

*Original Article*

# Comparison of Intravenous Ketamine and Midazolam Premedication on Emergence Agitation (EA) in Children following Tonsillectomy with or without Adenoidectomy under General Anaesthesia

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## **Abstract**

**Background:** Management of emergence agitation (EA) following tonsillectomy with or without adenoidectomy under general anaesthesia in children has been a major challenge for anaesthesiologists. Several medications have been investigated in an attempt to reduce the occurrence and severity of EA.

**Objectives:** The purpose of this study is to determine the effect of premedication with intravenous midazolam and ketamine on EA following tonsillectomy with or without adenoidectomy under general anaesthesia in children.

**Study design:** Randomised clinical study.

**Methods:** Sixty children of both sex, American Society of Anaesthesiologists (ASA) physical status I & II age 5 to 12 years scheduled to undergo elective tonsillectomy with or without adenoidectomy were randomly assigned into two groups. Patients in group K (n=30) received premedication of intravenous ketamine 0.25 mg/kg body weight in 5 ml total volume and in group M (n=30) received premedication 0.1 mg/kg body weight intravenous midazolam in 5 ml total volume. After completion of surgery patients were transferred to recovery. Incidences and severity of EA (Paediatric Anaesthesia Emergence Delirium Scale), pain score (Wong-Baker FACES Pain scale) and postoperative nausea and vomiting (PONV) were assessed at admission in the recovery (T0) and in the post anaesthesia care unit (PACU) at 5 min (T5), at 15 min (T15) and at 30 min (T30).

**Results:** Incidences of EA in Group K remained significantly lower than Group M at admission to the recovery and in the PACU at 5 min and 15 min ( $P < 0.05$ ). Severity of EA was significantly lower patients in Group K than Group M at admission in recovery and in PACU at 5 minute and 15 minute ( $P < 0.05$ ). There were no significant differences in pain scores between two groups. Regarding PONV there was no significant difference between two groups.

**Conclusion:** Premedication with ketamine was more effective than midazolam in the prevention of EA following tonsillectomy with or without adenoidectomy in pediatric patients under general anaesthesia.

**Key words:** Emergence agitation (EA), ketamine, midazolam, children, tonsillectomy, adenoidectomy, general anaesthesia.

BSA 2020; 33(2): 55-61

## **Introduction**

Postoperative agitation, also referred to as emergence agitation (EA) in international literature, is a well-documented clinical phenomenon, particularly in children. EA has been described as “a mental disturbance during the recovery from general anesthesia consisting of

hallucinations, delusions and confusion manifested by moaning, restlessness, involuntary physical activity, and thrashing about in bed.”<sup>1</sup> It is during the first 30 minutes after emergence that the greatest incidence of agitation is observed, and duration is generally limited and recovery spontaneous. However, prolonged episodes of

agitation lasting for up to 2 days have been described.<sup>2</sup>

The prevalence of EA in children generally ranges from 25% to 80%, depending on the definition of EA used to measure this phenomenon,<sup>3</sup> but may be as high as 80%.<sup>3,4</sup> The incidence of EA largely depends on age, anaesthetic technique, surgical procedure, and application of adjunct medication.<sup>5</sup> Surgical procedures that involve the tonsils, thyroid, middle ear, and eye have been reported to have higher incidences of postoperative agitation and restlessness.<sup>5,6</sup> Eckenhoff et al.<sup>7</sup> speculated that a "sense of suffocation" during emergence from anesthesia may contribute to EA in patients undergoing head and neck surgery.

Treatment strategies evolve largely around drug administration, manipulation, or administration of preventative drugs. Standard pharmacological interventions such as propofol, ketamine, midazolam and fentanyl have been shown to have prophylactic effects in preventing EA in children.<sup>8</sup> Ketamine has been one of the studied pharmacological agents in the management of EA. ketamine was effective in the prevention of EA without delay in awakening and both subhypnotic doses of ketamine 0.25 and 0.5 mg/kg were effective.<sup>9</sup> Midazolam is a commonly used sedative in children that has beneficial effects in reducing paediatric EA. Preoperative oral midazolam decreases both preoperative separation anxiety and the degree of EA observed with sevoflurane anaesthesia.<sup>10</sup>

The aim of the present study was to compare the effects of preoperative premedication with intravenous midazolam and ketamine on EA following tonsillectomy with or without adenoidectomy in pediatric patients under general anaesthesia.

### Patients and Methods

It was a randomized clinical study of sixty patients (thirty patients in each group) of both sexes age between 5-12 years, ASA physical status I and II scheduled to undergo elective tonsillectomy with or without adenoidectomy under general anaesthesia in Border Guard Hospital, Dhaka in one calendar year from January 2016 to December 2016. Patients with clinically significant neurological, respiratory, cardiovascular,

psychiatric diseases, hypersensitivity to ketamine or midazolam and children with developmental or cognitive disorder were excluded from the study. The study was conducted after approval from the Institutional review board. Pre-anaesthetic check up was done 24 hours prior to surgery and the procedure was explained to the parents and written consent was obtained from parents. All eligible patients were randomized in to two groups. Patients in group K (n=30) receive intravenous premedication of ketamine 0.25 mg/kg body weight in 5 ml total volume and in group M (n=30) receive intravenous premedication of midazolam 0.1 mg/kg body weight in 5 ml total volume. Operation was done under general anaesthesia with controlled ventilation. Fentanyl 1 mcg/kg body weight was given intravenously before induction of general anesthesia. Induction was done with Propofol 2 mg/kg body weight and atropine 0.01 mg/kg body weight intravenously. After oral intubation with vecuronium 0.1 mg/kg body weight, anaesthesia was maintained with 70% nitrous oxide in oxygen, halothane 0.5-1% and muscle relaxation was maintained with incremental doses of vecuronium. Patient's heart rate, blood pressure, ECG, respiratory rate, and SpO<sub>2</sub> were monitored and recorded in every 5 minutes interval. At the completion of operation the patients were extubated after reversal of muscle relaxant with neostigmine and atropine and then admitted to the post anaesthesia care unit (PACU). Postoperative analgesia was maintained with inj ketorolac 0.5mg/kg body weight intravenously.

Postoperatively, the EA was assessed in both the groups using Paediatric Anaesthesia Emergence Delirium (PAED) scale<sup>11</sup> (Table: IV) for initial 30 minutes. The incidence and severity of emergence delirium were measured upon admission to the recovery (T0) and in the PACU at 5 min (T5), at 15 min (T15) and at 30 min (T30). A PAED scale 10 or more was considered as positive cases of EA. Children were considered severely agitated if they had a PAED scale of 15 or higher. Pain score (Wong-Baker FACES Pain scale) were assessed at admission in the recovery (T0) and in the post anaesthesia care unit (PACU) at 5 min (T5), at 15 min (T15) and at 30 min (T30). The Wong-Baker FACES Pain scale<sup>12</sup> (Figure: 1) is often useful for assessing pain in patients who do not have ability

to use language to describe pain. This scale uses faces:

- Face 0 : is very happy because he doesn't hurt at all.
- Face 2 : hurts just a little bit.
- Face 4 : hurts a little more.
- Face 6 : hurts even more.
- Face 8 : hurts a whole lot.
- Face 10 : hurts as much as you can imagine.

Postoperative nausea and vomiting (PONV) were recorded every one hour during these six hours. Vomiting was defined as the forceful expulsion of gastric contents from the mouth and was brought about by the powerful sustained contraction of the abdominal muscle; nausea was defined as a subjectively unpleasant sensation associated with awareness of the urge to vomit.

All statistical analysis was carried out using SPSS (Statistical Package for social sciences) 22.0 for windows. All results are expressed as mean ± standard deviation (SD) or in frequencies as applicable. Results are considered statistically significant if  $p < 0.05$ .

### Results

The Patients criteria and anaesthetic data were shown in table I. Two groups were similar and fairly comparable with respect to age, body weight, sex, ASA physical status and differences were statistically not significant. Duration of surgery and duration of anaesthesia were almost similar and differences were statistically not significant. Incidences and severity of emergence delirium were shown in table II. Incidences of EA in Group K remained significantly lower than Group M at admission to the recovery and in the PACU at 5 min and 15 min ( $P < 0.05$ ). Severity of EA (PAED scale) in Group K remained significantly lower than Group B at admission to the recovery and in the PACU at 5 min and 15 min ( $P < 0.05$ ). Pain scores (Wong-Baker FACES Pain scale) and incidences of PONV were shown in table III. There were no significant differences in pain scores (Wong-Baker FACES Pain scale) between two groups at admission to the recovery and in the PACU at 5 min, 15 min and 30 min. Regarding the incidence of PONV, there was no statistically significant difference among the studied groups. These were no incidences of hemodynamic instability, or postoperative hallucinations or nightmares.



Figure 1: The Wong-Baker FACES Pain Scale

Table I Patients criteria and anaesthetic details

Variables	Group K (n=30)	Group M (n=30)	P Value	Result
Age in years	7.36±1.46	6.93±1.69	0.83	NS(Student 't' test unpaired)
Body weight in kg	18.47 ± 4.63	19.76 ± 4.91	0.86	NS(Student 't' test unpaired)
Sex				
Male	19(63.33%)	17(56.67%)	0.76	NS(Chi Square test)
Female	11(36.67%)	13(43.33%)	0.65	NS(Chi Square test)
Duration of surgery in minutes	39.79±9.76	42.17±10.07	0.57	NS(Student 't' test unpaired)
Duration of anaesthesia in minutes	45.53±12.27	47.29±11.83	0.52	NS(Student 't' test unpaired)
ASA physical status				
I	27(90%)	26(86.67%)	0.72	NS(Chi Square test)
II	3(10%)	4(13.33%)	0.68	NS(Chi Square test)

Values are expressed in mean±SD or percentage as applicable NS – Not Significant

**Table II** Incidence of EA and severity of EA (PAED scale).

Variables	Group K (n=30)	Group M (n=30)	P value	Result
Incidences of EA				
T0	1(3.33%)	3(10%)	0.021	Sig(chi square test)
T5	2(6.66%)	7(23.33%)	0.015	Sig(chi square test)
T15	2(6.66%)	5(16.66%)	0.025	Sig(chi square test)
T30	1	1	-	NS(Chi Square test)
Severity of EA (PAED scale)				
T0	9.78±3.22	12.6±2.89	0.034	Sig (Student 't' test unpaired)
T5	5.26±2.67	8.63±2.79	0.039	Sig (Student 't' test unpaired)
T15	4.34±2.71	7.61±2.37	0.043	Sig (Student 't' test unpaired)
T30	3.52±2.25	4.14±2.64	0.615	NS(Student 't' test unpaired)

Values are expressed in mean±SD or percentage as applicable

Sig – Significant NS – Not Significant

**Table III** Pain score (Wong-Baker FACES Pain scale) in recovery at different time and incidence of PONV

Variables	Group K (n=30)	Group K (n=30)	P Value	Result
Pain score				
T0	4.13±1.71	4.71±1.58	0.716	NS(Student 't' test unpaired)
T5	3.03±1.63	3.43±1.69	0.806	NS(Student 't' test unpaired)
T15	2.13±1.67	2.48±1.52	0.821	NS(Student 't' test unpaired)
T30	1.53±1.51	1.83±1.43	0.871	NS(Student 't' test unpaired)
Incidence of PONV	5(16.66%)	4(13.33%)	0.832	NS(Chi Square test)

Values are expressed in mean±SD or percentage as applicable

Sig – Significant NS – Not Significant

**Table IV** Paediatric Anaesthesia Emergence Delirium Scale (PAED) Scale. Score is sum of all values.

Behavior	Not at all	Just a little	Quite a bit	Very much	Extremely
Make eye contact with caregiver	4	3	2	1	0
Actions are purposeful	4	3	2	1	0
Aware of surroundings	4	3	2	1	0
Restless	0	1	2	3	4
Inconsolable	0	1	2	3	4

## Discussion

Tonsillectomy with or without adenoidectomy is a long practiced and one of the most frequently performed surgical procedures in paediatric age. These operations appear to exhibit an increased

incidence of EA.<sup>5</sup> It is speculated that the sensation of suffocation in otorhinolaryngological procedures may be responsible for these events. Post anesthetic EA is a self-limiting phenomenon and etiology of EA in children is not fully understood



but possible risk factors are intrinsic characteristics of an anaesthetic, rapid emergence from anaesthesia, postoperative pain, preschool age, otolaryngologic surgical procedures, preoperative anxiety, and child temperament.<sup>2</sup> This complication can be severe and prolonged, exposing the patient to physical harm, pain or bleeding, and prolong the recovery period.<sup>7</sup>

In this study, the incidence and severity of EA were significantly lower with premedication of intravenous low dose ketamine (0.25 mg/kg body weight). Yoon Sook Lee et al.<sup>13</sup> found that ketamine was effective in the prevention of EA without delay in awakening and both subhypnotic doses of ketamine 0.25 and 0.5 mg/kg body weight were effective. Kawaraguch et al.<sup>14</sup> reported that the administration of ketamine 1 mg/kg after the induction of anaesthesia and the instillation of ketamine 1 mg/kg body weight/hr during surgery in pediatric strabismus surgery succeeded in decreasing EA. Abu-Shahwan et al.<sup>15</sup> showed that an intravenous injection of ketamine 0.25 mg/kg body weight, 10 min before the end of surgery in a dental operation for young children under general anesthesia with sevoflurane decreased the incidence of EA without a delay in recovery. Dalens et al.<sup>16</sup> reported that the intravenous administration of ketamine 0.25 mg/kg body weight or nalbuphine 0.1 mg/kg body weight in general anesthesia with sevoflurane for young children undergoing magnetic resonance imaging was effective in preventing the incidence of EA without delaying awakening or recovery. Regarding the mechanism of ketamine in reducing the incidence of emergence delirium, Lerman et al.<sup>17</sup> suggested that ketamine inhibits the central nervous system effect in ether-linked inhalation anaesthetics.

Studies have demonstrated lower incidences of EA when midazolam are administered in the perioperative stage.<sup>18,19</sup> Eun Jung Cho et al.<sup>20</sup> reported intravenous administration of 0.03 mg/kg of midazolam just before the end of surgery reduces emergence agitation without delaying the emergence time in children having strabismus surgery with sevoflurane anesthesia. Chen J et al.<sup>21</sup> also reported intravenous administration of a subhypnotic dose of midazolam (0.05 mg/kg body weight), in addition to fentanyl before discontinuation of sevoflurane, was also found to

be effective in decreasing EA. In contrast, others found that intravenous midazolam did not reduce the incidence of EA,<sup>22,23</sup> which is similar to our findings. A meta-analysis of pharmacological prevention of EA in children indicated that midazolam was ineffective in the prevention of EA in this context.<sup>24</sup>

Regarding postoperative pain score the present study using Wong-Baker FACES Pain scale, pain score was almost similar with ketamine or midazolam. Abu-Shahwan et al.<sup>25</sup> showed that ketamine 0.25 mg/kg body weight at induction time did not decrease postoperative pain in pediatric patients undergoing tonsillectomy. Batra et al.<sup>26</sup> in another study found that postoperative pain score after tonsillectomy in pediatric patients was not decreased by small dose ketamine. De Conceicao et al.<sup>27</sup> reported that a single dose of ketamine (0.5mg/kg body weight) in the pediatric patients undergoing tonsillectomy could reduce postoperative pain and use of rescue analgesia. This study suggested that small dose of ketamine or midazolam had no effective role in reducing postoperative pain in pediatric population.

The incidence of PONV after adenotonsillectomy is more than 70% and may cause serious complications such as pulmonary aspiration, hypoxemia, and increase chance of bleeding.<sup>28</sup> Studies that used low dose ketamine to decrease postoperative pain showed that low dose ketamine did not increase the incidence of PONV.<sup>29,30</sup> Splinter WM et al.<sup>31</sup> reported intraoperative administration of intravenous midazolam reduced vomiting in children after tonsillectomy. The current study showed that the incidence of PONV did not increase significantly with ketamine than midazolam. This study did not encounter a case of hemodynamic instability, or postoperative hallucinations or nightmares.

### Conclusion

Premedication with intravenous ketamine 0.25 mg/kg body weight was more effective than intravenous midazolam 0.1 mg/kg body weight in the prevention of early postoperative in reducing EA following tonsillectomy with or without adenoidectomy in pediatric patients under general anaesthesia. Both have no significant effect at this dose in decreasing postoperative pain and PONV in these patients.

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