Original Research Article

Comparative study of intrathecal bupivacaine plus midazolam vs bupivacaine alone for duration of postoperative analgesia in the patients of caesarean delivery

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Abstract

Background: Regional anaesthesia in form of spinal anaesthesia is preferred for caesarean section. 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. Adding adjuvants drugs to intrathecal local anaesthetics improves quality and duration of spinal blockade, and prolongs postoperative analgesia. In present study we compared intrathecal bupivacaine plus midazolam vs intrathecal bupivacaine alone for duration of postoperative analgesia in the patients of caesarean delivery at our tertiary hospital. **Material and Methods:** This study was prospective, comparative, randomised study in pregnant women, 20-40 years age, ASA grade I/II, posted for elective Caesarean section. Patients were randomly selected and randomly divided into group B & group BM by chit method. The B group received 10 mg bupivacaine and the BM group received 10 mg bupivacaine combined with 2 mg of preservative-free midazolam. **Results:** Total 80 pregnant women were enrolled & 40 pregnant women each were allotted to group B (10 mg bupivacaine) and group BM (10 mg bupivacaine combined with 2 mg of preservative-free midazolam) Baseline maternal characteristics such as age, weight, height, pulse rate, systolic BP, diastolic BP were comparable in both groups. Early onset time of sensory block, reduced time to achieve complete sensory block & prolonged duration of effective analgesia was noted in group BM as compared to group B, and the difference was statistically significant. Complications such as bradycardia, hypotension, nausea and vomiting were noted in present study. Group B had increased number of complications than group BM, difference was not statistically significant. **Conclusion:** Intrathecal bupivacaine plus midazolam for caesarean section reduces the onset time of sensory block, prolongs the duration of analgesia with no increase in the incidence of complications.

Keywords: intrathecal, bupivacaine, midazolam, postoperative analgesia, caesarean delivery.

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INTRODUCTION

A dramatically increased number of caesarean section is noted in both the developed and developing countries.[1] Regional anaesthesia in form of spinal anaesthesia is preferred for caesarean section. 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. Adding adjuvants drugs to intrathecal local anaesthetics improves quality and duration of spinal blockade, and prolongs postoperative analgesia.[2]

Caesarean section requires high level of sensory block (T4) and this level of anesthesia requires a high dose of bupivacaine, which itself has side effects such as

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hypotension, nausea and vomiting, and prolonged recovery after surgery. The most commonly used drug for spinal anesthesia is bupivacaine, with a maximum effect time of 75 to 150 minutes.

Effective and rapid relief from pain is always a challenge, but is necessary for alleviating nocioception – induced responses like endocrine metabolic responses to surgery, autonomic reflexes with adverse effects on organ function, reflexes leading to muscle spasm, and other undesirable results.[3]

The discovery of various spinal receptors like 2-adrenergic, cholinergic, opioid, N-methyl-D-aspartate, gamma-aminobutyric acid (GABA),and benzodiazepine receptors triggered the usage of drugs like clonidine, neostigmine, opioids, ketamine, and midazolam for their synergistic effect with hyperbaric bupivacaine (0.5%) in prolonging the duration of analgesia.[4,5]

Midazolam, a water-soluble benzodiazepine is known to produce antinociception and enhance the effect of local anaesthetic when given epidurally or intrathecally5. Midazolam produces this effect by its action on gamma aminobutyric acid-A (GABA-A) receptors. GABA receptors have also been found in peripheral nerves.[6] In present study we compared intrathecal bupivacaine plus midazolam vs intrathecal bupivacaine alone for duration of postoperative analgesia in the patients of caesarean delivery at our tertiary hospital.

MATERIAL AND METHODS

This study was prospective, comparative, randomised study conducted in the Department of Anaesthesia, MGM Medical College, Aurangabad. Study was conducted between May 2019 to November 2019 (six months). Institutional ethical committee approval was taken.

Inclusion criteria

- Pregnant women, 20-40 years age, ASA grade I/II, posted for elective Caesarean section

Exclusion criteria

- Bad obstetric history and obstetric complications in present pregnancy.
- Evidence of foetal compromise and anomalies.
- Medical disorders such as heart disease, renal disease, liver disease.
- Patients with psychiatric diseases.
- Contraindication to spinal anaesthesia.
- Not giving consent for participation in study.

80 pregnant women scheduled for elective caesarean section were studied. Study was explained in local language & written informed consent was taken. Patients were randomly selected and randomly divided into group B & group BM by chit method. The B group received 10 mg bupivacaine and the BM group received 10 mg bupivacaine combined with 2 mg of preservative-free midazolam.

A detailed pre-anaesthetic evaluation and all relevant investigations were done & posted for elective caesarean section. In operation theatre, the standard monitoring devices SpO2, ECG, noninvasive blood pressure, temperature probe was attached to the patient and baseline parameters pulse rate, blood pressure, respiratory rate and SpO2 were recorded. Each patient was preloaded with 10 mL/kg Ringer lactated solution prior to spinal anaesthesia. Under all aseptic precautions, through midline approach, the lumbar puncture was done at L2-L3 or L3-L4 intervertebral space with 23G disposable Quincke's spinal needle. Oxygen was supplemented to each patient at a rate of 5 lit./min. via oxygen mask. Heart rate and blood pressure were monitored immediately after subarachnoid injection of drug and when patient is made supine.

Patients hemodynamic parameters including maternal pulse rate, non-invasive blood pressure, oxygen saturation, and respiratory rate measured periodically & were recorded. Standard postoperative care was provided. The duration of effective analgesia was taken from the time of intrathecal drug administration to the time of first supplementation with rescue analgesic.

The values of the two groups were compared and expressed as mean ± SD. Statistical analysis was done by using Student's paired t-test for quantitative and Chi-square test for qualitative parameters. The p value of <0.05 was considered as statistically significant.

RESULTS

Total 80 pregnant women were enrolled & 40 pregnant women each were allotted to group B (10 mg bupivacaine) and group BM (10 mg bupivacaine combined with 2 mg of preservative-free midazolam) Baseline maternal characteristics such as age, weight, height, pulse rate, systolic BP, diastolic BP were comparable in both groups.

Table 1: Baseline Information & Vitals of Study Groups

Characteristics	Group B (mean ± SD)	Group BM (mean ± SD)	p value
Age (years)	25.23 ± 5.2	26.1 ± 4.3	>0.05
Weight (kgs)	64.6 ± 8.7	65.5 ± 3.5	>0.05
Height (cms)	155.3 ± 5.3	153.5 ± 5.1	>0.05
Pulse Rate (per min)	81.6 ± 11.2	79.6 ± 10.1	>0.05
Systolic BP (mm Hg)	120.4 ± 10.5	118.3 ± 11.6	>0.05
Diastolic BP (mm Hg)	76.3 ± 7.9	74.6 ± 8.2	>0.05

Early onset time of sensory block, reduced time to achieve complete sensory block & prolonged duration of effective analgesia was noted in group BM as compared to group B, and the difference was statistically significant.

Table 2: Comparison of sensory parameters in two groups

Characteristics	Group B (mean ± SD)	Group BM (mean ± SD)	p value
Mean onset time of sensory block (min.)	4.15 ± 1.22	2.82 ± 1.7	<0.05
Time to achieve complete sensory block	8.9 ± 3.1	5.8 ± 2.1	<0.05
Mean duration of effective analgesia	161.6 ± 22.1	180.9 ± 29.5	<0.05

Complications such as bradycardia, hypotension, nausea and vomiting were noted in present study. Group B had increased number of complications than group BM, difference was not statistically significant.

Table 3: Complication

Complications	Group B (n=40)	Group BM (n=40)
Bradycardia	2	1
Hypotension	3	1
Nausea and vomiting	3	2
Total	**13**	**14**

DISCUSSION

The dose of the local anaesthetic (LA) decides the extent and duration of the block - too little dose will cause untimely wearing away of the block, visceral pain on exteriorization of uterus & handling of other abdominal contents, whereas too large a dose might result in an intensive block with the resultant hypotension, bradycardia and sometimes even cardiac arrest. The use of subarachnoid additives in spinal anaesthesia for cesarean section has two main objectives: to enhance spinal block and to produce effective and prolonged postoperative analgesia.

Midazolam is categorized under the benzodiazepine group of drugs, is used as a preoperative sedative or as a sleep medication during operations, and as a sedative drug during delivery, with analgesic effects.[7,8] Midazolam exerts its analgesic activity through benzodiazepine receptors, which are distributed in the gray matter of the cervical, thoracic, lumbar, and sacral regions of the spinal cord; the highest densities of receptors were localized within lamina II of the dorsal horn. The segmental analgesia produced by intrathecal midazolam is mediated by the benzodiazepine GABA receptor complex, which is also involved in other benzodiazepine actions .

Karbasfrushan *et al*.,[9] compared intrathecal midazolam 2 mg added to bupivacaine 10 mg versus plain bupivacaine in women undergoing elective cesarean. Patients treated with midazolam had significant pain relieve at 15 and 120 min after surgery, but there were no significant differences between the groups regarding the intensity of pain 5, 30, 60 and 240 min after the surgery. Request for first analgesic was 178.06±77.33 versus 142.18±55.19 min. Duration of analgesia and regression for sensory analgesia was similar in both groups, but nausea and vomiting were higher in the midazolam group.

In a study by Sharifi *et al*.[10] it was shown that adding midazolam to bupivacaine reduced the time required for spinal anesthesia, reduced the time required for motor block & increased the time of spinal anesthesia. Various studies have found that adding midazolam to bupivacaine significantly increases the duration of postoperative analgesia.[11] Similar findings were noted in present study.

In present study, episodes of hypotension and the associated vasopressor requirement, which were significantly high in the group B compared to the group. Sanwal *et al*. reported that this relationship may be due to the bupivacaine-sparing effect of midazolam and concluded that intrathecal midazolam may allow the dose of bupivacaine to be reduced while still providing the same surgical anaesthesia with fewer episodes of bradycardia and hypotension. They concluded that, with intrathecal midazolam 2 mg, it is possible to reduce the dose of bupivacaine from 2.2 mg to 1.5 mg to provide the same surgical anesthesia but with fewer incidence of hypotension and other side effects.

Further, the incidence of nausea and vomiting was also found to be low in the midazolam group. It has been postulated that a possible mechanism for the anti-emetic effect of benzodiazepines could be an action at the chemoreceptor trigger zone, which reduce the synthesis, release, and postsynaptic effect of dopamine.[13]

Ravichandra D *et al*.,[14] noted that intrathecal midazolam provides significant and effective postoperative analgesia along with stable intraoperative hemodynamics without affecting the level of sensory and motor blocks. Adequate postoperative analgesia can be achieved with minimal side effects using intrathecal midazolam in PIH patients. In the same study, duration of postoperative analgesia was significantly prolonged in the midazolam group compared to the control group (BC: 201.5 ± 1.83 vs. BM: 357.6 ±

9.74, P < 0.01); The duration of analgesia was also significantly prolonged in the midazolam group compared to the control group (260.6 ± 22.45 minutes. vs. 170.8±21.17 minutes). However, the duration of the motor block & sedation score were comparable in both groups.

Midazolam produces spinally mediated analgesia that is different in quality from that produced by the μ-opioid agonist fentanyl. The analgesic effects of intrathecal midazolam have been proposed to be due to its intrathecal spinal receptor interactions affecting the type A gamma-aminobutyric acid receptors.

Ho KM in a meta-analysis concluded that, adding intrathecal midazolam to other spinal medications improves perioperative or peripartum analgesia and reduces nausea and vomiting during caesarean delivery. A small diluted dose of intrathecal midazolam (1 to 2.5 mg) does not appear to increase the duration of motor blockade, the risk of respiratory depression or of short-term neurologic deficit.[15]

A large cohort study investigating the adverse neurological effects of intrathecal midazolam has also found no association between intrathecal midazolam and neurologic symptoms.[16]

CONCLUSION

Intrathecal bupivacaine plus midazolam for caesarean section reduces the onset time of sensory block, prolongs the duration of analgesia with no increase in the incidence of complications. Intrathecal bupivacaine plus midazolam should be promoted for elective caesarean section.

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