Research Article

Assessment of Effectiveness of Addition of Midazolam to Intrathecal Bupivacaine for Infra-Umbilical Surgeries in School-Age Children: A Randomised Controlled Trial

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ABSTRACT

Introduction: To increase the duration of spinal anaesthesia, many intrathecal adjuvants are used such as opioids, ketamine, clonidine and neostigmine. However, there are many drawbacks in their utility such as such as respiratory depression, cardiovascular instability, severe nausea and vomiting. Various studies have been conducted that have confirmed the effectiveness of intrathecal midazolam in post-operative analgesia in adults. But the data on efficacy and safety of intrathecal midazolam in children is limited.

Aims/ objective: To assess of effectiveness of addition of midazolam to intrathecal bupivacaine for infra-umbilical surgeries in school-age children and study the effect of adding intrathecal midazolam on quality and duration of anaesthesia and post-operative analgesia and sedation.

Materials and Method: After intrathecal administration of 0.5% hyperbaric bupivacaine, patients of control group were given 0.5 ml of normal saline intrathecally and patients of midazolam group were given 0.5 mg of midazolam via intrathecal route. Time to achieve sensory block, time to achieve motor block, effectiveness of post-operative analgesia using the observational pain–discomfort scale (OPS) and effectiveness of post-operative sedation using the modified Wilson Sedation Score (WSS) was recorded and compared.

Results: Time to reach sensory block and time to reach motor block was significantly lower in midazolam group ($p<0.05$). No significant difference was found between two groups with respect to duration of surgery, post-operative hospitalization, mean arterial blood pressure and heart rate. Significantly better postoperative analgesia and sedation was found in midazolam group with respect to OPS score, modified bromage score and modified WSS score.

Conclusion: Addition of Midazolam to intrathecal bupivacaine for infra-umbilical surgeries in school-age children was associated with better intra-operative and post-operative outcomes. Longer duration of spinal anaesthesia with better quality of sensory and motor block was achieved.

Keywords: Midazolam, Adjuvant, Spinal anaesthesia, Bupivacaine, Postoperative analgesia, sedation.

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INTRODUCTION

Most commonly used method of anaesthesia for infra-umbilical and lower limb surgeries is spinal anaesthesia.[1] Risk of general anaesthesia related complication and adverse effects is greater in Infants and children.[2,3] Thus, to avoid this complication, spinal anaesthesia can be an alternative to general anaesthesia in patients of chronic respiratory disease, or with respiratory tract abnormalities or in case of malignant hyperthermia.[4,5] Spinal anaesthesia in infants has low frequency of other negative outcomes during surgery such as low blood pressure, decreased oxygen saturation, bradycardia, and postoperative apnoea in comparison to general anaesthesia; [6,7] therefore, having advantage of better cardiovascular and respiratory stability.

An adjuvant is defined as the a drug acting synergistically with a local anaesthetic (LA) and leading to better quality and duration of the anaesthesia, postoperative analgesia, postoperative sedation and thus minimizing the chance of short duration of spinal anaesthesia in which is frequently seen in children.[8] Various clinical trials have been conducted on numerous adjuvants such as opioids, but many drawbacks have been documented such as opioid-related adverse effects.[9] To increase the duration of spinal anaesthesia, many intrathecal adjuvants are used such as opioids, ketamine, clonidine and neostigmine. However, there are many drawbacks in their utility such as such as pruritus, urinary problems, respiratory depression, cardiovascular instability, vision abnormalities, severe nausea and vomiting. [10-13]

Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter that has inhibitory effect on sensory and motor function of spinal cord. Drugs of benzodiazepine groups bind to α1–3- and α5-containing GABA receptors to exert their actions. Midazolam hydrochloride is one of shortest acting benzodiazepine derivative with an imidazole structure. [14] Midazolam is a commonly used drug and physicians are familiar to its sedative, hypnotic, amnestic, anxiolytic and anticonvulsant properties. [15]

Various studies have been conducted that have confirmed the effectiveness of intrathecal midazolam in post-

operative analgesia in adults. [16-18] But the data on efficacy and safety of intrathecal midazolam in children is limited. So, the present study was carried out to assess of effectiveness of addition of midazolam to intrathecal bupivacaine for infra-umbilical surgeries in school-age children and study the effect of adding intrathecal midazolam on quality and duration of anaesthesia and post-operative analgesia and sedation.

MATERIALS AND METHODS

The study design was a randomised controlled clinical trial, parallel design with 1:1 allocation. It was conducted from January 2022 to August 2022 after obtaining approval from the hospital ethics committee and informed consent, from the patients.

With anticipated observational pain–discomfort scale (OPS) score of 5.1 ± 015.in control group and 5 in midazolam group with the power of the study of 90% and confidence interval (CI) of 95% and α value of 0.05, minimum sample size was found to be 94. We enrolled 100 paediatric patients of both genders scheduled to undergo elective lower abdominal surgery.

Our Inclusion criteria for enrolment of study participants were patients with the American Society of Anaesthesiologists (ASA) physical status class I, age group between 3 to 12 years, body weight between 10 to 45 kg and those patients who were planned for infra-umbilical surgeries. The patients were excluded from the study if any contraindication to regional anaesthesia was found, a recent history of chronic use of analgesic medications was detected, any congenital anomalies of spine found during screening, any active skin infection in the back or if there was any history of hypersensitivity to the similar drugs under investigation.

After recruitment, all patients were screened before surgery in the pre-anaesthesia room. They were explained about the intervention and the risk factors associated. At the same time, baseline demographic data was obtained.

After enrolment, the study participants were randomly allocated to control and midazolam group of 50 each using web generated random numbers. Just after arrival of patient into the operation theatre, patients were evaluated for electrocardiography, heart rate (HR), Blood pressure, oxygen saturation (SpO2) and other critical parameters.

After pre-anaesthetic check-up, all patients were cannulated. Preload intravenous infusion of Ringer's lactate solution (10 ml/kg) and pre-anaesthetic medications such as intramuscular injection of atropine sulphate (0.01 mg/kg) or glycopyrrolate (4 µg/kg) according to availability was given. Then patients were sedated with ketamine hydrochloride with dose of 1 mg/kg to ensure their immobility during the lumbar puncture.

Spinal anaesthesia was given via midline approach with patients in left lateral position and their hips and knees flexed. To ensure asepsis, 0.5% chlorhexidine in alcohol was used to sterilise the skin of the back and then skin was covered with sterile drape. Lumbar puncture was done in between L4 and L5 with a standard 25 G or 27 G spinal needle and stylet. The direction of bevel was parallel to the longitudinal anatomy of Dural fibres. After checking a free flow of cerebrospinal fluid, 0.5% hyperbaric bupivacaine at dose of 0.4 mg/kg for children of weight between 5 to 15 kg and 0.3 mg/kg for children of weight greater than 15 kg was given to the patients of both groups. After this, patients of control group were given 0.5 ml of normal saline intrathecally and patients of midazolam group were given 0.5 mg of midazolam via intrathecal route.

A sterile dressing was applied just after removing the spinal needle and then patients were put on supine position. Baseline time was recorded just after giving spinal anaesthesia. Then, surgeries were carried out under spinal anaesthesia supplemented by sedation with intravenous propofol infusion at a infusion rate of 50–75 µg/kg/min which was adjusted with sensory and motor block assessment to maintain the patient in the state of moderate sedation. Spontaneous breathing of patients was ensured using oxygen supplementation with appropriate nasal cannula. Infusion rate of dextrose or normal saline was kept at a rate of 10 ml/kg/h. Monitoring of heart rate, respiratory rate, SpO2 and mean arterial blood pressure was being done throughout the entire anaesthetic procedure and the surgery.

Time to achieve sensory block was taken as the time taken from the baseline time that was the time of intrathecal injection of local anaesthetic to the time when sensory blockade at T10 level was achieved. Sensory block was checked by a skin pinch test. Time to achieve motor block was taken as the time taken from the baseline time that was the time of intrathecal injection of local anaesthetic to the time when patient was unable to move his/her ankle or toes. Motor power was evaluated using the modified Bromage scale.[19] In this method the voluntary movement of leg and feet as follows is given score 0 which means no motor loss, score 1 is given when patient is unable to flex the hip joint, score 2 is given when patient is unable to flex the knee joint also but is able flex the ankle and move his/her toes and score 3 is given when patient is unable to flex the ankle or move his/her toes.

Heart rate (HR) and mean arterial pressure (MAP) were recorded just before the confirmation of the spinal block taken as baseline, then after 15 minutes, after 30 minutes and lastly at the end of the operation. Post-operative (PO) assessment parameters were the effectiveness of post-operative analgesia evaluated by the observational pain–discomfort scale (OPS). [20] The OPS score give each of it's five variables that is 1) crying, 2) facial expression, 3) position of the torso, 4) position of the legs and 5) motor restlessness; a value of 1 if nothing observed, 2 if moderate and 3 if severe. So, the total score ranges from 5 to 15 and score of 5 denotes excellent analgesia and score of 15 denotes ineffective analgesia. If OPS score was found to be greater than 11 then rescue analgesia was given with

paracetamol at a dose of 15 mg/kg. The rescue analgesia was also given when any signs of pain was noted.

Duration of analgesia was taken as the time from the end of the surgery to the time when OPS was found to be greater than 11. The effectiveness of post-operative sedation was evaluated by the modified Wilson Sedation Score (WSS) at the time of 30 and 120 min after patient was shifted to recovery room. WSS scale gives score 4 when patient was in sleep and unable to arise by verbal command, score 3 if he is in sleep but can be aroused by verbal command, score 2 if patient was drowsy but not in sleep and score 1 if patient was alert. So, higher WSS score means better sedation.[21] Duration of hospital stay after surgery and any adverse drug reactions were also noted.

The primary end-point of our study was the effectiveness of post-operative analgesia that was evaluated using OPS score. The secondary end-point was determined as effectiveness of intraoperative spinal anaesthesia that was evaluated as time to reach T10 sensory block and time to reach Bromage score of 3 If patient failed to achieve spinal block then they were given general anaesthesia and were removed from statistical analysis.

Statistical Analysis

All data were presented in tabular form in Microsoft excel 365. Categorical data was presented in form of numbers (n) or percentage (%) and analysed using chi-square test. Continuous data were expressed in form of mean and standard deviation (SD) and compared using unpaired t test. Comparison of parameters within group was carried out using paired t test and repeated measure ANOVA. P-Value equal to or less than 0.05 was taken as a measure of significant difference.

RESULTS

One-hundred and twenty patients were taken up for evaluation; 20 patients were excluded from the study and remaining 100 patients were randomly and equally allocated to control group and midazolam group. Baseline demographic data and clinical parameters were comparable between two group with no statistically significant difference (P>0.05. [Table 1].

Table 1: Comparison of baseline demographic and clinical data between two study groups.

Parameters	Control Group (n=50)	Midazolam Group (n=50)	P- Value
Age in years (Mean ± SD)	8.1 ± 2.1	7.8 ± 1.9	0.4556 NS Unpaired t-test
Sex Male, n (%) Female, n (%)	 38 (76) 12 (24)	 36 (72) 14 (28)	0.6484 NS Chi-square test
Weight in kg (Mean ± SD)	23.9 ± 5.8	23.5 ± 5.3	0.7196 NS Unpaired t-test
Duration of Surgery in minutes (Mean ± SD)	74.3 ± 12.5	69.7 ± 13.4	0.0790 NS Unpaired t-test
Indication of Surgery			
Inguinal hernia	31	29	0.9675 NS Chi-square test
Cryptorchidism	8	9	
Bladder stone	5	6	
Round ligament stone	2	3	
Hypospadias	4	3	

S= Significant, NS = non-significant

Table 2: Comparison of Intra-operative parameters between two groups

Parameters	Control Group (n=50)	Midazolam Group (n=50)	P- Value
Duration of Surgery in minutes (Mean ± SD)	74.3 ± 12.5	69.7 ± 13.4	0.0790 NS Unpaired t-test
Number of patients requiring supplemental analgesic (%)	4 (8)	2 (4)	0.399703 NS Chi-square test
Time to reach **sensory block** in minutes (Mean ± SD)	3.5 ± 1.7	2.8 ± 1.3	**0.0228 S** Unpaired t-test
Time to reach score 3 on modified Bromage scale of **motor block** (Mean ± SD)	8.9 ± 2.1	8.1 ± 1.9	**0.0485 S** Unpaired t-test

MAP in mmHg (Mean ± SD)			
Baseline	64.3 ± 5.1	63.2 ± 4.9	0.2741 NS Unpaired t-test
15 minutes	63.9 ± 5.5	63.1 ± 4.7	0.4362 NS Unpaired t-test
30 minutes	63.5 ± 5.3	62.7 ± 3.9	0.3921 NS Unpaired t-test
End of Surgery	63.1 ± 4.8	62.3 ± 4.2	0.3773 NS Unpaired t-test
HR in beats per minutes (Mean ± SD)			
Baseline	113.6 ± 11.3	111.5 ± 10.9	0.3466 NS Unpaired t-test
15 minutes	109.7 ± 11.1	108.7 ± 10.3	0.6086 NS Unpaired t-test
30 minutes	110.2 ± 10.8	109.1 ± 9.8	0.5950 NS Unpaired t-test
End of Surgery	112.9 ± 11.6	111.2 ± 10.4	0.4422 NS Unpaired t-test

S= Significant, NS = non-significant

Table 3: Comparison of post-operative parameters between two groups

Parameters	Control Group (n=50)	Midazolam Group (n=50)	P- Value (Unpaired t-test)
Hospitalization after the surgery in Days (Mean ± SD)	10.1 ± 2.1	10.6 ± 1.8	0.2042 NS
Parameters on Sensory Block			
Total Duration of Sensory Block in minutes (Mean ± SD)	232.7 ± 65.6	256.7 ± 62.3	**0.0374 S**
OPS score after 30 minutes (Mean ± SD)	5.2 ± 0.1	5.1 ± 0.1	**<0.0001 S**
OPS score after 60 minutes (Mean ± SD)	5.9 ± 0.3	5.8 ± 0.2	0.0527 NS
OPS score after 120 minutes (Mean ± SD)	8.3 ± 0.9	6.9 ± 0.4	**<0.0001 S**
OPS score after 180 minutes (Mean ± SD)	10.6 ± 0.8	9.8 ± 0.7	**<0.0001 S**
OPS score after 300 minutes (Mean ± SD)	10.4 ± 0.9	10.1 ± 0.8	0.0812 NS
Parameters on motor block			
Total duration of motor block in minutes (Mean ± SD)	147.3 ± 26.4	161.6 ± 27.8	**0.0097 S**
Bromage score after 30 minutes (Mean ± SD)	3.0 ± 0.1	3.1 ± 0.1	**<0.0001 S**
Bromage score after 60 minutes (Mean ± SD)	2.2 ± 0.2	2.6 ± 0.3	**<0.0001 S**
Bromage score after 90 minutes (Mean ± SD)	1.1 ± 0.5	1.3 ± 0.4	**0.0295 S**
Bromage score after 120 minutes (Mean ± SD)	0 ± 0	0.4 ± 0.1	**<0.0001 S**
Bromage score after 150 minutes (Mean ± SD)	0 ± 0	0 ± 0	_
Post-operative sedation			
WSS score after 30 minutes	2.49 ± 1.1	2.92 ± 1.0	**0.0435 S**
WSS score after 120 minutes	1.21 ± 0.7	1.37 ± 0.6	**0.0383 S**

S= Significant, NS = non-significant

DISCUSSION

The result of this study on post-operative sensory block, motor block, post-operative sedation and analgesia confirms the effectiveness of intrathecal anaesthesia that was documented in earlier studies.[22,23] As documented in earlier studies, spinal anaesthesia was also found to be safe with no cardiovascular or respiratory negative outcomes in paediatric patients.[24]

Longer duration of post-operative analgesia was recorded from the patients of group midazolam group who were given midazolam as an adjuvant to bupivacaine as compared to patients of control group who were given bupivacaine only. The difference between two group was also statistically significant. There was also less consumption of post-operative analgesia in midazolam group. So, the result from our studies confirms the better efficacy of adding adjuvant to local anaesthetics in pain control under spinal anaesthesia. The better outcomes of adding other adjuvant to bupivacaine in spinal anaesthesia is also documented in previous studies. [25-27]

Only few studies have been conducted to evaluate efficacy and safety of adding midazolam in spinal anaesthesia in paediatric patients. Ahmed A. et al. demonstrated the effectiveness of midazolam as adjuvant in spinal anaesthesia and their result was similar to our studies. * But there is lack of enough studies that have assessed the safety of midazolam as an adjuvant in anaesthesia as neurotoxicity of midazolam is documented in some in vitro studies and its poor efficacy in nerve block. [28,29] However, some in vitro studies have also challenged this concern. Dittmar et al. assessed the extent of apoptosis in a vitro model of astrocyte-conditioned endothelial cells of human umbilical vein with western blot method and found that there was no significant effect midazolam on markers of apoptosis as compared to control. [30] In another study conducted by Ulbrich et al., the mitochondrial membrane potential of injured neuronal cells was checked after exposing them to different adjuvants of spinal anaesthesia and the result suggested that there was no role of midazolam could in protecting or aggravating injured neurons. [31]

This risk of neurotoxicity be midazolam has been challenged by some clinical trials in adults. In a literature review on different clinical trials of intrathecal midazolam in adults, findings similar to the result of our studies was documented. Similar findings have been documented in study conducted by Agrawal et al. who noted that combining bupivacaine with midazolam intrathecally has better outcomes on onset of sensory blockade and duration of postoperative analgesia with lower frequency of adverse neurological symptoms. [32] A study also compared intrathecal midazolam with fentanyl and found that there was longer duration of post-operative analgesia with midazolam but fentanyl was better in term of times to onset of anaesthesia. [33]

The better outcome of using midazolam to intrathecal bupivacaine in spinal anaesthesia with expect to quality of sensory and motor block, postoperative analgesia and sedation could be explained be the evidence of segmental analgesia mediated by binding of drugs of benzodiazepine groups to GABA receptor. The GABA receptor is located as a dense band within lamina II, specially in inner part of lamina II of the dorsal horn of spinal cord, and there is also high density of this receptor in laminae I and III.[34] Another explanation was given by Yilmaz-Rastoder et al. [35] who has attributed the longer duration of analgesia achieved after adding midazolam with bupivacaine to the action of midazolam on the compound action potentials from A- and C-fibres, as it had decreased wave amplitudes of both A- and C-fibres, but the action of midazolam on the C-wave was more potent.

Our study has certain limitations and small sample size was most important of them. The small sample size due to single centre design of the study. The study was limited to surgery of short durations and use of fixed dose of midazolam. Therefore, to generate more quality evidences, greater scale multicentre trials with a large sample size are necessary. Studies with different doses of midazolam on surgeries of longer duration should also be conducted to confirm or contradict the findings of our studies.

CONCLUSION

Addition of Midazolam to intrathecal bupivacaine for infra-umbilical surgeries in school-age children was associated with better intra-operative and post-operative outcomes. Longer duration of spinal anaesthesia with better quality of sensory and motor block was achieved with midazolam. Addition of Midazolam was also associated with longer duration of post-operative sedation and analgesia with no significant adverse effect. Studies with different doses of midazolam on surgeries of longer duration should be conducted to provide more evidences.

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