International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Comparative Study of Low Dose Intrathecal Midazolam and Fentanyl as an Adjuvant to Bupivacaine Heavy in Cesarean Section

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Abstract: ***Background and Aims: Although Bupivacaine has a short duration of action, it is the most used local anaesthetic for subarachnoid block in LSCS. Intrathecally administered adjuvants that are combined with bupivacaine lengthen post-operative analgesia and enhance blockade quality and duration. The study's main objective is to assess the post-operative analgesic durations of intrathecal midazolam with Bupivacaine heavy and intrathecal fentanyl with heavy bupivacaine. Evaluations of the motor and sensory characteristics, hemodynamic stability, APGAR score, and complications are secondary goals. Methods: After Ethical Committee approval, 76 patients following inclusion criteria, undergoing elective caeserian delivery under spinal anaesthesia were allocated randomly to 2 groups of 38 each using sealed envelope method: Group F-2ml Bupivacaine heavy (10mg)+0.25ml Fentanyl (12.5mcg); Group M-2ml Bupivacaine heavy (10mg)+0.2ml midazolam (1mg)+0.05ml normal saline. The sample size was determined after talking to the institutional review board and using the findings of our pilot trial, which included 5 patients in each group. After the procedure was finished, sensory and motor features, intraoperative hemodynamic stability, complications if any, and an assessment of pain every hour for the first 24 hours following the procedure were noted. Results: The average time of post-operative analgesia was 5.51+/-0.23 hours in group F and 5.06+/-0.40 hours in group M.Both groups' sensory and motor traits were comparable. When compared to group F, group M had sensory block earlier. Conclusion: For LSCS, fentanyl and midazolam are both effective adjuvants to hyperbaric bupivacaine in terms of hemodynamic stability and good APGAR score. When administered as an adjuvant in patients undergoing caesarean deliveries, intrathecal fentanyl offered superior post-operative analgesia versus midazolam.***

Keywords: Hyperbaric Bupivacaine, Fentanyl, Midazolam

1. Introduction

Cesarean section is one of the painful operations which need adequate intra-operative and post-operative analgesia. Spinalanaesthesia is most commonly used neuraxial technique as it is simple to perform, has higher accuracy rate and provides safe, simple and effective anaesthesia. Spinal anaesthesia also avoids depressant effect of general anaesthesia on neonate and risk of aspiration in mother. However most common local anaesthetic used is Bupivacaine heavy which has limited duration of effect around 1.5-2 hours[1] so various adjuvants such as opioids, midazolam, alphaagoinsts, neostigmine, ketamine etc have been tried to improve quality of spinal block and to increase post-operative analgesia.

Fentanyl produces strong analgesia through its activation of opioid especially the mu opioid receptors. Various studies have shown that it improves duration of sensory anesthesia and postoperative analgesia without producing significant side effects.[3]

Midazolam is a potent short acting, water soluble benzodiazepine. Intrathecal analgesic effect of midazolam is mediated through benzodiazepine-gamma aminobutyric acid (GABA) receptor complex within the intrathecal cord. Its antinociceptive effect is mediated via intrathecal delta opiate receptors (Edwards et al. 1990). 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.

2. Methodology

After seeking permission from *Scientific and Ethical Research Committee (Clinical Trial Registration Number:* CTRI/2022/06/043450) of Government Medical college and SSG Hospital, Vadodara, a double blinded randomized controlled trial was carried out. Total 76 adult, ASA I and II pregnant patients, between ages18-40 years with height 150cm and above, who were admitted and scheduled for elective caesarean section were selected. We excluded all patients who were contraindicated for spinal anaesthesia and also patient with bad obstetric history, obstetric complications in present pregnancy, fetal compromise, h/o drug allergy, patient not willing to participate in the study.

Sample size was estimated as follows:

- A pilot study was done with 5 patients in each group. The parameter 'the total duration of effective analgesia 293.4mins vs. 286.67mins' is taken as main parameter. A minimum of 38 patients per group (76 in total) to estimate mean difference of total duration of effective analgesia between two groups with 6.73mins with standard deviation (SD) = 9.91 (in group F) and 11.21 (in group M) mins at 95% confidence.
- Patients were thoroughly counselled during the pre-operative evaluation and properly explained about the procedure, purpose of the study, VAS Score and possible side effects of drugs and procedure before taking the written consent. The night before surgery, premedication was administered in the form of 150mg Tab Ranitidine. All patients were preloaded with 10ml/kg of Ringer's lactate solution in the operating room after a reliable venous access was established with an 20G cannula in forearm.15 minutes prior to spinal anaesthesia, all patients received premedication in the form of injection glycopyrrolate (5mcg/kg)iv and injondansetron (0.15mg/kg)iv. In neither group was a sedative premedication administered. Monitors such as NIBP (non-invasive blood pressure), ECG and pulse oximeter were attached after the patient was taken into operating room. Blood pressure, oxygen saturation and the baseline pulse rate were recorded. Aseptic and antiseptic measures were followed, the patient was positioned in a left lateral posture, and painting and drapingdone. A midline technique was used to introduce a 23G spinal needle after locating L3-L4 intervertebral region. Study medication was administered intrathecally once free CSF flow was confirmed.

Drug Preparation

Group F-Inj Bupivacaine 0.5%2ml+ Inj Fentanyl 12.5mcg 0.25 ml (with tuberculin syringe) (premix)

Group M– Inj Bupivacaine 0.5% 2ml + Inj Midazolam 1mg 0.2 ml+0.05ml sterile water (with tuberculin syringe) (premix)

Total Volume: 2.25ml

For ensuring **blinding,** the drug sealed in envelope which were numbered and were made to be opened by the designated consultant of the work area just before the administration of anaesthesia and drug was prepared using sterile technique according to group allocated. The drug was then handed over to the attending anaesthesiologist who would be unaware about the study design and the study groups. Myself as an observer was not present while subarachnoid block was being administered. After the induction I was called inside the operating room for observation of the case.

Pin-prick testing was used to evaluate the sensory block of spinal anaesthesia. Motor block assessed using Bromage scale. Vital signs such as pulse, blood pressure and spo2 were continually monitored intraoperatively at predetermined intervals. (baseline 1st, 3rd, 5th, 10th, 15th, 20th, 30th, then every 15 minutes until 60 minutes, and then half hourly until the completion of operation).Complications that occurred during surgery, such as bradycardia, hypotension, nausea and vomiting, were recorded and appropriately managed. Blood loss and fluid requirements were computed and replenished appropriately. After the surgery, a pain assessment was performed at 0 hours, then every hour for the first four hours, every two hours for the next twelve hours, and final twenty four hours. It has a 10 cm scale with a 0-10 rating, where 0 means there is no pain and 10 means the worst kind of agony. From the moment the spinal drug was injected until the patient achieved a VAS score of four or above, the period of effective analgesia was measured. At this point, rescue analgesia was administered to them in form of injection paracetamol (1gm) is given.

Mean and Standard deviation values were taken out. Statistical analysis of the data for the various parameters was done using student's 't' test for all continuous variables and chi-square test was used for qualitative (nonparametric) data using MedCalc software. P value was used to determine the significance of a statistical study. The p value < 0.05 was considered as significant and p value <0.01 was considered as highly significant.

3. Result

Table 1: Duration of Effective Analgesia

Parameter	Group F Mean ±SD	Group M Mean ±SD	P Value
Duration of effective analgesia (hours)	5.51+/-0.23	5.06+/-0.40	P<0.0001

Table 2: Rescue Analgesia

Parameter	Group F Mean ±SD	Group M Mean ±SD	P Value
Total no. of analgesia required in 24 hrs	2.+/-0.22	2.26+/-0.44	P<0.01

Table 3: Sensory and Motor Characteristics

Parameter	Group F (Mean+/-SD)	Group M (Mean+/-SD)
Onset of sensory block at L1 (secs)	100.68+/-13.65	67.13+/-7.23
Peak sensory level achieved	T6	T6
Time to achieve highest sensory level (secs)	3.78+/-0.31	3.00+/-0.42
Time of 2 segment Regression from highest level of block (mins)	168.42+/-6.31	156.55+/-3.614
Onset of motor block in seconds	156.55+/-3.61	102.57+/-1.44
Time to attain maximum motor block in minutes	5.17+/-0.11	4.93+/-0.28
Duration of motor block (minutes)	229.2+/-35.4	186.6+/-5.93

The two groups in our study were comparable to each other with respect to age, weight, height. **Time to achieve peak sensory level** was seconds in 3.78+/-0.31 in Group F and 3.+/-0.42 in Group M. The **mean time taken for two segment dermatomal regression** was 168.42+/-6.31 minutes in Group F and 156.55+/-3.614minutes in Group M.Thus, time for onset of sensory anaesthesia at L1 level and time to achieve maximum sensory level was early in Group M when compared to Group F which was statistically significant ($p<0.001$). Time for two segmental dermatomal regression was prolonged in Group F when compared to Group M which was statistically significant ($p<0.001$).The **mean onset time for motor block** was 156.55+/-3.61 seconds in Group F and 102.57+/-1.44seconds in Group M. **Time to attain maximum Bromage grade 3** was 5.17+/-0.11 minutes in Group F and 4.93+/-0.28 minutes in Group M. The **mean duration of motor block** was 229.2+/-35.4minutes in Group F and 186.6+/-5.93minutes.The mean onset time for motor block and time to attain maximum bromage score 3 was earlier in Group M when compared to group F and the mean duration of motor block was higher in Group F when compared to Group M. ($p<0.001$) There was no significant change in **pulse rate, mean oxygen saturation** and **respiratory rate** in either of the groups during intraoperative as well as post operative period. There was statistically significant difference ($p<0.05$) in **systolic blood pressure** between the two groups after **5 mins** of induction of spinal anaesthesia. There was also statistically significant difference ($p<0.05$) in **diastolic blood pressure** between the two groups after **5 mins** of induction of spinal anaesthesia. **The total duration of effective analgesia** was 5.51+/-0.23 hours in group F and 5.06+/-0.4 hours in group M. **The total no. of doses of rescue analgesic** required in 24 hours was 2.+/-0.22 in Group F 2.26+/-0.44 in Group M. The mean duration of effective analgesia was relatively lower in Group M when compared to group F and the result was significant ($p<0.001$) and the total number of rescue analgesia required in Group F was significantly lower when compared to Group M and the result was significant ($p<0.05$).In our study, 1 patient (2.63%) in group F and 0 patient in group M developed nausea/vomiting, 1 patient (2.63%) in group F and 1 patient (2.63%) in group M developed hypotension, 1 patient (2.63%) developed pruritus in group F, 2 patient (5.26%) in group F and 1 patient (2.63%) in group M developed shivering intraoperatively. 1 patient (2.63%) of group F developed complain of pruritus postoperatively. No other complications like, bradycardia, respiratory depression, urinary retention, dryness of mouth were noted in either groups in intra operatively and post operative

4. Discussion

Regional anaesthesia 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 parturient, is hypotension caused by blockade of sympathetic output. Decreasing the dose of local anaesthetic decreases the magnitude of hypotension but compromises upon the quality of anaesthesia with limited duration of post-operative analgesia.

Neuraxial adjuvants are used to improve and prolong the effects of local anaesthetic. Among many adjuvants Inj fentanyl which is an opioid is most commonly used. It is a highly potent lipophilic opioid and due to it high lipid solubility it rapidly binds dorsal horn receptors in spinal cord. It improves the quality of spinal anaesthesia as it intensifies sensory and motor blockade and prolongs the duration of action without any incidence of hemodynamic instability. Studies have shown that it improves duration of sensory anesthesia and postoperative analgesia without producing significant side effects. Various studies has been done with different doses of fentanyl7mcg, 10mcg, 12.5mcg, 15mcg, 20mcg as an adjuvant to Bupivacaine heavy in LSCS. Studies showed that clinical effect reached its ceiling at 12.5 mcg dose [(3)].We, in our study selected 12.5mcg because it is the least dose of drug which has good intra-operative as well as post-operative analgesia effect.

Midazolam exerts its analgesic activity through benzodiazepine GABA receptor complex, which are distributed in the gray matter of the spinal cord. Various doses of intrathecal midazolam1mg 2 mg given intrathecally as adjuvant with BUPIVACAINE for LSCS has been studied in different studies[4].We selected 1mg dose of intrathecal midazolam in our study. We were hesitant to use a higher dose in obstetric population because of possible depressant effects on the newborn. Tucker et al (Tucker et al 2004) have also used intrathecal midazolam and concluded that when it is given 0.03mg/kg, it is safe in human. He also concluded from his studies on neurotoxicity concerns that up to 2mg of intrathecal midazolam did not increase the occurrence of neurological symptoms.[9]According to study conducted by Pooja Daramwar1, SuyogTannirwar-Addition of midazolam in intrathecal Bupivacaine for caesarean section prolongs duration of postoperative analgesia with no increase in the incidence of complications [(10)]

In our study, early onset of sensory anaesthesia was observed in Midazolam group. Post-operative analgesia was prolonged in fentanyl group as compared to midazolam group.

5. Limitations of Study

In our study we evaluate pain using VAS score as interpreted by patients. So it becomes very subjective and might vary from patient to patient with their understanding and pain tolerance. Scoring system could be better supplemented with objective scoring system like Wong Baker scale. In our study, we did not compare control group without adjuvants. Hence we are unable to compare with baseline effect of block with local anaesthestics only group. We were not able to find out equipotential dose ratio of fentanyl to midazolam. This suggest requirement of further studies.

6. Conclusion

In nutshell, intrathecal low dose fentanyl and midazolam both are good adjuvants to hyperbaric bupivacaine 0.5% for caesarean section, as in both groups, stable maternal hemodynamic profile and normal neonatal APGAR score were noticed. Intrathecal Fentanyl provides prolonged post-

operative analgesia than intrathecal midazolam as adjuvant to hyperbaric bupivacaine heavy.

Financial Support and Sponsorship
None

Conflicts of Interest
None

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