Section: Anesthesiology

Original Research Article

A PROSPECTIVE, RANDOMIZED CONTROL STUDY COMPARING CAUDAL BLOCK USING BUPIVACAINE WITH BUPIVACAINE AND MIDAZOLAM FOR POST OPERATIVE ANALGESIA IN CHILDREN UNDERGOING ELECTIVE LOWER ABDOMINAL SURGERIES

Revathi Thulasiraman[1], Rajasekar Arumugam[2], Deepa Gopal[3]

[1,3]Assistant Professor, Department of Anesthesiology, Government Vellore Medical College, Vellore, Tamilnadu, India.
[1]Consultant Intensivist, Naruvi Hospital, Vellore, Tamilnadu, India.

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Corresponding Author:
Dr.Revathi Thulasiraman,
Assistant Professor, Department of Anesthesiology, Government Vellore Medical College, Vellore, Tamilnadu, India.
Email: revst06@gmail.com

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ABSTRACT

Background: Post-operative discomfort secondary to pain can be extremely annoying for both child and their parents, necessitating the excessive use of opioids and NSAIDS which carries numerous undesirable effects. Addition of an adjuvant like midazolam to bupivacaine injected into the caudal space could prolong post-operative analgesia with minimal side effects. The purpose of this study is to compare the efficacy and safety of combination of preservative free midazolam (50 microgram per kg) with 0.25 % bupivacaine vs plain 0.25% bupivacaine into the caudal epidural space for providing postoperative pain relief in children undergoing elective lower abdominal surgeries.

Materials and Methods: This is a prospective randomized case control study carried out on 60 children between 2 to 8years of age belonging to American society of anaesthesiologist (ASA)Grade I and II undergoing lower abdominal surgeries under standardized general anaesthesia. Children recruited in the study were randomly allocated into two groups namely, GROUP-B and Group-BM. Children in Froup B received caudal block with 1 ml per kg of plain 0.25% heavy bupivacaine, while those recruited to Group BM received caudal block with 1 ml per kg of 0.25% heavy bupivacaine with 50 microgram per kg of preservative free midazolam. All children were continuously observed in recovery room for two hours after which they are shifted to recovery room. Afterward, the FLACC pain score, Ramsay sedation score and vitals were recorded at regular intervals for up to 24 hours post-surgery.

Results: In the immediate postoperative period, the FLACC pain scores in both the groups were initially comparable for first one-hour, Thereafter, children belonging to Group BM had experienced lower pain scores compared to those in Group B. The mean duration of post-operative analgesia in group BM was 12.49 ± 1.19 hours compared to 5.11 ± 0.50 hours for group B which was statistically significant with a p value < 0.05. Furthermore, the Ramsay sedation scores were higher in the Group BM for initial one hour compared to group B without any appreciable difference in adverse effects. Also, there were no significant difference in the hemodynamic parameters in both the groups.

Conclusion: To conclude, administration of preservative free midazolam with bupivacaine for caudal epidural block increases the duration of post-operative analgesia without any associate adverse effects compared with plain bupivacaine. Thus, low dose preservative free midazolam can safely be administered as an adjuvant with bupivacaine in the caudal epidural space for prolonging analgesic effects in the postoperative period.

Keywords: Bupivacaine, Midazolam, caudal analgesia

INTRODUCTION

The term 'PAIN' meaning penalty is derived from the term 'poena' which is defined as an "unpleasant emotional or sensory experience with associated potential or actual tissue damage".[1-4]It is a proven fact, that regardless of age, neonates, infants, children, even a preterm child could perceive pain often associated with significant stress response to the painful stimuli.

PAIN PATHWAY

The noxious stimulus induces a local inflammatory response in the periphery i.e. sensitization of nociceptors and primary hyperalgesia. The noxious input is then conducted to the central nervous system via the 'A' delta and 'C' nerve fibres that initiates a sequence of events i.e. reflex withdrawal from stimulus, aversive behavior and pain perception. With sustained noxious stimuli, input from 'C' fibres produces central sensitization which alters sensory processing in spinal cord (neuroplasticity) resulting in allodynia and hyperalgesia at the site of injury. [5-9]

PAIN ASSESSMENT IN CHILDREN

Objective evaluation of pain in children poses enormous difficulty, especially in neonates and infants. Thus, in order to measure the intensity of pain, a vast range of physiological and behavioral responses, cognitive abilities, and psychological assessment are characterized under two broad categories as described below,

Self-report measures

- VAS - Visual Analog Scale
- FACES pain rating Scale
- Manchester pain Scale.

Observational behavioral measures

- FLACC- Faces, Legs, Activity, Cry and Consolability
- CHEOPS- Childrens Hospital of Eastern Ontario pain scale
- CRIES- Crying Requires increased oxygen administration Increased vital signs Expression Sleeplessness
- COMFORT
- Objective pain score

FLACC behavioral pain score: total score 0_10

Criteria	Score 0	Score 1	Score 2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, uninterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth tense	Arched, rigid or jerking
Consolability	Content relaxed	Reassured by occasional touching, hugging or being talked to distractible	Difficult to console or comfort

Postoperative assessment of sedation in children

Post op sedation was assessed using Ramsay sedation score as follows:

Score 1: Anxious, agitated or both
Score 2: Cooperative oriented, tranquil
Score 3: Response to commands onl
Score 4: Brisk response to loud auditory stimulus
Score 5: Sluggish response to loud auditory stimulus
Score 16 No response to loud auditory stimulus

Objective

The purpose of our study is to compare the efficacy and safety of caudal epidural administration of midazolam 50microgram/kg with 0.25% bupivacaine vs 0.25% plain bupivacaine in providing postoperative pain relief in children undergoing elective lower abdominal surgeries.

MATERIAL AND METHODS

The study was conducted after obtaining approval from the institutional ethical committee study. Children satisfying the inclusion criteria as mentioned below were subjected to single blinded prospective randomized trial with a written informed consent from parents or guardian.

Eligibility Criteria

Children aging between 2 and 8years, belonging to ASA grade I and II, undergoing elective minor lower abdominal daycare surgery with an anticipated duration of less than 90min were. While those with signs of infection at the site of caudal block, those with suspected coagulopathies or known liver disease or uncontrolled systemic disorder, child with developmental delay or any neurological disease, presence of any skeletal

deformities or known to be allergic to the study drugs were excluded from the study.

CONDUCTION OF THE STUDY

The study was performed in the department of Anesthesia, Institute of child Health and Hospital for children between August and September of 2014. We compared the effect of addition of preservative free midazolam as an adjuvant to caudal bupivacaine with that of plain bupivacaine with regard to duration of postoperative analgesia and the effects on hemodynamic, neurological and respiratory parameters in sixty children between the age group 2 to 8 years scheduled for elective minor lower abdominal and genitourinary daycare surgeries under general anaesthesia were randomly divided into two groups namely Group B (Bupivacaine) and Group BM (Bupivacaine with midazolam).

Standard protocol was followed in provision of general anaesthesia to the study participant. Preoperative fasting protocols were strictly adhered without any premedication. On arrival to the operative theatre, standard ASA monitors such as electrocardiography, non-invasive blood pressure, pulse oximeter, nasopharyngeal temperature and precordial stethoscope monitoring were connected. An intravenous access was secured with 22G or 24G IV cannula into the vein on the dorsum of hand after applying EMLA cream. Induction of anaesthesia was carried out using propofol 3mg/kg and ketamine 0.5mg/kg, and appropriate size classic laryngeal mask airway and anaesthesia was maintained with a inhalation mixture of 50%Nitrous oxide and 50%02 with 1 to 2 minimum alveolar concentration of sevoflurane and allowed to breath spontaneously using Jackson Rees modification of Ayre's T piece circuit. After ensuring adequate plane of anaesthesia, the child was turned to left lateral position, and children allocated to Group BM received caudal epidural block with 1ml per kg of 0.25% bupivacaine with 50microgram/kg of midazolam. While, children in Group B received caudal epidural block with 1ml per kg of 0.25% plain bupivacaine using 23Gneedle.

Intraoperatively, heart rate, blood pressure, respiratory rate, oxygen saturation and temperature were recorded regularly at 5minutes intervals. Caudal block failure was considered if the heart rate or mean arterial pressure rose above 20% of pre-incision values ad rescued with intravenous fentanyl 1mcg/kg was administered for pain relief. After the completion of the procedure, the child was observed in the recovery room for 2 hours before getting shifted to ward.

The severity of pain and the level of sedation were assessed by using FLACC pain score and Ramsay Sedation score respectively. In addition, the heart rate, blood pressure, respiratory rate, SPo2 and presence of any adverse effects were also documented. Postoperative pain was managed using intravenous paracetamol 15mg/kg, if the pain score is 4 or above. Oral liquid feeds were allowed 2 hours after the procedure. All these children prior to discharge were examined for clinical evaluation of neurological system.

RESULTS

Statistical Analysis

All statistical analysis was carried out using SPSS on windows version 20.0 and the results are expressed as mean and standard deviation. Student's t-test was applied for analyzing the parametric data like age, weight, heart rate, blood pressure, while non-parametric data such as type of surgery, post-operative complications were analyzed using chi-square test and fisher's exact test and a p value of <0.05 was considered as statistically significant.

Both the groups showed even distribution of samples in terms of age, sex, weight, type and duration of surgery without any considerable statistical difference between the groups and the details are presented in Table 1 to 5.The mean duration of analgesia in group B was 306.7+/30.4 minutes and in group BM was 749.6+/71.8 which was statistically significant with a p value of 0.000 as shown in Table 6. Those who received midazolam in caudal epidural space had an effective analgesia up to 8 hours in the postoperative period as indicated by the FLACC score of less than 4, while those who received plain bupivacaine had analgesia just for 4 hours, the findings are presented in Table 7.This table shows the frequency distribution of FLACC score among the two groups over the period of 16 hours measured every two hours. Out of the sixty patients, thirty patients had experienced a score of zero in group BM in the 4th hour compared to zero patients in group B (Table 8).The FLACC Score was comparable between the two groups for the first two hours that was statistically insignificant with a p value of 0.321, whereas the FLACC score at 4th and 6th hour was lower in the midazolam group as opposed to bupivacaine group. FLACC score of 4 was attained only at the 12th hour and sixth hour in group BM and group B respectively.

The sedation score as assessed by Ramsay sedation score was significantly higher inmidazolam group in the first one hour, following which, there was no statistical difference between the two groups [Table 9]. With regard to hemodynamic parameters such as systolic, diastolic and mean arterial pressure showed no significant difference. The incidence of respiratory depression was similar in both groups and postoperative nausea and vomiting occurred only in one patient in the control group.

Table 1: Demographic Profile: Age

Group	N	Mean	Std. Deviation	P value
Group B	30	3.817	1.6634	0.321
Group BM	30	3.367	1.8144	

Table 2: Demographic Profile: Sex

Sex	Group B		Group BM		P value
	No	%	No	%	
Male	28	93.3%	26	86.7%	0.389
Female	2	6.7%	4	13.3%	

Table 3: Demographic Profile: Weight

Group	N	Mean	Std. Deviation	P value
Group B	30	13.97	2.798	0.533
Group BM	30	13.47	3.35	

Table 4: Comparison of Type of Surgery

Surgery	Group B		Group BM		P value
	No	%	No	%	
Circumcision	17	56.7%	15	50.0%	0.226
Herniotomy	12	40.0%	10	33.3%	
PV sac ligation	1	3.3%	5	16.7%	

Table 5: Duration of Surgery

Duration of Surgery	Group B		Group BM		P value
	No	In min	No	In min	
Circumcision	17	435	15	390	0.266
Herniotomy	12	360	10	315	
PV sac ligation	1	25	5	150	

Table 6: Duration of Analgesia

Group	N	Mean	Std. Deviation	P value
Group B	30	306.7	30.466	0.000
Group BM	30	749.6	71.809	

Table 7: FLACC Score of the two Groups

			Group B		Group BM		P value
Time	N		Mean	StdDeviation	Mean	StdDeviation	
0 hour	30	30	0.00	0.00	0.00	0.00	-
2nd hour	30	30	0.07	0.37	0.00	0.00	0.321
4th hour	24	30	2.63	0.02	0.00	0.00	0.000
6th hour	0	30	4.00	0.00	0.83	0.53	0.000
8th hour	0	30	-	-	1.70	0.47	-
10th hour	0	28	-	-	2.18	0.39	-
12th hour	0	30	-	-	2.93	0.69	-
14th hour	0	24	-	-	3.63	0.50	-
16th hour	0	9	-	-	4.00	0.00	-

Table 8: FLACC Score of Frequency Distribution

FLACC score hours	Zero		One		Two		Three		Four		Total	
	B	BM	B	BM	B	BM	B	BM	B	BM	B	BM
0 hour	30	30	-	-	-	-	-	-	-	-	30	30
2nd hour	29	30	-	-	1	-	-	-	-	-	30	30
4th hour	-	30	4	-	9	-	11	-	6	-	30	30
6th hour	-	7	0	21	0	2	-	-	24	-	24	30
8th hour	-	-	-	9		21	-	-	-	-	0	30
10th hour	-	-	-	-	-	23	-	5	-	-	0	28
12th hour	-	-	-	-	-	8	-	16	-	6	0	30
14th hour	-	-	-	-	-	-	-	9	-	15	0	24
16th hour	-	-	-	-	-	-	-	-	-	9	0	9

Table 9: The Ramsay Sedation Score of the Two Groups

Hours	N		Group B	Group BM	P value
30 min	30	30	3	5.149	0.000
60 min	30	30	3.205	4.216	0.000
90 min	30	30	2.846	3.205	0.07

2nd hr	30	30	2.284	2.405	0.156
3rd hr	20	30	1.96	2.153	0.243
4th hr	8	30	2.035	2.209	0.09
5th hr	3	30	1.907	1.476	0.373
6th hr	1	30	1	1	0.256

Table 10: Comparison of Intra-Operative Heart rate between the Two groups

Minutes	N	Group B	Group BM	P value
Baseline	30	111.449	115.389	0.262
After Induction	30	106.542	108.903	0.969
5 min	30	110.062	114.661	0.813
10 min	30	102.186	106.768	0.325
15 min	30	100.574	103.463	0.551
20 min	30	99.511	103.365	0.657
25 min	30	99.028	103.976	0.609
30 min	30	96.539	100.878	0.148
35 min	30	97.464	99.359	0.771

Table 11: Comparison of Post-Operative Heart rate between the Two groups

Minutes	N	Group B	Group BM	P value
0 hour	30	98.844	102.332	0.321
2nd hour	30	98.369	102.247	0.267
4th hour	30	98.773	102.583	0.25
8th hour	30	111.14	105.883	0.089
12th hour	30	111.393	107.081	0.235
16th hour	30	108.763	112.137	0.241
20th hour	30	110.495	114.329	0.260
24th hour	30	108.092	112.467	0.061

Table 12: Intra operative Systolic Blood pressure of the Two groups

	Group B	Group BM	P value
Baseline	102.132	98.629	0.213
After Induction	93.417	91.248	0.099
5 min	96.405	93.608	0.058
10 min	94.705	93.112	0.096
15 min	95.115	91.997	0.341
20 min	96.048	90.443	0.136
25 min	97.64	92.105	0.208
30 min	97.165	92.318	0.148
35 min	91.493	-	-

Table 13: Post-operative Systolic Blood pressure

	Group B	Group BM	P value
0 hour	96.35	91.93	0.137
2nd hour	95.30	91.25	0.174
4th hour	96.00	91.05	0.595
8th hour	102.34	97.41	0.586
12th hour	97.57	93.66	0.182
16th hour	96.43	92.35	0.191
20th hour	96.29	94.23	0.772
24th hour	96.83	93.42	0.358

Table 14: Comparison of Mean of Diastolic Blood pressure between the two groups – Intra-operative period

Minutes	N	Group B	Group BM	P value
Baseline	30	59.888	59.954	0.552
After Induction	30	56.145	54.757	0.053
5 min	30	57.428	59.544	0.57
10 min	30	57.986	58.645	0.784
15 min	30	57.03	57.286	0.461
20 min	30	57.317	57.265	0.366
25 min	30	57.828	58.597	0.144
30 min	30	57.773	-	0.148
35 min	30	64.404	-	0.771

Table 15: Comparison of Mean of Diastolic Blood Pressure Between the two groups – Post-operative period

	N	Group B	Group BM	P value
0 hour	30	56.496	57.896	0.191
2nd hour	30	59.149	57.536	0.558
4th hour	30	58.576	58.238	0.593
8th hour	30	60.687	58.372	0.67

12th hour	30	57.651	59.155	0.513
16th hour	30	58.204	59.487	0.795
20th hour	30	58.845	59.567	0.147
24th hour	30	60.277	60.4	0.918

Table 16: Mean Arterial Pressure Intra operative period in both The groups

	N	Group B	Group BM	P value
Baseline	30	73.324	72.583	0.362
After Induction	30	67.747	66.721	0.514
5 min	30	69.579	70.536	0.732
10 min	30	69.613	69.927	0.626
15 min	30	69.334	68.58	0.9
20 min	30	69.646	68.046	0.973
25 min	30	70.285	69.237	0.586
30 min	9	69.878	-	-
35 min	3	72.928	-	-

Table 17: Mean Arterial Pressure Post-operative period in both The groups

	N	Group B	Group BM	P value
0 hour	30	69.306	68.813	0.774
2nd hour	30	70.624	68.542	0.355
4th hour	30	69.73	68.823	0.518
8th hour	30	73.261	69.097	0.088
12th hour	30	69.866	69.478	0.731
16th hour	30	70.401	70.08	0.8
20th hour	30	70.999	70.712	0.35
24th hour	30	71.947	71.071	0.674

Table 18: Respiratory depression in both the groups

	N	Group B	Group BM	P value
Respiratory Depression (Absent)	30	50.0%	50.0%	-

Table 19: PONV in both the groups

PONV	N	Group B	Group BM	P value
Present	1	1	0	0.313
Absent	29	49.2%	50.8%	-

DISCUSSION

Single shot caudal epidural anesthesia is an effective means of providing pain relief in children. Apart from offering adequate intra operative and postoperative analgesia it has numerous beneficial effects. It reduces the levels of stress hormone produced during the perioperative period and reduces the perioperative analgesic requirements in the form of narcotics and NSAIDS, ultimately facilitates faster emergence wake up times, helps in early ambulation and less hospital stay, thereby alleviating most of the anxiety and burden of the child's parents.

Though it produces excellent analgesia the analgesic effect lasts for a relatively short duration of action compared to continuous epidural local anaesthetic infusion, resulting in excessive use of opioids postoperatively, increases the incidence significant respiratory depression and post-operative nausea and vomiting. Though continuous caudal catheter technique can be used to provide postoperative analgesia, it carries the drawback of residual motor block and limiting early ambulation.

Numerous adjuvants like adrenaline, ketamine, clonidine, dexmedetomidine and neostigmine were studied with local anesthetics to prolong their analgesic effect, one such adjuvant used was midazolam, a GABA agonist. Which could prolong the duration of analgesia without any significant side effects. Accordingly, we studied the effects of midazolam as an adjuvant to single shot caudal bupivacaine and we found that addition of midazolam favorably prolonged the duration of analgesia provided by bupivacaine without any significant adverse impact on the cardiovascular, neurological and respiratory system.

In the bupivacaine and midazolam group, effective postoperative analgesia as assessed by FLACC score was lasted up to 8hours longer than the group without midazolam. The mean duration of postoperative analgesia in the bupivacaine with midazolam group was 12.49+/1.19 hours while that of plain bupivacaine group was 5.11+/0.50 hours which was statistically significant with a $p < 0.05$. Our findings were similar to the results of Mahajan et al which reported addition of 50 mcg per kgmidazolam to bupivacaine provides longer duration of analgesia (11+/0.5hr) compared to bupivacaine group (7.4+/2.1hr).Additionally, the sedation scores were higher in the first hour post-surgery concurrent with the results of Banoet et al. Finally, midazolam was not associated with any undesirable effect.

CONCLUSION

We conclude that administration of preservative free midazolam with bupivacaine for single shot caudal epidural block satisfactorily increases the duration of post-operative analgesia compared with plain bupivacaine, without any undesirable effects. Thus, low dose preservative free midazolam is a cost effective adjuvant that can safely be used as an additive with bupivacaine in caudal epidural anesthesia for prolonging its analgesic effect.

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