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A comparative study of caudal bupivacaine and bupivacaine with midazolam for post-operative analgesia in pediatric patients

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Abstract
Background: *Pain in children received even less interest than pain in adults and has been an essentially ignored dimension of care. Caudal extradural block is the most popular central neuraxial block in pediatric practice. It is used with general anesthesia for intra operative and post-operative analgesia in patients having procedures involving lower limbs, ano-perineal, genitourinary and abdominal surgery below the umbilicus. Most commonly employed group of drugs in caudal analgesia are local anesthetics and opioids. Other alternative agents to prolong the duration of caudal analgesia are Ketamine, Neostigmine and Midazolam*
Materials and Methods: *It was a prospective randomized control study in sixty children undergoing elective inguinal herniotomy, orchiopexy and circumcision after obtaining informed consent from parents. Patients were randomly allocated into two groups, of 30 each.*
Group I - patients received 0.25% preservative free bupivacaine in the dose of lml/kg, mixed with 50µg/kg of preservative free midazolam
Group II - patients received 0.25% preservative free bupivacaine in a dose of lml/kg.
The duration of post-operative analgesia was assessed
Results: *Patients who received midazolam for caudal block has extended post-operative analgesia when compared to those who received bupivacaine alone. The incidence of sedation was not significant in the study group.*
Conclusion: *The addition of midazolam with bupivacaine for caudal epidural block will prolong the duration of post-operative analgesia.*
Keywords: *Midazolam, Caudal epidural block, Post-operative analgesia.*

Introduction

Most feared symptom of a disease perhaps is the pain. Pain in children received even less interest than pain in adults and has been an essentially ignored dimension of care. However, over the past 15 years, attention has focused on this problem and major physiological shifts and technical advances have occurred in the management of pain in children.

In the past, infants and children used to be under treated, in the concept that they do not perceive pain or react to pain as adult do. Fears of respiratory depression, cardiovascular collapse, depressed level of consciousness, vomiting and

ultimately addiction were other reasons for withholding analgesia. Recently pain pathways have been identified in children and present belief is that children do perceive pain in as much the same way as adults do, both in physical and emotional aspects. Hence measures for the control of pain in children are currently receiving worldwide attention.

Caudal extra dural block is the most popular central neuraxial block in pediatric practice. It is used with general anesthesia for intra operative and post-operative analgesia in patients having procedures involving lower limbs, ano perineal, genitourinary and abdominal surgery below the umbilicus. It is safe, easy to perform, easily adaptable, gives reliable results and is acceptable to the Patients.

Most commonly employed group of drugs in caudal analgesia are local anesthetics and opioids. A single caudal injection with local anesthesia provides analgesia only to the duration of action of the local anesthetic. The addition of opioids to local anesthetic mixture prolongs the duration of caudal analgesia, but the possibility of resp. depression had limited the use of such mixtures. The commonest method to prolong the duration of caudal analgesia is to add adrenaline, but its effect tends to be modest. Other alternative agents to prolong the duration of caudal analgesiaare Ketamine, Neostigmine and Midazolam[1]. Midazolam exerts its analgesic effects by action on GABA receptors and has been shown to improve the duration and quality of analgesia provided by the caudal block[2].

Aim of Study

The study was designed to compare the duration of post-operative analgesia on addition of Midazolam 50g/kg with Bupivacaine 0.25%, and Bupivacaine 0.25% alone on caudal blockade in pediatric patients.

Materials and Methods

It was a prospective randomized control study in sixty children undergoing elective inguinal hemiotomy, orchiopexy and circumcision after obtaining informed consent from parents.

Inclusion Criteria

1. ASA physical status - 1
2. Age between 2-7 years
3. Weight between 10 - 20 kg

Exclusion Criteria

1. Age less than 2 years and more than 7 years
2. Co - existing systemic illness
3. Patients with known allergy to local anesthetics or benzodiazepines
4. Patients with sacral deformities or other congenital deformities
5. Patients with seizure disorder
6. Patients with heart disease
7. History of coagulopathy and bleeding
8. History of aspirin ingestion in the preceding week
9. Infection at the site of caudal administration

Plan of study

All subjects were examined thoroughly on the previous day. After explaining the procedure to the parents, informed consent was obtained.

Pre-operative Fasting

Milk and solids were restricted after midnight, but clear fluids were allowed up to*2* hours prior to induction.

Pre-Medication

Premedication was given with Triclofos sodium 75mg/kg and atropine 0.03mg/kg dose given only l-2hours before surgery. No opioid premedication was given.

The anesthesia machine was checked and working laryngoscope, appropriate size endotracheal tubes, oropharyngeal airway, and stylet were kept ready. The anesthetic breathing system used was Jackson Ree's modification of Ayre's T piece. All drugs were prepared before the patient was brought to the theatre.

Induction

On arrival in the operating room, anesthesia was induced with oxygen, nitrous oxide and halothane.

By the use of constant conversation and a 0.5% increase in inspired concentration of halothane every third to fourth breath; a smooth transition to general anesthesia was produced.

Continuous ECG and oxygen saturation monitoring was established. Blood pressure was monitored using a mercury sphygmomanometer with a Riva -

Rocci Cuff of approximate size. A precordial stethoscope was also attached. A 20/22/24 G intravenous cannula was inserted in the dorsum of the hand. Ringer's lactate infusion was set, and fluid administered according to calculated requirements as per Holiday Segar formula.

Anesthesia was maintained with 0.5-2% halothane and 66% N_20 in oxygen through a facemask with the patient on spontaneous ventilation during caudal block and surgery. Fresh gas flow was kept two to three times minute ventilation.

Caudal block

After induction of anesthesia and when all vital signs were stable, the child was gently placed in the lateral position, with the leg flexed at the hip and operative side down. Vitals were checked once again. Back was cleared using povidone iodine and spirit and draped. Caudal block was performed under strict aseptic precautions. A 23G scalp vein set was used for the block.

Sacral hiatus' was identified by running the thumb from the coccyx towards sacrum. A 23G scalp vein needle with its bevel facing anteriorly was inserted at an angle of 45° to the skin, in a sagittal plane in the midline. As the needle passes the sacral ligament, a distinctive 'give' will be felt. Needle is now in the caudal space. Advance the needle for l-2mm in a plane parallel to the spinal axis. Loss of resistance to injection of normal saline also elicited. Aspirate to rule out dural puncture or vein puncture. After negative aspiration the drug was administered at a rate of 0.2ml/sec in 3ml increments. Volume of dead space of the needle and tubing was replaced.

After the injection was complete, needle was removed, and the child was placed supine. A close watch was kept on the adequacy of the airway throughout the procedure. No analgesic was given by any route preoperatively *or* intra operatively. Anesthesia was maintained with 0.5-2% halothane and 66% N2O in oxygen through a facemask with the patient on spontaneous ventilation throughout surgery.

Drug and Dosage

Patients were randomly allocated into two groups, of 30 each.

Group I - Study group

Group II - Control group

Group I - patients received 0.25% preservative free bupivacaine in the dose of lml/kg, mixed with 50µg/kg of preservative free midazolam diluted to lml with normal saline.

Group II - patients received 0.25% preservative free bupivacaine in a dose of lml/kg; to which added lml of normal saline., Maximum volume injected was 20ml.

0.25% *preservative free* bupivacaine is available in the market. Preservative free midazolam is available as lml ampoule containing 5mg/ml of midazolam. This is diluted to 5ml using normal saline, so that lml contains lmg of midazolam. Then the required dose is taken with an insulin syringe (40divisions/ml); and diluted to lml and added to the local anesthetic solution.

Eg: If the patient weighs 13 kg, then he/she requires 650 µg of midazolam.

1 ml contains -1000 µg

1 division - $\frac{1000}{40}$ = 25 µg

For 650 µg, $\frac{650}{25}$ = 26 divisions of midazolam

This is then diluted to lml and added to the local anesthetic solution toget injected.

Monitoring

Monitoring includes continuous electrocardiography, oxygen saturation and precordial stethoscope. Arterial blood pressure was recorded every 5 minutes with a mercury sphygmomanometer and proper size pediatric cuff. Pulse rate and respiratory rate were also

continuously monitored. The time of caudal blockade and duration of surgery was noted.

Recovery

Anesthetic agents were discontinued at the completion of skin closure. 100% oxygen through facemask was administered for 3-5mintes. Once the vital signs were stable, the child was shifted to the recovery room and placed in semi prone position. The time from discontinuation of anesthetic to spontaneous eye opening was noted.

When the child maintained good color without oxygenation and external airway support/ and stable hemodynamics, they were transferred to post-operative ward.

Assessment

Assessment was done for a period of 12 hours after caudal block the observer was unaware of the mixture used for caudal injection.

The AIIMS pain discomfort scale was used for assessment of post-operative pain in these children. **Pain discomfort scale (AIIMS)**

Respiratory rate	+ 20%	Post-	0
	+ 20 - 50%		1
	> 50%		2
Heart rate	+ 10%	Pre-operative	0
	+ 20%		1
	+ 30%		2
Discomfort	Calm		0
	Restless		1
	Agitated		2
Cry	No cry or		
	Cry responding to water, food parental		0
	Cry responding to tender		1
	Cry not responding to tender		2
Pain at the site of operation	No pain		0
	Can state pain vaguely		1
	Can localize pain		2

The assessments were made at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, & 12 hours after caudal block.

Requirement of analgesia

Supplementary analgesia using oral paracetamol 15mg/kg was given to patients who had pain score equal or more than 4 at any time during the 24hours.

Side effects

1) Sedation: The time from discontinuation of anesthesia to spontaneous eye opening was noted.
2) Motor weakness: The duration of motor blockade was assessed by determining when the children began to move their legs.
3) Delay in micturition: The first time of micturition was noted.
4) Nausea & Vomiting - Frequency of nausea & vomiting was noted.

Any episode of hypotension or respiratory depression was also noted. Patients were discharged 24hour after the surgical procedure.

Results

Statistical interpretation

The data collected were entered in the master charts and statistical tables were prepared statistical constants like mean, median, range, standard deviation and percentages were computed for getting valid inference about the data. Statistical tests like students[1]!' test, chi square test, Mann Whitney U test were computed by using statistical package to see whether the difference in the means, the association between variables were statistically significant. Diagrams and chart were also drawn wherever necessary to give importance to salient findings.

Age

Table No: 1 Mean and Standard deviation of age and its level of significance

Group	N	Age in years		t value	P value
		Mean	S. D.		
I-Bupivacaine with Midazolam	30	4.43	1.478	0.528	0.599
II - Bupivacaine alone	30	4.23	1.455		
[t value > 2 and 'p' value < 0.05 is significant]					

From table- 1 it can be seen that mean age in group I was 4.43 years, whereas in group II it was 4.23. In order to find the equality of mean age, the student Y test was applied, and it was found not significant. Thus, it was established that both the groups were in identical age.

Weight

Table – 2 Mean and Standard deviation of weight and its significance

Group	n	Weight in kg.		t value	p value
		Mean	S. D.		
I	**30**	14.13	2.529	0.054	0.957
II	**30**	14.10	2.218		

While considering the weight of patients in each group, mean weight was computed as 14.13 in group I and 14.10 in group II. The difference in mean weight was not statistically significant when student 't' test was applied.

Sex

Table No: 3 Distribution according to sex

Group	Male		Female		Total
	No	%	No	%	
I	**14**	**47**	**16**	**53**	**30**
II	**21**	**70**	**9**	**30**	**30**

Duration of Surgery

Table No: 4 Mean and Standard deviation of duration of surgery and level of significance

Group	Duration of surgery in minutes		t value	p value
	Mean	S. D.		
I	24.77	4.576	0.81	0.936
II	24.87	5.002		

The mean duration of surgery was 24.77 in group I compared to 24.87 in group II. The difference in duration of surgery between the two groups was not statistically significant.

Sedation

Table no: 5 Mean and Standard deviation of time taken for spontaneous eye opening and its level of significance

Group	Time taken for spontaneous eye opening (in minutes)		t value	p value
	Mean	S. D.		
I	37.11	4.531	0.508	0.613
II	37.46	4.097		

The mean time taken for spontaneous eye opening after discontinuation of anesthesia was observed. In group I it was 37.11 minutes and in group II it was 37.46 minutes. The difference was not statistically significant.

The time taken for spontaneous movement of legs after caudal block was assessed.

Table No: 6 Mean and standard deviation of time taken for spontaneous movement of legs and its level of significance:

Group	Time taken for spontaneous leg movement (in minutes)		t value	p value
	Mean	S. D.		
I	88.00	3.851	0.469	0.641
II	88.50	4.385		

Group I patients took 88.00 minutes, whereas group II patients took 88.50 minutes. The difference noted in the meantime taken between the groups was not statistically significant.

Micturition

Table no: 7 Mean and standard deviation of item taken for micturition and its level of significance:

Group	Time taken for micturition (minutes)		t value	p value
	Mean	S. D.		
I	283.67	14.016	0.327	0.745
II	285.00	17.370		

The mean time taken for micturition after caudal block was 283.67 minutes in group I, compared to 285.00 minutes in group II. The difference between these groups was not statistically significant.

Table No: 8 Comparison of mean time of first analgesia in group I & group II

Group	n	Time taken in first analgesia (hrs.)			t value	p value
		Mean	S. D.			
I	30	**10**	**9.37**	3.01	4.07	<0.01
II	30	**6**	5.43	2.86		

The mean time taken for first analgesia in group I was 9.37 hours compared to 5.43 hours in group II. The difference in the time taken for analgesia between the two groups was statistically significant. Thus, the mean duration of action of bupivacaine -Midazolam mixture was significantly longer than bupivacaine alone.

Requirement of paracetamol in first 12 hours

Table No: 9

Group	PARACETAMOL				Total
	Required		Not required		
	No	%	No	%	
I	8	27	22	73	30
II	19	63	11	37	30
X^2 = 8.15 d.f= 1 p<0.01					

It was observed that out of 30 patients in group I, 8 required (27%) paracetamol for analgesia; but the corresponding figure was 19 (63%0 in group II. Thus, patients in group II had 2 times increased requirement of paracetamol than group I; and the association was found .to be highly significant.

Distribution according to the frequency of administration of paracetamol in first 12 hours:

While considering frequency of administration of paracetamol, in group I, all the 8 patients (27%) who required paracetamol were given only one dose.

In group II, 33% were given paracetamol once, 30% were given twice. Thus, group II received significantly more doses of paracetamol than group I in first 12 hours.

Table No: 10

No: of doses given	GROUP			
	I		II	
	No:	%	No:	%
0	22	73	11	37
1	8	27	10	33
2	-	-	9	30
3	-	-	-	-

Table no: 11 Pain scores and its level of significance Assessed by Mann - Whitney U test

Time of assessment	Pain scores				Mean Rank		Sum of ranks		Significance
	Range		Median						
(Hours)	I	II	I	II	I	II	I	II	
1	0	0	0	0	30	30	900	870	1
2	0	0	0	0	30	30	900	870	1
3	0	0	0	0	28.5	31.5	855	1090	1
4	0	0-2	0	2	21.15	39.85	634.50	1195.50	0.000
5	0	2-3	0	2	20.05	29.95	604.50	1156.50	0.000
6	0	0-4	0	2	18.85	31.15	680	1280	0.000
7	0	0-4	0	2	16.15	33.85	552	1238	0.000
8	0-2	0-4	0	4	15.72	45.28	471.50	1358.50	0.000
9	0-2	0-4	0	4	15.40	44.12	446.50	1323.50	0.000
10	0-4	0-4	2	4	25.50	34.50	928	1038	0.111
12	0-4	0-4	4	4	27.93	33.07	838	992	0.213

The AIIMS pain discomfort scale scores were assessed at hourly interval from first to 10thpost-operative hours and at 12 hours after caudal block. At 1, 2, 3, 4 and 5 hours, Group I patients had zero pain scores. In Group II pain score was zero at 1 & 2 hours, but scores ranged from 0 - 2 at 3rd and 0 - 3 at 4th hours.

In Group I, pain scores ranged from 0 - 2 at 6, 7, 8 and 9 hours, 0 - 4 at 10 + 12th hour.

The median pain score in Group I was zero up to 9 hours but 2 at 10th and 4 at 12th hour. In Group II, pain scores ranged from 0-4 from 5th hour onwards. The median pain score was 2 from 4th and 7th hour and 4 from 8, 9, 10 and 12th hour.

The difference in pain score became significant from 4th hour onwards and continued to be so till 10th hour. At 12 hours the difference in pain scores was not statistically significant.

Table No: 12 Incidence of Nausea and Vomiting

Group	N	Incidence of Nausea and Vomiting		
		No:	o/o	p value
I	30	3	10	0.640
II	30	2	6.6	

3 patients in group I & 2 patients in group II had nausea & vomiting, but the difference was statistically not significant.

Discussion

Post-operative pain delays ambulation and recovery. Inadequate treatment of pain in children can result in short- and long-term morbidity. So, the provision of post-operative analgesia is mandatory during the administration of any anesthetic.

In this study, caudal epidural block using bupivacaine with midazolam and bupivacaine alone was used for providing post-operative analgesia.

Only ASA physical status I patients undergoing inguinal herniotomy, orchiopexy, circumcision and urethroplasty were included in the study. The variations in the duration of surgery and anesthesia were not statistically significant in the study group and control group.

Since the spread of analgesic is unpredictable and failure rate is also high in children older than 7 years, children belonging to 2 - 7 years were included in the study. Other than the test drug, no other analgesics were administered either pre - operatively or intra operatively to prevent additive effect. Inhalational induction using oxygen, nitrous oxide and halothane was followed in all cases. All the caudal blocks were performed using the same technique and same type of needle.

Though several formulas have been demonstrated for calculation of dose of local anesthetic, the simple and satisfactory Armitage formula was used.

Assessment and quantification of post-operative pain has proved to be difficult in pediatric age group. Manifestations of pain in children are multivariate and include behavioral, cognitive and physiological methods. Since the study included small children, self-report measures like visual analogue scale could not be used for pain assessment.

The observation in Pain Behavior Rating

Scale (PBRS) and Children Hospital of Eastern Ontario Pain Scale (CHEOPS) HAVE an observer bias. The overlapping of scores for similar behaviors could give falsely high score. In objective pain scale also, there is an overlapping of behaviors such as movement, agitation, and posture which gives a falsely high score.

Crying has been attributed to pain only, whereas thirst, hunger and parental separation can be important cause of the same. The All India Institute of Medical Sciences (AIIMS) pain discomfort scale provides allowances for thirst, hunger and parental separation. It also avoids duplication of behaviors and includes physiological changes such as heart rate and respiration which can be measured without causing discomfort to the patient.

It has been validated against visual analogue scale in children upto 5 years. So, the AIIMS pain discomfort scale was used for pain assessment in this study.

Fauzia Bano, Saeeda Haider, S Tipu Sultan[3], in their study comparing duration of post-operative analgesia has concluded that after receiving 1 ml/Kgof 0.25% bupivacaine and midazolam (50jKj/Kg) patients were having significantly longer duration of analgesia (9.97 ± 2.25 hours) than that of bupivacaine alone (0.25%, 1 ml/Kg) (5.27+_1.08 hours.

There was no significant difference in heart rate, blood pressure and incidence of side effect in both groups and provided longer duration of post-operative analgesia.

Gulec S, Baijukkidan B Oral N et al[4] suggested that caudal administration of a bupivacaine - midazolam mixture produces a longer duration of post-operative analgesia (bupivacaine 0.25%/ 1 ml/kg ± 50(^g/Kg midazolam). (10.05 + 2.28 hours) compared to bupivacaine alone (bupivacaine 0.25% 1 ml/Kg) (5.58 +_1.86 hours). Therefore, no difference in the incidence of adverse effect or changes in vital parameters was observed.

M. Naguib, MelGammal et al[5], compared the analgesic efficacy of caudal administration of midazolam, bupivacaine, or a mixture of both drugs in 45 children, undergoing inguinal herniotomy. They concluded that there was no difference in the quality of pain relief post-operative behavior, or analgesic requirements between the midazolam group and the other two groups.

The time of first analgesic administration was longer in the bupivacaine midazolam group, than in other two groups; also, they received fewer doses of paracetamol.

This study confirmed the findings of previous workers that the addition of midazolam 50 jig/Kg to bupivacaine, prolonged the duration of caudal block, more than bupivacaine alone (0.25%, lml/Kg).

Significantly fewer doses of analgesics were required for the bupivacaine -midazolam group than bupivacaine group in first 12 hours.

There was no significant difference in post-operative sedation, between the groups, as shown by spontaneous eye opening.

The degree of motor blockade, and delay in micturition with midazolam supplementation of bupivacaine was not greater than when bupivacaine alone was used. This finding confirmed the result of previous studies.

There was no significant difference in the incidence of post-operative nausea and vomiting between the two groups.

Summary

Sixty children aged 2-7 years, schedules for elective below umbilical surgical procedures, belonging to ASA Class I were chosen. After obtaining informed consent, they were randomly allocated to two groups of thirty each.

Group I - Study group

Group II - Control group

Group I received 0.25% bupivacaine 1 ml/Kg with 50>g/Kg of midazolam caudally.

Group II received 0.25% bupivacaine lml/Kg caudally.

Post-operative pain was assessed using AIIMS pain discomfort scale, and oral paracetamol 15mg/Kg was administered if this score reached 4 or more. The mean duration of analgesia was 9.37 hours in Group I, compared to 5.43 hours in Group II ($p< 0.01$).

Subjects in group II required significantly more doses of analgesics than group II ($p < 0.05$). There was no difference between the groups in the incidence of motor block, delay in micturition, post-operative vomiting or post-operative sedation.

Conclusion

In conclusion, when midazolam 50µg/kg was added to 0.25% bupivacaine l ml/Kg for caudal block in children, the duration of analgesia was significantly longer, and requirement of post-operative analgesia was significantly less than that seen with 0.25% bupivacaine lml/kg caudally. There was no significant difference between the groups in the incidence of side effects.

Recommendation

From the study it is recommended that midazolam in a dose of 50µg/Kg is a safe adjuvant to caudally administered local anesthesia to prolong the duration of post-operative analgesia with a comfortable post-operative period.

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