 Effects of Ketamine and Midazolam on Emergence Agitation after Sevoflurane Anaesthesia in Children Receiving Caudal Block: A Randomized Trial

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ABSTRACT

Introduction: Emergence agitation is a common post anaesthetic complication in children after sevoflurane anaesthesia. We aimed to compare the effects of ketamine and midazolam administered intravenously, before the end of surgery, for prevention of emergence agitation in children who received caudal block for pain relief under sevoflurane anaesthesia.

Material and Methods: 100 American Society of Anaesthesiologists status I children aged 4-11 years scheduled for inguinal hernia repair, circumcision or orchidopexy were enrolled to the study. Anaesthesia was induced with sevoflurane 8% in a mixture of 50% oxygen and nitrous oxide. After adequate depth of anaesthesia, a laryngeal mask was placed and caudal block was performed with 0.5 mL kg⁻¹, 0.125% bupivacaine. At the end of the surgery, ketamine 0.25 mg kg⁻¹ or midazolam 0.03 mg kg⁻¹ were given to their respective groups. Agitation was assessed using Paediatric Anaesthesia Emergence Delirium scale and postoperative pain was evaluated with modified Children's Hospital of Eastern Ontario Pain Scale.

Results and Conclusion: modified Children's Hospital of Eastern Ontario Pain Scale scores were found higher in midazolam group as compared to ketamine group at 0 minutes and 5 minutes while after 10 minutes, the scores became insignificant. Paediatric Anaesthesia Emergence Delirium scores were found to be higher in midazolam group at 0, 5 and 10 minutes as compared to ketamine group, but at 30 minutes, the delirium scores became comparable. Thus, ketamine was able to prevent Emergence Delirium as well as decrease pain scores better than midazolam following sevoflurane anaesthesia in children with caudal block.

Keywords: Caudal Block, Children, Emergence Agitation, Sevoflurane Anaesthesia, Ketamine, Midazolam

INTRODUCTION

Emergence agitation (EA) is a common and well–recognized phenomenon in paediatric patients observed after general anaesthesia. Eckenhoff et al.¹ in 1961 were the first to report the signs of hyper-excitation in patients emerging from ether, cyclopropane or ketamine anaesthesia. In children, Halothane was the pre dominant anaesthetic for decades. With the recognition of postoperative pain management in children and the increased use of analgesics, the incidence of EA was attenuated. However, with the introduction into clinical practice of the new, short-acting, volatile anaesthetics like Sevoflurane and Desflurane, the problem of EA re-emerged. There is no unique definition of ED (Emergence Delirium) because of its heterogeneous clinical presentation. Emergence delirium was initially defined as a dissociated state of consciousness in which the child is inconsolable, irritable, uncompromising or uncooperative, typically thrashing, crying, moaning or incoherent.² ³ It was only in 2004 that Sikich and Lerman⁴ came up with a standardized definition which states EA as "a disturbance in a child's awareness of and attention of his/her environment with disorientation and perceptual alterations, including hypersensitivity to stimuli and hyperactive motor behavior in the immediate post-anaesthesia period." Emergence agitation and emergence delirium have been used interchangeably in most of the literature. Although EA is self-limiting and short lived, it can be very frightening and disturbing for the parents. Restless recovery from anaesthesia may not only cause injury to the child or to the surgical site, but may also lead to the accidental removal of surgical dressings, IV catheters, and drains. It occurs within the first 30 min after anaesthesia and lasts for a few minutes to hours.⁵ The incidence of EA ranges from 5% to 15% with some studies reporting an incidence as high as 80%.⁶ It was also seen that children younger than five years of age are more likely to have EA after Sevoflurane anaesthesia. A variety of explanations have been proposed for the etiology of emergence agitation including the lack of a young child's ability to adapt to sudden changes due to an unfamiliar environment after awakening, immature neurological development, anxiety from being separated from their parents, type of anaesthetics used in the surgical procedure, increased pain sensation and sympathetic hyperactivation.⁷ However, the etiology of EA has not yet been identified clearly. The predisposing factors are preschool age,

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preoperative anxiety, lack of premedication, type of surgery and awakening in a strange environment. Pain is thought to be a major contributor to EA. The recent surge in EA cases is a reflection of the gaining popularity of Sevoflurane and Desflurane.

To reduce the incidence of EA, several drugs have been used as an adjuvant to general anaesthesia including Propofol, Midazolam, Ketamine, opioids and alpha 2 agonists etc. Hence, we took up the two trial drugs Ketamine and Midazolam to evaluate whether they could successfully prevent emergence agitation in children in the post operative period following Sevoflurane anaesthesia and compare which one was superior.

**MATERIAL AND METHODS**

The study was conducted in the operation theatre of Paediatric Surgery, Assam Medical College after the approval from the Institutional Ethics Committee (AMC/EC/PG 2153) and with written informed consent from the parents of the children after explaining the study procedure to them in their own language. We followed the CONSORT 2010 checklist for this study. On the assumption that 50% of the cases with use of either drug would yield a good result and that 20% is the allowable error hundred ASA I children of 4-11 years of age scheduled for inguinal hernia repair, circumcision or orchidopexy during the study period (July 2016-June 2017) were undertaken for the study. Exclusion criteria were parents of the children unwilling for the trial, co-morbid abnormalities, mental retardation, physical developmental delay, preoperative agitation, emergency surgeries and contra-indication for caudal block.

**Case selection:** After taking a detailed history and thorough clinical examination, children were kept fasting for 6 hours for solid foods, 4hrs for milk and 2 hrs for water on the night before operation. Children were randomized into 2 groups as: Ketamine Group (Group–K) and Midazolam Group (Group–M) and cases were divided randomly by sequentially numbered sealed envelope method into two groups of 50 each. The anaesthetist (care provider) and the study participants remained blinded with regards to the drug used.

**Technique:** After arrival of the child in the OT, the child was positioned in the OT table and standard monitors were connected. No premedication was given. Induction was carried out with inspired Sevoflurane 8% in a mixture of 50% oxygen and nitrous oxide. After loss of consciousness, a peripheral vein was cannulated and IV fluid was connected. Inj. Glycopyrrolate @ 5mcg/kg was injected intravenously followed by Inj. Fentanyl citrate @ 1 mcg/kg. After achieving adequate depth of anaesthesia, a laryngeal mask was placed and anaesthesia was maintained with Sevoflurane 2% in 50% oxygen-nitrous oxide mixture on spontaneous respiration in Jackson Rees circuit. The children were positioned in the lateral decubitus position for caudal anaesthesia. 0.5 mL kg−1, 0.125% plain bupivacaine was injected using a 22G needle in the caudal space. No other hypnotic, muscle relaxant or analgesic drug was administered during surgery. They received intravenous normal saline (10–20 ml/kg) throughout the procedure. Skin incision was made 10 minutes after the block. Caudal block was accepted adequate if heart rate and blood pressure did not increase more than 20% of baseline value after skin incision. The children with failed block were excluded from the study.

As the final bite of the skin was taken, Ketamine 0.25 mg kg−1 and Midazolam 0.03 mg kg−1 volumes were administered intravenously to children who belonged to Group K and Group M respectively over a period of 30 seconds and thereafter Sevoflurane was discontinued and subsequently nitrous oxide was cut – off. Laryngeal mask was removed and the children were allowed to breathe 100% oxygen for 3 minutes via face mask and then when patent airway and spontaneous respiration assistance were confirmed, patients were transferred to the Post Anaesthesia Care Unit (PACU). In the PACU, their parents were present and the child were assessed by the Anaesthetist. Agitation was assessed using PAED (Paediatric Anaesthesia Emergence Delirium) scale at 0, 5, 10 and 30th min and mCHEOPS (modified Children's Hospital of Eastern Ontario Pain Scale) was used to evaluate postoperative pain at 0, 5, 10 and 30th min in the recovery room. Children were observed for a period of 30 minutes in the PACU and then discharged to the ward. All agitated children having a PAED score of more than 10 were managed with inj. Propofol iv 1mg/kg. Pain was taken into consideration for mCHEOPS scores of or more than 6 who received a rescue analgesic. The side effects like nausea, vomiting, bronchospasm, laryngospasm, desaturation (if any) were also recorded.

**Scales used:** PAED and mCHEOPS

**STATISTICAL ANALYSIS**

The data were recorded on predesigned and pretested proforma and was tabulated and master chart was prepared. Demographic data, baseline preoperative characteristics like Heart Rate (HR), Systolic BP, Diastolic BP and peripheral saturation of Oxygen SPO2, type and duration of surgery, duration of anaesthesia, pain scale mCHEOPS and emergence delirium scale PAED were tabulated as Mean ± SD for both the groups. Statistical significance were tested by Student’s t-test and Chi square test wherever applicable using the computer program Graph Pad Instat. Microsoft Word and Excel have been used to generate graphs and tables and a p value of < 0.05 was considered to be significant in the cases which were undertaken.

**RESULTS**

100 patients of either sex between 4-11 years of age of ASA I physical status were selected and were divided into two groups namely, Group K receiving IV Ketamine (0.25mg/kg) and Group M receiving IV Midazolam (0.03mg/kg). The characteristics of the patients including age, sex and gender and the duration of surgery and anaesthesia and types of surgery were similar between the groups as shown in table 1.
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| Parameter                          | Group K              | Group M              | p Value |
|------------------------------------|----------------------|----------------------|---------|
| Age (years)                        | 6.72 ± 2.51          | 7.46 ± 2.46          | 0.13    |
| Sex (M/F)                          | 37/13                | 40/10                | 0.47    |
| Weight (Kg)                        | 16.62 ± 4.68         | 17.44 ± 4.21         | 0.36    |
| Duration of surgery (min)          | 29.12 ± 2.11         | 29.54 ± 2.14         | 0.32    |
| Duration of anaesthesia (min)      | 50.02 ± 3.16         | 50.94 ± 2.62         | 0.11    |
| Types of surgery (IHR/O/C)         | 26/3/21              | 28/2/20              | 0.68    |

Table-1: Demographic profile. Values expressed as mean ± SD

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The baseline preoperative characteristics including heart rate, systolic and diastolic blood pressure and SPO2 were comparable between the groups (fig 1)

Pain was assessed with the help of mCHEOPS scoring and the mean and SD values in the immediate post operative period for group K and M at 0 minutes, 5 minutes, 10 minutes and 30 minutes were evaluated. The mean values were found below 6 in all the subjects and no rescue analgesic was needed. The p values at 0 minutes, 5 minutes, 10 minutes and 30 minutes were <.001, <.001, 0.021 and 0.087. Hence, it was found that
pains were statistically significant between the two groups at 0 minutes, 5 minutes and 10 minutes, but as the duration of the postoperative period increased and went onto 30 minutes, the pain scores between the two groups became insignificant and comparable. (Fig 2)

Emergence Delirium was assessed with the help of PAED scale and the mean and SD values in the immediate postoperative period for group K and M at 0 minutes, 5 minutes, 10 minutes and 30 minutes were evaluated. None of the subjects had a PAED score of 10 or more in Group K while 2 patients (case no. 8 and 48) had a PAED score of 11 and 12 respectively in group M at 5 minutes. We waited for a further period of 5 minutes as Emergence Delirium resolves spontaneously. But even at 10 minutes the PAED scores were found to be 11 and 11 respectively and hence we proceeded with the rescue technique which involved the administration of IV Propofol at 1mg/kg to calm the child. The p values at 0 minutes, 5 minutes, 10 minutes and 30 minutes were <0.05, <.001, <.001 and 0.069. Hence, it was found that Emergence Delirium was statistically significant between the two groups at 0 minutes, 5 minutes and 10 minutes, but as the duration of the postoperative period increased and went onto 30 minutes, the Emergence Delirium scores between the two groups became insignificant and hence comparable.

No side effects like nausea, vomiting, bronchospasm, laryngospasm or desaturation were recorded. All patients were discharged from the PACU after 30 minutes.

DISCUSSION

Various methods have been used over the years to nullify EA. In the present study, the effects of ketamine and midazolam were assessed in patients who were at a risk of EA. Aono et al.7 had mentioned about the higher incidence of EA in pre-school children. Beskow A et al.9 had also concluded that incidence of EA is greater in younger children undergoing minor surgeries.

EA has been on the rise ever since the expanded use of Sevoflurane and Desflurane. Pain has formed a major contributing factor so much so that it is difficult to distinguish pain from EA in most of the cases. There is no doubt that the use of opioids as an adjunct does result in clinically relevant prolongation of postoperative analgesia. M. Somri et al.17 showed that iv Fentanyl at 2mcg/kg when added to caudal block for the operative procedure and postoperative period. Aouad et al.11 had shown that the incidence of EA and pain scores in patients receiving caudal block were significantly lower compared to those receiving intravenous Fentanyl under Sevoflurane anaesthesia for inguinal hernia repair. Hence, in our study we used a multimodal approach to neutralize pain as we included intravenous Fentanyl at 1mcg/kg to the caudal block for the operative procedure and postoperative pain management. We used mCHEOPS scoring system to evaluate and to exclude pain as a contributing factor of EA. Ozcan A et al. had found greater significance in using this scale for comparison of postoperative pain in children.12 A score of 6 or more suggested pain. In our study, all the caudal blocks were functioning and all the patients were considered to be free of pain.

Although pain is thought to be important in aetiology, EA is also seen in pain free procedures.13 This may due to rapid emergence in an unknown environment with altered cognitive function. Therefore, agents that provide sedation at the time of emergence may be helpful in prevention of EA. Paediatric Anaesthesia Emergence Delirium (PAED) scale is preferred in most of the studies.4 The PAED scale incorporates cognitive and agitation assessment items and is generally acknowledged to be the most valid and reliable. A score of 10/20 on the PAED scale was reported as the best threshold point for determining the presence of EA.14 However, Bajwa et al. reported that a PAED score greater than 12 had greater sensitivity than a score of ≥10.15 In our study, we used a score of ≥10 on PAED scale for the assessment of EA.

Sevoflurane when used alone is associated with a higher incidence of emergence agitation in children. The rapid removal of residual anaesthetics due to low blood solubility of Sevoflurane has been suggested to cause emergence agitation in some patients.15 Eom et al. postulated that alternative splicing of the γ2 subunit is related to emergence agitation on the basis of characteristics of Midazolam, Sevoflurane and γ2 subunit.16 One of the drugs that we used in our study to combat EA was Ketamine. It does not cause respiratory depression at small doses (<1 mg/kg), and has little effect on the heart rate and blood pressure. The incidence of arousal responses, such as nightmares or hallucinations is also lower at small doses (<1 mg/kg) compared to opioids.17 Kawaraguch et al.18 reported that the administration of Ketamine 1 mg/kg after the induction of anaesthesia and the instillation of Ketamine 1 mg/kg/hr during surgery in paediatric strabismus surgery succeeded in decreasing EA. Abu-Shahwan et al.19 showed that an intravenous injection of Ketamine 0.25 mg/kg, 10 min before the end of surgery in a dental operation for young children under general anaesthesia with Sevoflurane decreased the incidence of EA without a delay in recovery. Yoon Sook Lee et al.20 compared the effects of small doses of Ketamine, 0.25 mg/kg and 0.5 mg/kg groups and it showed a decrease in the incidence of EA and a significant decrease in pain intensity at the PACU. Compared to the K 0.25 group, the K 0.5 group showed a significant decrease in pain intensity at the PACU but not in the incidence of EA, which suggests that an increase in the Ketamine dose was effective in analgesic action, whereas the increase in dose did not affect the incidence of EA. Hence, a dose of Ketamine 0.25 mg/kg alone administered before the end of surgery would reduce the incidence of EA due to the combined analgesic and sedative action of Ketamine which we did in our study. Several studies have suggested that Midazolam can benefit patients by decreasing the incidence of postoperative agitation. According to Lapin et al.21 preoperative oral Midazolam decreased the amount of postoperative agitation in children having myringotomy surgery with Sevoflurane anaesthesia. Kim YH et al.22 measured the effect of...
Midazolam or Propofol at the end of surgery on emergence agitation after Sevoflurane anaesthesia where he found that Propofol or Midazolam administration before the end of surgery may be effective in reducing the incidence of EA. Eun Jun Cho et al.\textsuperscript{7} designed the study to test the hypothesis that a dose of Midazolam less than 0.05 mg/kg suppresses emergence agitation while having a minimal effect on the emergence time and their results vindicated. Therefore, it seems reasonable that the possibility of reanesthetization can be excluded when 0.03 mg/kg of Midazolam is given intravenously before the end of surgery. Thus similar dosage was used in our study.

We can opine that emergence delirium lasts usually for a period of 15 -30 minutes and resolves more or less spontaneously. However to combat the initial period certain drugs are required. Here, in our case, IV Ketamine provided a quieter and a calmer child than IV Midazolam hence making it superior for use. Probably its analgesic and sedative qualities resulted in such an outcome. It can be hypothesized that as an N-methyl-D-aspartate receptor blocker, Ketamine can provide a level of dissociative sedation that could be advantageous in the early stages of recovery when EA is prevalent. Ketamine can also provide postoperative analgesia that can also reduce child anxiety.

Limitations of this study included a small group of 50 patients each in both the groups. Pre school age groups (3 to 5 yrs) in whom EA is mostly seen were not the major focus in our study. Pre-operative anxiety evaluation was not done which would have definitely had a co-relation with the post operative emergence delirium. Anti emetics were not used although opioids like IV Fentanyl were administered. Duration of surgery varied from surgeon to surgeon and this might have altered the post operative scores to an extent. Even with the use of the various scores, it is difficult to assess pain and also it can be confusing to differentiate pain and EA as both of them have certain features which are synchronous to each other.

CONCLUSION

We can come to a conclusion that Inj. Ketamine 0.25mg/kg or Inj. Midazolam 0.03 mg/kg when administered intravenously just before discontinuation of Sevoflurane anaesthesia in children with caudal block were both able to prevent Emergence Agitation, with Inj. Ketamine showing better results when compared with Inj. Midazolam IV administered at the same time period during paediatric elective surgeries like inguinal hernia repair, orchidopexy and circumcision. Moreover, IV Ketamine was able to lower the pain scores post operatively more than IV Midazolam when administered just before discontinuation of Sevoflurane anaesthesia.

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