POST-OPERATIVE PAIN MANAGEMENT IN CHILDREN: A COMPARATIVE STUDY OF CAUDAL EPIDURAL MORPHINE VS. MORPHINE-KETAMINE

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ABSTRACT

BACKGROUND

Ketamine is a N-Methyle-D-Aspartate (NMDA) antagonist inhibiting the central sensitization due to peripheral nociception and might thus potentiate the central analgesic effect of morphine. This study was conducted to assess the perioperative analgesic effect of adding ketamine to caudal morphine and secondly to assess if a lower dose of caudal morphine would be adequate when caudal ketamine is added.

METHODS

It is a double blind randomized study. Forty children between the age group 1-12 years belonging to ASA I and II, posted for major surgery were randomly assigned to 2 groups of 20 children each. After conventional general anaesthesia, caudal epidural block was given with the following regimens. Group I children were given morphine 50 ug/kg body weight in 0.25% bupivacaine and those belonging to Group II were given Morphine 30 ug/kg body wt and ketamine 0.5 mg/kg body wt in 0.25% bupivacaine. The volume of Bupivacaine was 1.25 mL/kg, 1 mL/kg and 0.5 mL/kg depending on the level of the surgical procedure. Perioperative vital parameters, degree and duration of pain relief, administrations of rescue analgesia and related side effects were monitored. VAS score and AIIMS pain score was used.

RESULTS

The perioperative vital parameters and the incidence of side effects in both the groups are similar. However, there is statistically significant reduction in the perioperative narcotic requirements in the ketamine group. Kruskal-Wallis test and Chi Square Analysis were used for statistical analysis.

CONCLUSION

Addition of ketamine 0.5 mg/kg to morphine 30 ug/kg in 0.25% Bupivacaine administered through caudal epidural route provides better quality and longer duration of analgesia in the post-operative period in children.

KEYWORDS

Caudal Epidural, Morphine, Ketamine, Bupivacaine, Post-Operative Pain.

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INTRODUCTION

Pain managements in children are often inadequate historically due to the wrong notion that children and infants do not feel pain and even if they do so they do not remember it. Another reason was fear of the side-effects due to use of parenteral narcotics, which constitute the main regimen of post-operative analgesics in adults. It is a well-known fact that inadequately treated pain will lead to numerous unwanted short-term and long-term complications. Nowadays almost all the available modalities of pain management including drugs like narcotics, NSAIDs, NMDA antagonists and enteral, parenteral routes of drug administration including central neuraxial and peripheral nerves blockade are well extended to these group of patients.

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The search for an ideal analgesic, which is having no or minimal side-effects with adequate analgesia enabling early ambulation is still on. Many studies have proved the benefits of epidurally administered morphine with bupivacaine including the better quality of analgesia and lesser side effects like respiratory depression even though side-effects still persist.[1,2] Ketamine, a non-competitive NMDA receptor antagonist inhibits central sensitization after tissue injury and might potentiate the analgesic effect of epidural morphine.[3,4] Thus, this double blind randomized controlled trial was carried out to assess – i) If ketamine when added to morphine – bupivacaine in epidural block improves the quality and duration of pain relief in children and ii) If lower dose epidural morphine would be adequate when combined with ketamine.

METHODS

After obtaining prior approval from the Institutional Ethics Committee and informed consent from the legal guardians, forty children in the age group 1-12 years, ASA I or II coming for routine major surgical procedures other than head and neck surgery were included. Patients with abnormal sacral hiatus or infected sacral area or with history of allergy to any of the study drugs were excluded. The consecutive patients who fulfil the inclusion criteria were randomly allocated to

any one of the groups I or II. All children were given standard inhalational general anaesthesia with controlled ventilation and standard monitoring with ECG, SPO2, NIBP and EtCO2 and a single dose caudal block as below was administered by an anaesthesiologist blinded to the drug mixture:

- Group I – Morphine 50 ug/kg body wt in 0.25% Bupivacaine.
- Group II – Morphine 30 ug/kg body wt with ketamine 0.5 mg/kg body wt in 0.25% Bupivacaine.
- The volume of bupivacaine in both the groups were according to the desired level of block.
- Above T10 (Upper abdominal and thoracic) – 1.25 ml/kg body wt.
- Below T10 (Lower abdominal) – 1.0 mL/kg body wt.
- Below L1 (Genital, perineal and lower extremities) – 0.5 mL/kg body wt.

Intraoperative anaesthesia was maintained with O2, N2O, Sevoflurane, Vecuronium Bromide and caudal block. Rescue analgesia with incremental dose of Morphine 50 ug/kg IV at a time was given when two or more of the following clinical parameters, viz. a) Sweating, b) Increase in HR by 20% or more, and c) Lacrimation were seen. All patients were followed up and observed at half hourly intervals up to the first three hours and every 6 hourly afterwards up to 72 hours in the post-operative period. Post-operative analgesia was provided with Inj. Pethidine 0.5 mg/kg, IV when VAS (In children more than 5 yrs. old) and AIIMS Pain Score (In children less than 5 yrs. old, Annexure I) is more than 4.

Statistical analysis was done using Chi square analysis and Kruskal Wallis test. Age and weight were analysed by Kruskal-Wallis test and sex distribution by Chi Square. Since the age ranges from 1 yr. to 12 yrs., physiological parameters (HR, BP, RR) are compared by working out the number of children falling outside the 90th percentile of the age group. Intra-operative and post-operative physiological parameters were subjected to descriptive statistics and analysed by working out the range of the individual patients for all the measurements at different times and calculating the medians of the range. The median values of the range of changes in the Heart Rate (HR), Systolic Blood Pressure (BP) and Respiratory Rate (RR) are analysed by Kruskal-Wallis test. Post-operative Pain Scores and analgesic requirements were analysed by Chi Square. A P value of less than 0.05 was taken as statistically significant.

RESULTS

The demographic profiles (Table I) are comparable and there is no statistically significant difference. Depending on the site of the surgical incisions, type of surgery were divided into Upper abdominal and thoracic (Above T10), Lower abdominal (Below T10) and Perineal and Lower extremities (Below L1). There was no statistically significant difference (p=0.68) (Table II).

The number of children whose physiological basal parameters are more than 90th percentile as shown in Table III. Six children in Group I and 4 children in Group II has PR more than 90th percentile (p=0.37). For basal systolic BP, the figures are 5 each and that of RR were 2 and 1 respectively (p=1.0). There is no statistically significant difference.

The median ranges of intra-operative PR in Group I and II are 27.5 and 15 (p=0.37) (Table IVa) and that of the systolic BP are 20 and 18.5 respectively (p=0.36) (Table IVb). The values are comparable with no statistically significant difference. The intra-operative SPO2 and EtCO2 remain within normal limits in all the patients in both the groups.

The changes in the post-operative PR, systolic BP and RR at various time intervals were compared. The mean±SD of the ranges of post-operative PR of the groups are 35.2±12.16 and 29.3±10.1 and the medians of the same are 36 and 30 respectively (p=0.47) (Table Va). The mean±SD of the ranges of post-operative systolic BP are 17.45±7.24 and 13±4.52 and the medians of the ranges are 18 and 20 (p=0.47) respectively (Table Vb). The mean±SD of the ranges of post-operative RR are 11.9±3.47 and 11±3.7 and the medians of the ranges are 12 and 11 respectively (p=4.7) (Table Vc). There was no statistically significant difference in these parameters.

The number of patients having pain score more than 4 out of maximum 10 were directly compared. Upto 36 hours in the post-operative period, Group II had fewer children having pain score more than 4 (Table VI). The finding is statistically different at 6 hrs. and 12 hrs. post reversal, but the differences do not reach statistically significant value 18 hours onwards. None of the children in both the groups had pain score more than 4 at 42, 48, 60, 66 and 72 hours. Only one subject in Group I had pain score more than 4 at 54 hours, which is not statistically significant.

The narcotic analgesic requirements during intra-operative period and post-operative period at various time intervals were noted in terms of number of subjects requiring the same and total number of doses required. Thirteen subjects in Group I and 6 in Group II required narcotic analgesia during intra-operative period (p=0.019) (Table VIIa). The difference is statistically significant.

The number of children requiring post-operative narcotic in Group I is more than Group II. The numbers of subjects who had received doses of narcotics are shown in Table VIIb. Four children in Group I and 8 children in Group II did not require any post-operative narcotic. Four children in Group I and 12 in Group II required one dose of narcotic analgesic each. None of the children in Group II required more than 1 dose of narcotics. In Group I, 8 children received 2 doses, 3 children received 3 doses and 1 child received 4 doses of narcotic analgesic. The differences in the groups are strongly significant (p=0.0005).

Complication like nausea and vomiting, pruritus and respiratory depression were monitored in the two groups (Table VIII). Urinary retention could not be observed as majority of the children were catheterized post-operatively. There were 4 cases of nausea and vomiting in Group I and 5 in Group II, 1 case of pruritus in Group I and none in Group II. None of the children in both groups had serious complications like respiratory depression. The difference is not statistically significant.

	Group I	**Group II**
Age in yrs. [mean SD]	4.83±3.69	4.08±2.81
Weight in kg [mean SD]	14.85±7.60	12.47±3.73
Male:Female	14:6	11:9

Table I: Demographic Data

Upper abdominal & thoracic [<T10]	2	5
Abdominal [<T10]	17	13
Lower extremities & perineal [<L1]	1	2

Table II: Distribution of Children According to Site of Surgical Incision

	Group I	Group II
PR (No. of cases having > 90th percentile)	6	4
B.P (No. of cases having > 90th percentile)	5	5
RR (No. of cases having > 90th percentile)	2	1

Table III: Basal Pulse Rate (PR), Systolic Blood Pressure (BP) & Respiratory Rate (RR)

	Group I	Group II
Mean	28.8	19.4
Median	27.5	15
S.D	14.39	11.32
Range	53	45
Minimum	7	5
Maximum	60	50
Confidence level (95.0%)	6.74	5.30

Table IVa: Descriptive Statistics of Ranges of Intra-Operative Pulse Rate

(P=0.37)

	Group I	Group II
Mean	23	17.85
Median	20	18.5
S.D	10.44	4.39
Range	35	15
Minimum	5	10
Maximum	40	25
Confidence level (95.0%)	4.89	2.06

Table IVb: Descriptive Statistics of Ranges of Intra-Operative BP

(P=0.36)

	Group I	Group II
Mean	35.2	29.3
Median	36	30
S.D	12.16	10.10
Range	42	34
Minimum	20	10
Maximum	62	44
Confidence level (95.0%)	5.69	4.73

Table Va: Descriptive Statistics of Ranges of Post-Operative Pulse Rate

(P=0.47)

	Group I	Group II
Mean	17.45	19.55
Median	18	20
S.D	7.24	10.83
Range	22	44
Minimum	10	0
Maximum	32	44
Confidence level (95.0%)	3.39	5.07

Table Vb: Descriptive Statistics of Ranges of Post-Operative BP (Systolic)

(P=0.47)

	Group I	Group II
Mean	11.95	11
Median	12	11
S.D	3.47	3.70
Range	14	14
Minimum	8	4
Maximum	22	18
Confidence level (95.0%)	1.62	1.73

Table Vc: Descriptive Statistics of Ranges of Post-Operative RR

(P=0.47)

	6 hr	12 hr	18 hr	24 hr	30 hr	36 hr	54 hr
Group I	*3	**7	4	10	4	2	1
Group II	0	2	3	5	1	1	0

Table VI: Number of Patients whose Pain Score >4

*P=0.04 (Statistically significant)

**P=0.006 (Statistically significant)

	No. of Subjects	No. of Doses	Mean Dose
Group I	*13	16	0.8
Group II	6	6	0.3

Table VIIa: Number of Patients Requiring Intra-Operative Narcotic

*P=0.019(Statistically significant)

	0 Dose	1 Dose	2 Doses	3 Doses	4 Doses
Group I	*4	**4	***8	****3	1
Group II	8	12	0	0	0

Table VIIb: Number of Patients Receiving Post-Operative Doses of Narcotic

(*P=0.035) **P=0.0316, ***P=0.0006, ****P=0.0425(Statistically significant)

	Vomiting	Pruritus	Respiratory Depression
Group I	4	1	0
Group II	5	0	0

Table VIII: Number of Subjects with Complications

All India Institute of Medical Sciences,
Pain Discomfort Scale

Respiratory Rate	+ 20% Pre-Op	0
	+ 20-50% Pre-Op	1
	≥ 50% Pre-Op	2
Heart Rate	+ 10% Pre-Op	0
	+ 20% Pre-Op	1
	+ 30% Pre-Op	2
Discomfort	Calm	0
	Restless	1
	Agitated	2
Cry	No Cry, Cry Responds to Water, Food, Parental Presence	0
	Cry Responds to Loving Tender care	1
	Cry not Responding to Loving Tender Care	2
Pain At Site of Operation	No Pain	0
	States Pain Vague	1
	Can Localise Pain	2
0 – 4, Mild Pain	5 – 6, Moderate Pain	> 6, SeverePain

DISCUSSION

It is now a well-accepted fact that children and infant do feel and un-treated pain especially postoperative pain causes psychological, economic and social harm to all concerned.[5,6] The importance and benefit of regional techniques for post-operative pain management in children is no more in doubt. Epidural analgesia is most commonly provided using combination of local anaesthetic and an opioid. Combination of these two provides superior postoperative analgesia with lower local anaesthetic doses and less opioid related side effect.[7,8] Certain studies have shown that NMDA receptor antagonist inhibits hyperalgesia caused by inflammation, tissue and nerve injury.[9]

Clinical studies have shown that ketamine potentiates pain control.[10] and epidural administration of ketamine along with morphine reduces post-operative morphine consumption and provides effective analgesia in adult patients undergoing major upper abdominal surgeries.[11,12,13] But there have been concerns regarding the neurotoxicity of neuro-axial ketamine. However, single and repeated administration of diluted epidural ketamine has been found to be devoid of neurotoxicity. In the study by Krane et al[14] using 30, 70 and 100 µg/kg of caudal morphine estimated duration of action was 9.5, 10.5, 12.5 hrs. respectively. In our study, we observed that children receiving morphine-bupivacaine had a median duration of action of 6-12 hours, which is comparable to the results of Krane et al,[15] whereas the duration of action is shorter than the results of Atia et al.[16]

Naguib et al[17] using caudal ketamine 0.5 mg/kg with or without bupivacaine demonstrated better quality and longer duration of analgesia as compared to caudal bupivacaine in children undergoing hernia surgery. In our study, addition of ketamine to morphine bupivacaine has increased the duration of action and intensity of pain relief as 50% of the patients did not require any additional analgesic and the rest 50% except for 1 patient requiring only 1 top up dose up to a period of 72 hrs. This confirms the finding of Naquib et al and Cook et al[18] that ketamine increased the quality of postoperative analgesia. This could be due to the potentiation of morphine action by Ketamine. Similar results were seen in the study of Wonq et al and Chia et al, where Ketamine is shown to potentiate the action of morphine in adults.

The incidence of nausea and vomiting are similar in both the groups, whereas there was no incidence of pruritus in Group 2, while there were 10% incidence in Group 1. Though the observation is statistically not significant, it could be clinically significant. This suggests that with addition of ketamine to morphine-bupivacaine, morphine dose could be reduced with similar analgesic effect and probably less side-effects. This could be because of potentiation of action of morphine by ketamine.

CONCLUSION

We conclude that addition of ketamine to morphine and bupivacaine administered through epidural route provides better quality and longer duration of analgesia in post-operative period. The addition of ketamine also reduces morphine requirement and thus decreases the incidence of side effects. Hence, caudal epidural with 0.25% bupivacaine with 30 ug/kg morphine and ketamine 0.5 mg/kg provides excellent post-operative pain relief in children undergoing major surgical procedures.

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