Considering the onset of sensory block, our results are comparable with other previous studies. [3, 7, 8] They also did not find any statistically significant difference among the groups, but the addition of midazolam and fentanyl caused earlier sensory blockade of higherdermatomes.

Onset of motor block was also similar in all three groups, this is in accordance with other studies.[5, 7, 8] In this study,we observed that the addition of midazolam or fentanyl has no effect on the duration of motor block achieved by bupivacaine, similar results were obtained in other studies.[1, 4, 5]

The most significant finding of our study is the significant prolongation of sensory blockade as well as duration of postoperative analgesia which is reflected by the time to request first rescue analgesic and two dermatome sensory regression time of sensory block, after intrathecal injection of midazolam or fentanyl with hyperbaric 0.5% bupivacaine in patients undergoing elective lower abdominal surgeries. Fentanyl has more pronounced analgesic effect as compared to midazolam. Similar results were obtained in several other studies.[1,2,4,5,7,9,10]

Considering the intraoperative hemodynamic variables, the result of our study is comparable with other studies.[1,2,3]They also did not find statistically significant difference in heart rate, arterial blood pressure in their studies. Incidence of hypotension and bradycardia is found to be similar in both groups.

We found no significant difference in the incidences of shivering, nausea and vomiting during intraoperative as well as in the postoperative period. None of the patient had sedation and respiratory depression in any of the group.Though intrathecal opioids are known to cause respiratory depression.Reason for it may be, fentanyl being highly lipid soluble, rapidly penetrates neuronal tissues, hinders cephalad migration induced by CSF currents to produce sufficient concentration to cause respiratory depression.

Pruritus was reported in 10% patients in fentanyl group but none of the patient in midazolam or bupivacaine group. Pruritus is a common complication associated with opioids.Direct stimulation of serotonin type 3 receptors in dorsal horn of the spinal cord and in medulla by intrathecal opioids may be a possible mechanism for pruritus.

5. Conclusion

From present study, we conclude that addition of 2 mg midazolam or 20 mcg fentanyl to intrathecal hyperbaric 0.5% bupivacaine had no effect on the onset of sensory-motor block, duration of motor block buy provides prolonged duration of postoperative analgesia without causing any hemodynamic instability and adverse effects. Fentanyl seems to be superior to midazolam as an adjuvant to intrathecal bupivacaine in patients undergoing gynaecological surgeries under spinal anaesthesia.

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