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A Comparative Study Of Caudal Bupivacaine And Bupivacaine-Midazolam Mixture For Post-Operative Analgesia In Children Undergoing Genitourinary Surgery

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Abstract:
Introduction: Adequate pain control remains a major challenge after ambulatory surgery. Midazolam as adjunct to local anaesthetics in caudal epidural analgesia has been found effective with minimal adverse effects.

Objective: The study was carried out to evaluate the analgesic efficacy of caudal bupivacaine and midazolam in children undergoing genitourinary surgeryfor post operative analgesia and to study the side effects and complications of bupivacaine and midazolam.

Subjects and methods: Sixty children, aged2-12 were randomly selected from routine cases of pediatric genitourinary surgery in NSCB Medical college and Hospital, Jabalpur.Group B receive 0.25% bupivacaine 0.5ml/kg [n=30] and group BM receive combination of 0.25% bupivacaine 0.5ml/kg with 50 microgm/kg midazolam[n=30].Throughout the study period heart rate,arterial BP, respiratory rate were monitored. Postoperative pain was assessed by MODIFIED TODDLER PRESCHOOLER POST OPERATIVE PAIN SCALE [TPPPS].Rescue analgesia was given when pain score was 4 or more than 4. Sedation was evaluated by four point sedation score.

Results: Lowest pain score were observed in BM group. The mean duration of postoperative analgesia in group B was 7.6+1.5hrs and in group BM was 10.43+0.95 hrs' which was statistically significant[p<0.05]. There was no significant changes in HR,BP and respiratory rate in both groups. The incidence of nausea and vomiting were equal in both groups. No respiratory depression,motor paralysis or urinary retention in both groups during the period of study.

Conclusion- Caudal administration of bupivacaine , midazolam mixture prolongs postoperative analgesia compare to bupivacaine alone without causing any adverse effects and complications.

Key words; analgesia,bupivacaine,midazolam,TPPS.

Study Design: Observational Study.

1. INTRODUCTION

Pain is a perfect misery, the worst of all evils and when excessive, overturns all patience. Postoperative pain remains a major challenge despite remarkable advances in anaesthesia in recent years globally. Postoperative pain control is an essential need of any surgical,helps in quick return of the patient to normal routine life. Pain after surgery can delay discharge, lead to unanticipated hospital stay and increase cost. Caudal epidural analgesia remains one of the most commonly performed regional blocks in paediatric anaesthesia due to it safety,reliability, and ease of performance. However even when long acting local anaesthetics are used, short duration of effect is a drawback of single dose caudal analgesia.Addition of various adjuvants to local anaesthetics to prolong the duration of analgesia has been explored in recent years. While significant prolongation of analgesia was not achieved with epinephrine, opioids were found to prolong analgesia but their use may be marred by unpleasant side effects including nausea, vomiting, pruritis, urinary retention and delayed respiratory depression.Hallucination and potential for toxicity in the event of inadvertent intrathecal injection are limitations to the use of ketamine, and neostigmine is associated with nausea and vomiting though it prolongs duration of analgesia. These side effects have been reported to be either minimal or absent in children by some clinician. Midazolam with good anxiolytic, amnestic, sedative, hypnotic, anticonvulsant, and skeletal muscle relaxant properties has been demonstrated to possess analgesic property when deposited in the epidural space since its early trials in the 1980s. A dose of 50µg/kg co-administered with local anaesthetics has been shown to extend period of analgesia without substantial side effects. However, higher sedation score during the first postoperative hour has been reported. A recent work comparing intrathecal midazolam and low dose clonidine suggested that midazolam provides superior analgesia to clonidine in subarachnoid block with fewer adverse effects. Although, concerns with possibility of toxic effects of the epidural use of midazolam particularly in neonates continue to persist, available evidences so far suggest that a small diluted dose of less than 1mg/mL preservative-free intrathecal and epidural midazolam appears free of neurotoxicity. The use of caudal epidural midazolam has not been previously explored among children undergoing ambulatory surgery; this study was conducted to explore the analgesic benefits of caudal midazolam as an adjuvant to caudal bupivacaine in ambulatory paediatric groin procedures, and to study the recovery and side effect profile of the drug Adequate pain control after ambulatory surgery remains a major challenge. Midazolam as adjunct to local anaesthetics in caudal epidural analgesia has been found effective with minimal side effects. This study was carried out to evaluate its analgesic efficacy and recovery profile in children who underwent genitourinary surgeries.

2. MATERIAL AND METHOD

In the present study our aim was to evaluate the postoperative analgesia of caudal epidural bupivacaine and midazolam mixture. Ethical approval was obtained from the Hospital's

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Ethics and Research Committee, and informed consent was obtained from the parents/guardians of the children before recruitment into the study. 60 pts of either sex,ASA I AND ASA II aged 2-12yrs were randomly selected from the routine cases of pediatric genitourinary surgery in NSCB Medical College and Hospital Jabalpur.
Pre-anestheticexaminationwere done by anaesthesiologist to rule out any condition contraindicated to procedure. A thorough study was taken, base line parameter were recorded, informed consent was taken. Caudal epidural bupivacaine and midazolam was given according to their body weight.

Group B received Bupivacaine (0.25%) 0.5ml/kg.
Group BM received combination of Midazolam (50ug/kg) and Bupivacaine (0.25%) 0.5ml/kg.

Children with local infection of the caudal area,history of allergic reactions to local anaesthetics, bleeding disorders, pre existing neurological or spinal diseases, mental retardation and neuromuscular disorders were excluded from the studied.

3. PROCEDURE

To avoid any complication a patent vein was secured by IV drip and initial reading of PR,BP, and RR was taken. After pre medication with injection atropine 0.03mg/kg , Patients were induced with thiopentone4-5mg/kg and tracheal intubation was facilitated by using suxamethonium 1.5-2 mg/kg.Anaesthesia was maintained with Halothane 1-1.5%+ oxygen +nitrous oxide gas[40:60]+atracurium 0.1mg/kg. Patients were allocated randomly to receive one of two solutions.Then the patients were allowed to lie in right or left lateral decubitus position with the hip and knees flexed on abdomen and slight flexion of neck.After taking all aseptic precautions draping was done..With the use of 23 guage needle caudal epidural epidural procedure was done.Aspiration test for blood and CSF when found negative a test dose of selected drug or drugs were injected,and patient was watched for 5 mins to detect any untoward effects. The total requisite dose of the drug was injected then .No other preoperative analgesia was given. Anaesthesia was discontinued when the wound dressing had been applied. Residual neuromuscular block was antagonised with neostigmine 50microgm/kg given together with atropine 20microgm/kg and the patients were extubated before transfer to recovery room.When patient was awake in the recovery room, all vitals and pain score was recorded.

4. MONITORING

All the vital parameters [BP,RR,PR]was monitored after surgery at 30mins and every 60 mins for the next 12hrs.
Pain was assessed by Modified Toddler PreshcoolerPost Operative Pain SCALE [TPPPS]. A TPPPS score modified to give maximum score of 10 was used to assess pain over a 5min period every hour.

Table 01: Pain score[TPPPS]

Variable	**Score 0**	**Score 1**	**Score 2**
1. Verbal complaint / cry	None	Once only	> Once
2. Groan/ Moan/ Grunt	None	Once only	> Once
3. Facial expression	Neutral	Once grimace	Grimace > Once

4.	Restless motor behaviour	None	One episode	> One episode
5.	Rub – touch painful area	None	Once only	> Once

Rescue analgesia was given when pain score was 4 or more than 4. Oral paracetamol 15- 20 mg/kg body weight when pain score was 4 or more than 4. Sedation was evaluated by four point sedation score.
0 – eyes open spontaneously
1-eyes open to speech
2-eyes open when shaken
3- unarousable
Children were observed for development of any complications.

5. RESULT

The mean duration of postoperative analgesia in group B was 7.67+1.5hours, while in group BM was 10.43 + 0.95 hrs. The difference in the duration of analgesia between the groups was found to be statistically significant. In group B and group BM patients there was no significant difference during initial two hours of observation. From 3-7 hours. Group B showed higher pain score as compared to group BM and this was significant ($p<0.05$). There was no statistically difference in pain score between groups from 8-12 hours. ($p>0.05$) comparison between the two groups did not show statistically significant difference in complications or adverse effects. In both the groups the incidence of nausea and vomiting were equal. No incidence of respiratory depression, motor paralysis or urinary retention was seen during the period of study.

Table No. 2 Indication Of Caudal Epidural Block

The main indication of this block has been post operative pain relief in genitourinary operations. Table below shows the type of operation in which caudal block has been given.

S.NO.	**OPERATION**	**GROUP B**		**GROUP BM**	
		No.	**%**	**No.**	**%**
1.	Urethroplasty	10	33.33	13	43.33
2.	SuprapubicCystolithotomy	11	36.66	8	26.66
3.	Herniotomy	4	13.33	3	10
4.	Orchiopexy	4	13.33	6	20
5.	Vaginal Repair	1	1.33	-	-
	Total no. of cases	**30**		**30**	

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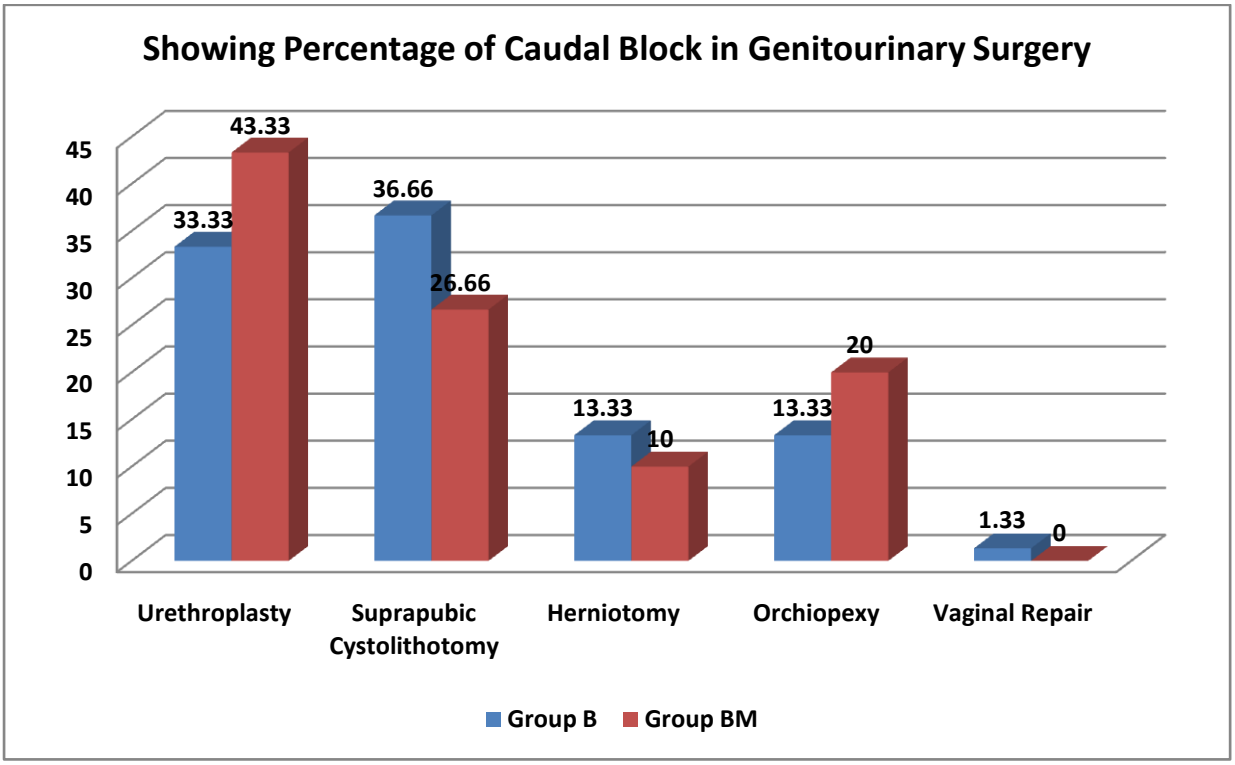

Table No. 3 Showing Sedation Score Of The Study

Time in hours	**Group B** **Mean sedation score**	**Group BM** **Mean sedation score**
imme. Post operative	0.29 ± 0.5	0.31 ± 0.47
30 min	0.3 ± 0.5	0.34 ± 0.48
1	0.2 ± 0.5	0.29 ± 0.49
2	0.2 ± 0.5	0.2 ± 0.4
3	0.2 ± 0.4	0.2 ± 0.38
4	0.2 ± 0.5	0.3 ± 0.52
5	0.2 ± 0.5	0.2 ± 0.4
6	0.2 ± 0.5	0.2 ± 0.5
7	0.2 ± 0.5	0.2 ± 0.4
8	0.2 ± 0.4	0.21 ± 0.48
9	0.2 ± 0.5	0.2 ± 1.41
10	0.24 ± 0.4	0.21 ± 0.35
11	0.2 ± 0.4	0.22 ± 0.5
12	0.2 ± 0.4	0.2 ± 0.5

The table above shows four point sedation score. There was no significant differences between the two groups in mean hourly sedation score. Fro group B the mean sedation was 0.21 ± 0.04 and for group BM it was 0.23 ± 0.68.

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Table No. 4 Pain Score

Time in hours	**Group B** **Mean sedation score**	**Group BM** **Mean sedation score**
imme. Post operative period after injection	0.66 ± 0.24	0.42 ± 0.22
30 min	0.63 ± 0.26	0.4 ± 0.28
1	0.7 ± 0.36	0.52 ± 0.34
2	0.8 ± 0.4	0.58 ± 0.36
3	1.23 ± 0.82 **	0.60 ± 0.36
4	1.66 ± 0.87 **	0.64 ± 0.42 *
5	1.92 ± 0.76 **-	0.71 ± 0.63*
6	1.98 ± 0.67 **	0.86 ± 0.92*
7	2.03 ± 0.82**	1.60 ± 0.88*
8	2.08 ± 0.61 **	1.92 ±0.77 **
9	2.19 ± 0.78 **	1.98 ± 0.81**
10	2.30 ± 0.92**	2.08 ± 0.91 **
11	2.39 ± 0.82 **	2.11 ± 0.51 **
12	2.46 ± 0.62 **	2.16 ± 0.15**

** P<0.05 (Significant), ** P<0.01 (Highly Significant)*

The table shows patients in both the groups showed a significant difference in pain score (Modified TPPPS) as measured during the study period. In group B patients who received bupivacaine, high degree of pain relief was achieved at 30 minutes (0.63 ± 0.26) postoperatively following which pain score gradually increased. At 3 hrs.pain scores showed a highly significant increase and peak level of 2.46 ± 0.62 at 12 hrs. This increased pain score from 3 to 12 hrs. Was highly significant (P<0.01). Groups BM patients had lower pain score ranging from 0.42 ± 0.22 to 0.60 ± 0.36 up to 3 hours Postoperatively. After this score increased to a significant level (P<0.05) at 4 hrs to 7 hrs (1.60 ± 0.88). During rest of period of observation further increased in pain score was highly significant in group BM patients. (P<0.01).

In group B and group BM patients there was no significant difference during intial 2hrs. of observation. From 3 to 7 hrs Group B showed higher pain score as compared to Group BM and this was significant (P<0.05.).

There was no statistically differences in pain score between groups from 8 to 12 hrs. (P>0.05)

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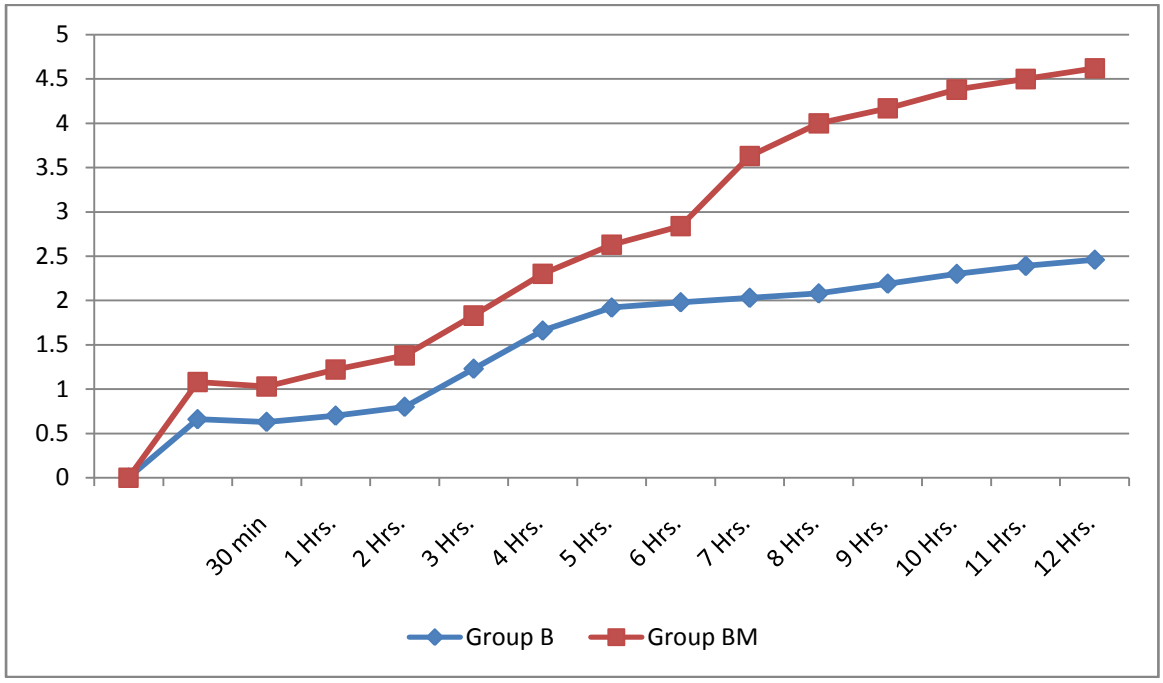

Table No. 5 Mean Duration Of Analgesia

Group	**No. Of Cases**	**Mean Duration of Anallgesia (Hrs.)**
B	30	7.67 ± 1.5
BM	30	10.43 ± 0.95

This table shows mean duration of analgesia in two groups. In group B it was 7.67 ± 1.5 and in group BM it was 10.43 ± 0.95. There was statistically significant differences between the two groups (P<0.05)

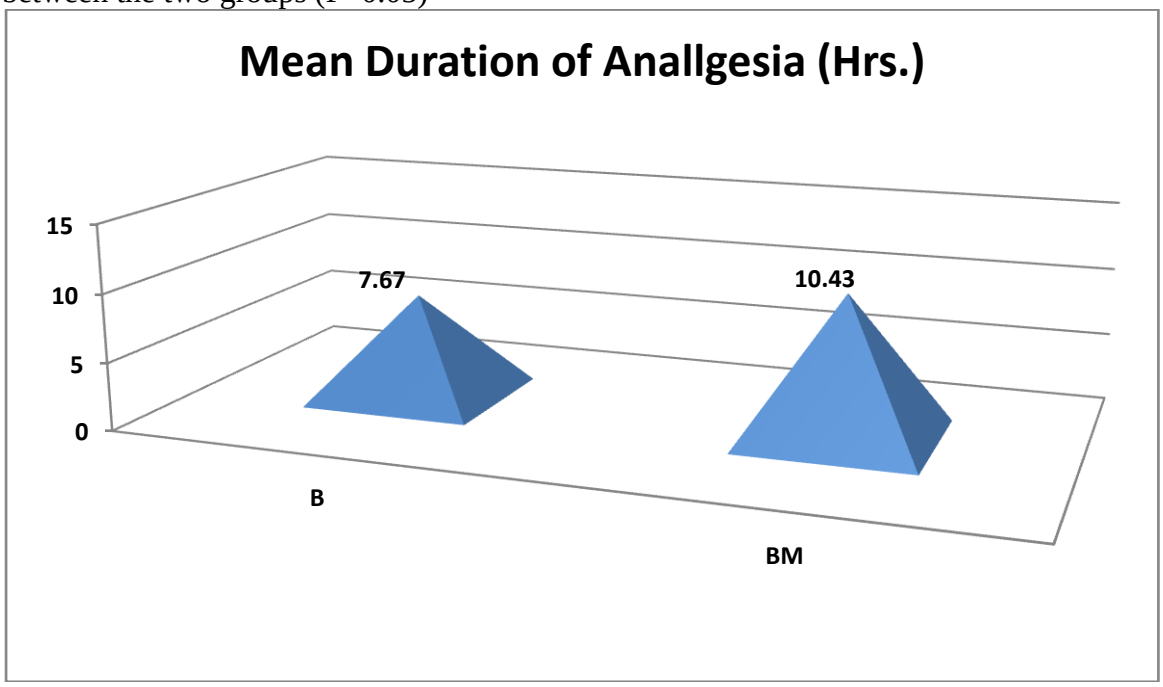

Table No. 6 Complications

S.NO.	COMPLICATION	GROUP B		GROUP BM	
		No.	%	No.	%
1.	Nausea and Vomiting	3	10	3	10
2.	Respiratory depression	-	-	-	-
3.	Convulsion	-	-	-	-
4.	Pain at puncture site	2	6.66	1	3.33
5.	Motor paralysis	-	-	-	-
6.	Urinary retention	-	-	-	-

Comparison between the two groups did not show statistically significant difference in complications or adverse effects. In group B and group BM the incidence of nausea and vomiting were equal. No incidence of respiratory depression, motor paralysis or urinary retention was seen during the rest of period of study.

6. DISCUSSION

Sixty children, aged 2-12 were randomly selected from routine cases of pediatric genitourinary surgery in NSCB Medical college and Hospital, Jabalpur.

The study conducted by Mahajan R, et al[1] 2001 with the 0.25%, 0.5ml/kg bupivacaine and 50 □ g/kg midazolam in a paediatric patients for genitourinary surgery, when given caudalepidurally. The mean duration of analgesia in bupivacaine group was 7.4 ± 2.1 hrs and in group bupivacaine- midazolam it was 11 ± 0.5 hrs. They given caudal epidural block just after the intubation but in our study the caudal block was gien just after the end of surgery. The doses were similar to that of our study but duration of analgesia in both groups were little higher than that of our study groups.

Many studies have postulated a synergistic analgesic effect of local anaesthetic agents and opioids when given by centroneuroaxialroute.

There is much of objective evidence to quantitate such an effect to explain mechnism of synergy. Tejwaniet al[2] have found in study on rats that bupivacaine potentiated the antinociception by intrathecal administration of 10 □ g/kg of morphine. At higher doses of morphine (20 □ g/kg), bupivacane decrease the total duration of morphine induced antinociception, They also noted that binding of opiods ligands to spinal receptors who was inhibited at high doses of bupivacaine. Therefore extent of interaction between these two drugs depend upon their relative concentration at the site of action. Lower pain score in group BM patients who received combination of bupivacaine and midazolam as compared to bupivacaine due to synergistic effect of combination of midazolam and bupivacaine.

However, in study on children, Naguibet al[3] has fail to demonstrate such synergistic action of combination of midazolam 50 □ g/kg and bupivacaine (0.25%) 1ml/kg. In our study we used midazolam in same doses of 50 □ g/kg but bupivacaine was used in the lower dose of bupivacaine along with midazolam 50 micro/kg by caudal route to have an optimal synergistic effect.

Till date there is no clinical data regarding the onset of action of midazolam when administered by causal or epidural route. Bupivacaine is effective with in 15-20 minutes of administration by caudal route

Higher concentration of bupivacaine more than 0.25 percent do not offer any analgesic advantage over 0.25 percent bupivacaine when giving alone (Wolf AR 1988)[4].

Addition of ketamine (Naguib M)[3] have been found to improve reliability and duration of analgesia. In the benzodiazepine group, only midazolam has been administered by centroneuraxial route and there are stiduessupposting its analgesic effect (Nishiyama T et al[5],

Serra O JM[6]). In our study it was observed the quality of analgesia was comparatively omproved in patients who received bupivacaine and midazolam than bupivacaine alone. This is supported by observation of lower pain score recorded during 12 hrs postoperative period in group BM. The finding of out study was similar with Mahajan R et al[1].

Various animal studies have shown to absence of deleterious efffects on spinal function or morphological features after subarachnoid midazolam . Moreover safety of neuroaxial administration of midazolam in humans has been demonstrarted by several investigators (Serra O JM[6], Rigoli M[7]).

Various families of spinal receptors which modulate the processing of nociceptive stimul, among these are GABA receptors. The receptor for Benzodiazepine is a GABA receptor chloride ion channel complex (Serra O JM[8])GABA has been long been implicated in spinal cord antinociceptive mechanism. (Niv D et al, WhitWam et al)[9]

Binding sites for benzodiazepines have been demonstrated in the spinal cord and endogenous benzodiazepine like substances have been discovered in the human CSF. The highest density of bindings sides was found with in the lamina II of the dorsal horn, a region which plays a prominent role in the processing of nociceptive information. GABA receptors on primary afferent terminals in dorsal horn mediate the presynaptic inhibition. GABA produces mild depolarization of these primary afferents, thereby decreasing the release of excitatory transmitters on to the second order neurons in the spinal cord and brain stem (Hafely et al 1998)[11]. Besides this midazolam has also been shown to inhibit reuptake of GABA from synaptosomes within the brain (Cheng SC 1981)[10].

The results of our study hereby confirm and support previous study that extradural administration of midazolam exerts modulatory influences on the postoperative pain mechanism.

Addition of Midazolam 50 □ g/kg to 0.25% bupivacaine improved analgesia as compared to bupivacaine alone without an increase in the incidence of side effects.

Most of the patients in our study was operated for uretheral repair. They were catheterized so the urinary retention could not assessed. In the rest of patients none developed urinary retention.

In a study,it was noted thatnegligible urinary disorder after caudal block. They attributed this prolonged postoperative analgesia provided by caudal block without motor paralysis. Our findings are consistent with those of Mahajan R (2001)[1].

Nausea and Comiting occurred in 3 cases in both groups. This did not cause distress to the patients and no treatment was given. No patient in any group comprised of respiratory depression, motor paralysis, numbness or convulsions. All these complications are also described by Naguib M (1995)[3],,Mahajan R (2001)[1].

Three patients one in group B two in group BM complained of pain at the site of caudal block post operatively the pain was mild in nature and occurred in patients in whom manipulation was done to locate the sacral canal. The pain disappeared after 1-2 days.

7. CONCLUSION

This study reveals that addition of midazolam to caudal bupivacaine provide longer duration of analgesia and reduced requirement for supplemental analgesia among children undergoing Genitourinarysurgeries. There was no significant adverse effect and complications observed with its use in the setting of this study when compared with bupivacaine alone.

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