Original Research Article

A comparative study of efficacy and safety of intrathecal midazolam plus bupivacaine versus bupivacaine in sub-arachnoid block for cesarean section

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Abstract

Introduction: Spinal anaesthesia, which is one of the techniques for infraumbilical surgeries, is most commonly criticized for limited duration of postoperative analgesia. Several adjuvants have been tried along with local anesthetic for prolonging the duration of analgesia. **Aim**: To study the bupivacaine sparing effect of intrathecal midazolam in sub-arachnoid block for cesarean section **Materials and methods:** A hospital-based interventional study 100 Patients scheduled for elective cesareansection . From the study population two groups of 50 each were observed to assess the selected parameters. Group B - receiving 2 cc of 0.5%Hyperbaric Bupivacaine (10mg) intrathecal Group BM- receiving 1.6 cc of 0.5%Hyperbaric Bupivacaine (8mg) + 0.4cc of 0.5% preservative free midazolam (2mg) intrathecal. Onset times of sensory and motor blockade, duration of sensory and motor blockade, duration of effective analgesia, Ramsay sedation score, newbornAPGAR score and side effects were recorded. **Results**:. Duration of sensory block is signifcantly high in group BM when compared to Group-B. Duration of effective analgesia is significantly high in Group BM than that of Group-B. There is a statistically significant difference (p-value< 0.05) in the incidence of hypotension between the 2 groups with patients receiving midazolam in combination with low-dose bupivacaine having significantly lesser incidence of hypotension. Comparing nausea/vomiting between the groups the result is statistically significant at p<0.05. APGAR scores of the newborns were comparable between the groups and there was no statistically significant difference. **Conclusion:** Intrathecal midazolam as an adjuvant to Bupivacaine is safe and effective.

Keywords: Hemiarthroplasty, Harris Hip Score, Femoral neck, Fracture.

Introduction

Sub-Arachnoid Block is the preferred technique for cesarean section owing to its benefits of simplicity, reliability, low rates of airway complications and aspiration, awake mother at the time of birth of the child that establishes maternal-infant bonding and successful breastfeeding. However this procedure has only a limited duration of analgesia and causes maternal hypotension perioperatively which may be deleterious. Neuraxial blockade with sympathetic block by the local anaesthetic administered has been implicated for this side effect of hypotension in a dose dependent manner. Decreasing the dose of local anaesthetic decreases the magnitude of hypotension but can compromise upon the quality of anaesthesia. Intrathecal adjuvants are helpful in that owing to their synergestic effect with local anaesthetic, they allow for decreasing the dose of local anaesthetic, thus decreasing the incidence of hypotension without compromising on the quality of anaesthesia. Also by prolonging the duration of analgesia they provide pain free post-operative period which is valuable especially following cesarean section so that new mothers may care for and bond with their neonates.

The benzodiazepines are used primarily for anxiolysis, amnesia and sedation. The discovery of benzodiazepine receptors in the spinal cord triggered the use of intrathecal midazolam for analgesia. Several investigations have shown that the intrathecal or epidural administration of midazolam provides a dose-dependent modulation. of spinal nociceptive processing in animals and humans and is not associated with neurotoxicity, respiratory depression or sedation. Various researchers have evaluated the effectiveness of intrathecal midazolam in post- operative analgesia in normal cesarean patients[1,2].

Our experience with intrathecal midazolam as adjuvant for spinal anaesthesia for cesarean section in our setup is nil. So we conducted this study to evaluate the feasibility of decreasing the dose of bupivacaine for sub-arachnoid block, thus decreasing the incidence of hypotension, as well as prolonging the duration of analgesia by addition of midazolam.

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Materials and Methods

A hospital-based interventional study was undertaken in the department of Anaesthesiology And Critical Care, Gandhi Medical College And Hospital, Secunderabad, Telangana State.

Inclusion Criteria

Age group of 20 to 40 years ,Healthy parturients of ASA grade I or II Undergoing elective cesarean section.

Exclusion Criteria

Weight > 90kg, Height <150cms or >165cms, Any fetal compromise, Any major systemic illness and any contraindication to regional anaesthesia. Institutional ethical committee approval was obtained. Written, informed consent from the study population of 100 healthy parturients fulfilling the inclusion criteria was taken. A thorough pre-anaesthetic evaluation with clinical assessment and baseline investigations including Complete Blood Picture, blood grouping and typing, bleeding time, clotting time, blood sugar, blood urea, serum creatinine and ECG were performed. All the patients were kept nil per os for 8 hrs prior to surgery and were given 150 mg ranitidine

tablet to be taken orally at bedtime, the night before surgery. In the morning , around 30-45 minutes before shifting to Operation Theatre injection ranitidine 50 mg and injection metoclopromide 10 mg slow IV were given. In the operating room, standard monitors (electrocardiogram, non invasive blood pressure cuff and pulse oximeter) were attatched to patients and baseline readings were recorded. A peripheral IV line was secured with an 18 guage cannula in one of the upper limbs . Lactated ringer's solution was started to co-load with around 15ml/kg of crystalloid over 20 minutes. A sub-arachnoid block was instituted in the left lateral position with the 25 G QB spinal needle in L3-L4 interspace under full aseptic precautions. After obtaining free flow of CSF, the study drug was injected slowly and the patient turned supine and wedge placed under the right hip.

From the study population two groups of 50 each were observed to assess the selected parameters.

Group B- Patients receiving 2cc of 0.5% H bupivacaine (10mg)

Group BM- Patients receiving 1.6cc of 0.5% H bupivacaine (8mg) + 0.4cc of 0.5% preservative free midazolam (2mg).

Intraoperatively BP is measured at every 3minutes for 1st 30minutes and every 5minutes thereafter.Onset times of sensory and motor blockade , duration of sensory and motor blockade , duration of effective analgesia ,Ramsay sedation score, newborn APGAR score

Post-operatively, the patients are observed for the duration of effective analgesia using the Numerical Rating Scale (NRS) at 1 hour intervals for 2 hours followed by half an hour intervals until the supplementary analgesia was required which was given when NRS is more than or equal to 4. In our study, hypotension was defined as the fall in SBP by more than 25% from the baseline and was managed with intravenous crystalloids and incremental doses of phenylephrine as required.

APGAR score was assessed at 1 minute, 5 minutes and 10 minutes and the newborn clinically monitored for 6 hours.

Statistical Methods

The sample size was calculated on the basis of previous studies for detecting a significant difference in the incidence of hypotension , assuming a power of 80% and a significance level of 5%. Numerical variables are presented as mean + SD whereas categorical variables are presented as number of cases and percentage. Statistical comparisons are carried out using independent student's t -test for numerical variables and Chi-square test or Fischer's exact test for categorical variables as appropriate . A p-value of < 0.05 is considered statistically significant.

Results

Table 1: Demographic details in study

Details	Group-B	Group-BM	P-Value
Mean age of the patients (years)	27.18+2.94	26.82+2.97	0.54
Height of the patients (cms)	154.2+2.27	153.66+2.39	0.25
Weight of the patients (kgs)	55.54+3.34	54.36+4.18	0.12

Thus there were no statistically significant differences (p-value > 0.05) in the demographic profiles between the 2 groups and the patients were comparable with respect to their age, height and weight.

Table 2:Onset and duration of blocks

Means	Group-B	Group-BM	P-Value
Onset of sensory block (minutes)	2.06 +0.47	2.2 +0.64	0.21
Onset of motor block (minutes)	3.66+0.66	3.78+0.65	0.36
Duration of sensory block (hours)	2.37+0.43	3.54+0.45	<0.001*(significant)
Duration of motor block (hours)	4.02+0.46	4.13+0.37	0.15

Duration of sensory block is siginifcantly high in group BM when compared to Group-B. onset of both sensory and motor block also duration of motor block are insignificant in groups.

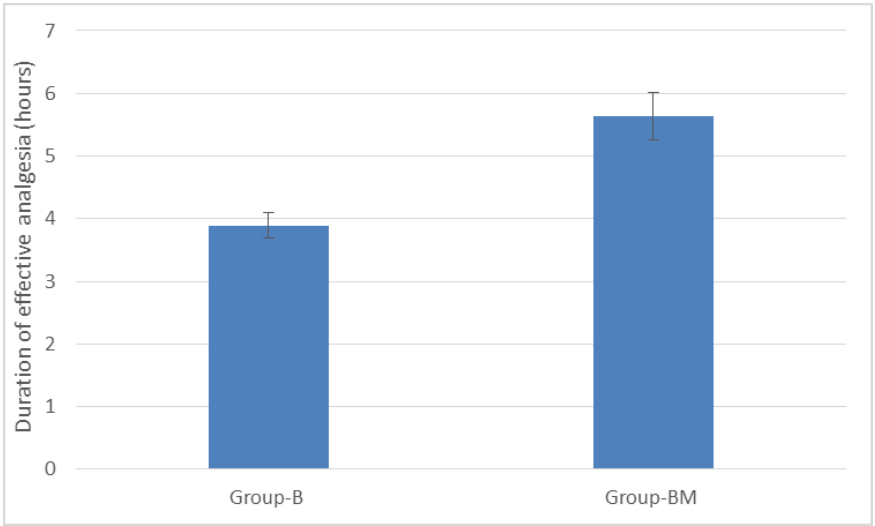

Fig. 1: Duration of effective analgesia (hours)

p-value< 0.001 (significant)

Duration of effective analgesia is significantly high in Group BM than that of Group-B

Table 3: Incidence of hypotension

	Hypotension		No Hypotension		Total
	Observed	Expected	Observed	Expected	
B	11	7	39	43	50
BM	3	7	47	43	50
Total	14		86		100

Chi-square value= 5.3156 Degrees of freedom=1 p-value= 0.02 There is a statistically significant difference (p-value< 0.05) in the incidence of hypotension between the 2 groups with patients receiving midazolam in combination with low-dose bupivacaine having significantly lesser incidence of hypotension.

In this study, hypotension is defined as fall in SBP > 25% from the baseline. In group B, 11 out of 50 patients had hypotensive episode. Incidence of hypotension in Group B = (11/50)x 100= 22% In group BM, 3 out of 50 patients had hypotensive episode. Incidence of hypotension in Group BM= (3/50)x 100= 6%.

Chi-square test is performed to compare these groups. A 2X2 contingency table with observed and expected values is made.

Table 4:Comparing other side-effects

Side effect	Number of patients(out of 50 in each group)	
	Group B	Group BM
Bradycardia	0	0
Nausea/vomiting	8	1
Shivering	3	1
Respiratory depression	0	0

The side effects are compared using Fisher's exact test. Comparing nausea/vomiting between the groups the Fisher's exact test statistical value is 0.0309 . The result is statistically significant at p<0.05 Comparing shivering between the groups, the Fisher's exact test statistical value is 0.6173. The result is not statistically significant. Also there are no patients with Bradycardia or respiratory depression in either of the groups.

Sedation scores

All the patients in both the groups were co-operative, oriented and tranquil with Ramsay sedation score= 2, as assessed at 30 min and 1 hour post-spinal. Thus there was no difference between the groups with respect to sedation.

Table 5: Distribution of APGAR Score

	Group B		Group BM		'p' value
	Mean	SD	Mean	SD	
APGAR Score at 1 min	9.94	0.24	9.96	0.20	0.65
APGAR Score at 5 min	10	0	10	0	1.000
APGAR Score at 10 min	10	0	10.	0	1.000

APGAR scores were evaluated at 1min, 5minutes and 10 minutes after birth.

3 out of 50 in group B and 2 out of 50 in group BM had APGAR score of 9 at 1st minute. All of them had APGAR score of 10 at 5 and 10minutes. APGAR scores of the newborns were comparable between the groups and there was no statistically significant difference.

Discussion

Sub-arachnoid block is the most commonly used anaesthetic technique for cesarean section because of its simplicity, rapid onset of action , awake mother at the time of birth of the child and less complications in both the mother and neonate. However this has only limited duration of analgesia and maternal hypotension perioperatively which may be deleterious. Decreasing the dose of local anaesthetic reduces the magnitude of hypotension but compromises upon the quality of anaesthesia. Intrathecal adjuvants owing to their synergistic action will allow for decreasing the dose of Local anaesthetic and prolong the duration of analgesia.

The gate theory of pain has had considerable influence on the anaesthesiologists management of pain by focussing attention on the unique pharmacology of the dorsal horn of the spinal cord. By using the intrathecal and epidural injections, anaesthesiologists have learned to suppress nociceptive transmission at the first synaptic relay in the spinal cord. The technique has implications in acute and chronic pain therapy. Neuraxially administered drugs can provide analgesia without some of the systemic side effects of the intravenously administered drugs. A typically modern view of perioperative pain is to view it as an impediment to recovery. Aggressive methods are often used to minimise pain to facilitate hospital dischrge and a rapid return to normal functional activity.

Intrathecal adjuvants are one of the easiest and most accessible methods of offering pain relief.

Opioids are the commonest adjuvant drugs added to the local anaesthetics for improved intraoperative and post-operative analgesia provided by 0.5% hyperbaric bupivacaine, when administered through intrathecal route.However sedation, itching, urinary retention, nausea-vomiting , and the risk of respiratory depression are the important concerns with opiods. In the quest for newer, safer local anaesthetic additives, researchers have found that benzodiazepines lead to segmental block of nociception without any adverse effects on cardiovascular and respiratory systems.

Benzodiazepines are not normally considered to be analgesics. When these drugs are given by any route that causes high blood levels of the drug, it is impossible to demonstrate analgesic effects over and above their effects on consciousness and anxiety. However one may confine the action of midazlolam to the spinal cord by giving it intrathecally, thus allowing access to receptors that mediate analgesia.

Intrathecal midazolam has been shown to potentiate the effect of local anaesthetic in sub-arachnoid block by acting through the BZD-GABA receptor complex at the spinal cord level leading to segmental analgesia without any neurotoxic effects[3]. BZD receptors are distributed in the grey matter of cervical, thoracic, lumbar and sacral regions of the spinal cord; the highest densities of receptors were localized within lamina II of the dorsal horn[4]. Intrathecal midazolam reduces the neurotransmission in interneurons, leading to a decreasein the excitability of the spinal dorsal horn neurons through GABA mediated action. GABA is synthesised from the glutamate in the presynaptic nerve ending and is generally inhibitory in effect.

GABA on binding with the GABA receptor, opens ligand gated chloride channels causing increased chloride conductance which leads to hyperpolarisation and presynaptic inhibition of afferent terminals in the spinal cord. This results in less central propagation of action potential carrying nociceptive stimuli information.

Addition of 1-2 mg of preservative free midazolam as intrathecal adjuvant was reported to significantly prolong the duration of analgesia, be it in abdominal, orthopaedic surgeries or chronic pain[1].The earliest study using midazolam as spinal additive in obstetric patients was conducted by Valentine et al[5], in parturients undergoing elective cesarean section and reported a significant decrease in post- operative pain and analgesic requirement with midazolam. Prakash et al[1] conducted a prospective randomized controlled trial in 60 patients undergoing elective cesarean section and observed a significant difference in duration of analgesia when 2mg midazolam was added as adjuvant to bupivacaine in subarachnoid block. Tucker et al[3] investigated the use of intrathecal midazolam fentanyl combination for labour pain and reported that the addition of intrathecal midazolam increased the potency and duration of analgesia of intrathecal fentanyl for laboranlgesia without any maternal or fetal adverse effects.

In a prospective randomised study conducted by Sanwal et al[6] in parturients posted for elective cesarean section with varying doses of bupivacaine in combination with 2 mg of midazolam, found that 7.5 mg bupivacaine with 2mg of midazolam intrathecally is aoptimum dose combination which can result in significantly prolonged anlagesia and decreased incidence of hypotension without compromising on intraoperative surgical anaesthesia. Dodawad et al[7] also reported significant reduction in incidence of hypotension and prolongation of analgesia in Pregnancy Induced Hypertension patients posted for elective cesarean section.

In view of above considerations, our study was undertaken to evaluate the feasibility of using preservative free intrathecal midazolam as an adjuvant to bupivacaine in patients undergoing cesarean section allowing for decreasing the dose of intrathecal bupivacaine and thereby reducing the incidence of hypotension and prolonging the duration of effective analgesia through its spinally mediated analgesic effects. The primary objectives of our study were to compare duration of effective analgesia and incidence of hypotension between the groups. The secondary objectives were to compare other characteristics of sub-arachnoid block namely onset of sensory and motor blocks , duration of sensory and motor blocks and to compare other side effects namely bradycardia, nausea/vomiting, shivering, respiratory depression, Ramsay sedation score and newborn APGAR score. In our study, both the groups were comparable with respect to age, height and weight.

Duration of effective analgesia was taken as the time when NRS (Numerical Rating Scale) score is more than or eual to 4, when rescue analgesic was administered. It was significantly longer in the Bupivacaine- midazolam group. {5.64 ± 0.38 hours in BM group vs 3.89 ± 0.2 hours in B group}. This finding is consistent with the studies of Prakash et al[1] , Valentine et al[5] and Dodawad et al[7].

Table 6: Comparison with other studies with respect to our study

Duration of effective analgesia (hours)	Group B	Group BM	p-value*
Prakash et al[1]	3.8 ± 0.5	6.1 ± 1.0	< 0.001
Dodawad et al[7]	3.36 ± 0.03	5.96 ± 0.16	< 0.001
Present study	3.89 ± 0.2	5.64 ± 0.38	< 0.001
Incidence of hypotension			
Sanwal et al[6]	26.7%	6.7%	<0.05
Dodawad et al[7]	36.6%	6.6%	< 0.01
Present study	22%	6%	0.02

*p< 0.05- significant

In the study conducted by Prakash et al[1] the mean duration of post-operative analgesia determined by the request for the rescue analgesic was 3.8 ± 0.5 hours in group receiving 10 mg bupivacaine when compared to 4.3 ± 0.7 hours and 6.1 ± 1.0 hours in groups receiving 1 mg and 2 mg of preservative free intrathecal midazolam as intrathecal adjuvant respectively and so concluded that 2mg intrathecal midazolam provided moderate prolongation of post-operative analgesia in cesarean patients.

In the study conducted by Dodawad et al[7] with 2 mg preservative free midazolam as adjuvant to 10 mg of 0.5% hyperbaric bupivacaine in pregnanacy induced hypertension patients scheduled for elective cesarean section , post-operative analgesia was significantly longer in midazolam group (5.96 ± 0.16 hours) compared to the control group (3.36 ± 0.03 hours), consistent with the present study.

Other than caesarean patients , similar observations were also provided for patients undergoing other types of surgeries. Kim and Lee[8] reported that addition of 1mg or 2 mg of intrathecal midazolam prolonged the post-operative analgesic effect by approximately 2hours and 4.5 hours , respectively, compared to the controls after hemorrhoidectomy and used fewer analgesics in the first 24 hours after surgery.

In our study, hypotension was defined as the fall in SBP by more than 25% from the baseline. Incidence of hypotension was significantly lower in the low dose Bupivacaine- midazolam group. { 6% in BM group vs 22% in B group}. This is consistent with the studies by Sanwal et al[6] and Dodawad et al[7].

Sanwal et al[6] 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 hypotension. Varying doses of 0.5% hyperbaric bupivacaine (7.5 mg, 6 mg, 5 mg) were used in combination with 2mg midazolam in each group and compared with the control group receiving 11mg of bupivacaine and in their study, found that 7.5 mg bupivacaine with 2 mg midazolam as the optimum dose ratio combination with signifacantly lesser incidence of hypotension (6.7%) when compared to the control group (26.7%).

A similar observation was reported by Dodawad et al[7] in their study in pregnancy induced hypertension patients posted for elective cesarean section with significantly lesser incidence of hypotension (6.6%) in the group receiving 2 mg intrathecal midazolam as adjuvant compared to the control group (36.6%) receiving plain 0.5% hyperbaric bupivacaine 10 mg without the adjuvant.

The onset time for sensory block was taken as the time taken for the loss of pin prick sensation at T6 level and it was comparable in both groups { 2.06 ± 0.47 minutes in group B and 2.2 ± 0.64 minutes in group BM } , similar to the findings of Bharti et al[9] and Sanwal et al[6] whereas Vaswani et al[10] lreported a faster onset of sensory block with midazolam(2.26 ± 0.19 minutes vs 3.41 ± 0.41 minutes in control group).

In the study conducted by Sanwal et al[6] the onset times for sensory block taken as time taken for complete loss of pin prick sensation at T6 level, were comparable in the contol group receiving 11 mg 0.5%

H bupivacaine (onset time- 1.86 ± 0.41 minutes) and the group receiving 2 mg intrathecal midazolam plus 7.5 mg of 0.5% hyperbaric bupivacaine (onset time- 1.96 ± 0.31 minutes) consistent with the findings of our study.

Dodawad et al[7] reported a faster onset time for sensory block in patients receiving midazolam (1.10 ± 0.35 minutes) versus in the control group (2.96 ± 0.5 minutes) probably because in their study they used different dosage of bupivacaine that is10mg in the group receiving midazolam unlike our study which used reduced dosage of bupivacaine of 8 mg in combination with midazolam. Moreover in their study, they defined the onset time as time taken for the sensory block to reach T10 unlike our study where the onset time was taken as time taken for sensory block to reach T6. These differences in the study probably could have resulted in differing onset times for the sensory block with faster onset time with midazolam unlike our study and other studies[6,9] which did not find any significant difference in the onset times in both the groups. The onset time for motor block was taken as the time taken to achieve bromage motor score of 3 and it was comparable in both groups, {3.66 ± 0.66 minutes in group B and 3.78 ± 0.65 minutes in group BM }, similar to findings of Sanwal et al[6] who also did not report any significant difference in the onset times for motor block (2.40 ± 0.38 minutes in the midazolam group versus 2.26 ± 0.71 minutes in the control group receiving bupivacaine without the adjuvant).

The duration of sensory block was taken as the time taken for the sensory block to regress to T12 and it was significantly longer in midazolam group. { 3.54 ± 0.45 hours in group BM vs 2.37 ± 0.43 hours in group B }, consistent with the findings of Dodawad et al[7] who reported a signifacantly longer duration of sensory block (4.34 ± 0.37 hours) in the midazolam group versus the control group (2.85 ± 0.35 hours). The duration of motor block was taken as the time taken for the bromage score to become zero and it was comparable in both groups-{ 4.02 ± 0.46 hours in group B and 4.13 ± 0.37 hours in group BM }. This finding is consistent with the study of Shadangi et al[11] and Dodawad et al[7], whereas Bharti et al[9] reported a prolonged motor block in their midazolam group . The result in our study was in accordance with Muller et al[12], who reported an antispasticity effect of intrathecal midazolam with little effect on normal motor function.

The Ramsay sedation scores in the mother and the newborn APGAR scores were comparable in both groups which is consistent with the findings of previous studies[6,7]. The addition of intrathecal midazolam also decreased the incidence of side effects such as nausea/vomiting, similar to the findings of Prakash et al[1], Bharti et al [9] and unlike Shadangi et al[11] who did not find any significant difference in the incidence of side effects. It has been postulated that a possible mechanism for the antiemetic effect of benzodiazepines could be an action at chemoreceptor trigger zone, which reduce the synthesis, release and postsynaptic effect of dopamine. Other side effects such as bradycardia, shivering were comparable between the groups and there were no patients with respiratory depression in either of the groups.

Limitations

Some of the limitations of the study are - it is a single centre study - it is a non-blinded study leading to observer bias-Although pain is a multidimensional aspect, multidimensional pain rating scales have not been employed in our study. Rather single dimensional pain rating scale- NRS-Numerical Rating Scale –has been employed owing to its simplicity and ease of usage.

Conflict of Interest: Nil
Source of support:Nil

Conclusion

Duration of effective analgesia and duration of sensory block were significantly longer and Incidence of hypotension was significantly lesser in the Bupivacaine- Midazolam group. Both groups were comparable with respect to onset of sensory and motor blocks, duration of motor block, Ramsay sedation score and Newborn APGAR score. Incidence of nausea/ vomiting was significantly lesser in Group BM and both the groups were comparable with respect to other side effects of bradycardia, shivering and respiratory depression. Intrathecal midazolam as an adjuvant to Bupivacaine is safe and effective with advantages of prolonging effective analgesia and decreasing the incidence of hypotension. Thus adequate post-operative analgesia can be achieved with minimal side effects.

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