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Evaluation of Safety Profile of Procedural Sedation and Analgesia using a combination of Intravenous Ketamine and Midazolam in the Paediatric Intensive Care Unit

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Abstract
Background: *Procedural sedation and analgesia (PSA) is a method of administering sedatives, analgesics and dissociative agents for sedation, anxiolysis and motor control for painful diagnostic and therapeutic procedures among the children. Various sedative or dissociative agents are employed during but they are associated with adverse events. In this backdrop, the present study was done to evaluate the safety profile of Ketamine and Midazolam as PSA agents in children.*
Materials and Methods: *This was a prospective and retrospective hospital based observational study conducted among the 294 children subjected to PSA for various diagnostic and therapeutic procedures. The primary outcome measure was any change in the hemodynamic variables during the PSA procedure. The secondary outcome was to identify the risk factors associated with adverse events during PSA.*
Results: *In this study the main indication for PSA was diagnostic in 65.3% of children. The overall success rate of PSA procedure was 99.5%.There were totally 56 primary outcome and the major outcome was change in blood pressure (>20%) in 6.5% of the patient. In primary outcome, two cases of laryngospasm and 1 case of convulsion were reported as serious adverse event. Regarding secondary outcome, dose of ketamine and midazolam and ASA status showed no significant association with adverse event. Meanwhile, children with age < 6months were significantly associated with adverse event (p=0.04).*
Conclusion: *The combination of ketamine and midazolam was found to be safer with high success rate in children undergoing PSA.*
Keywords: *Procedural sedation and analgesia, children, ketamine, midazolam, adverse events.*

Introduction

Procedural sedation and analgesia (PSA) is a treatment approach encompassing administration of sedative, analgesic agents with dissociative properties to reduce patient's consciousness to various levels. These agents augment the effective completion of painful interventions, with good safety profile without any airway complication such as agitation or difficulty in breathing.[1] The need of PSA outside the operation area displayed

a rampant growth for therapeutic and diagnostic modalities particularly in the emergency and the intensive care unit departments. [2] In children attending the emergency care, managing the pain, anxiety and fear is a challenging task for the pediatricians. If these symptoms are not properly recognized or treated it may lead to physiological and psychological stress among the children and impose long term morbidity.[3,4]

Wide range of clinical intervention needs an optimal sedation and analgesia for the successful outcome, physician's satisfaction and also to minify the anxiety and fear among the patients and their satisfaction. PSA outside the operation theatre always elicits marked advantage in terms of timely and economic care to the patients.[5]

The effective PSA agents must have promising effects on the regulation of the sedation, analgesia, amnesia, and motor function. Further, the PSA agents with faster onset time, stable and quick recovery with low adverse event profile are usually preferred. Albeit, numerous agents are available, none of the agents are superior over the others. So, various combinations of analgesics and sedatives are used in the clinical set up to achieve the desired effect and also to reduce the adverse effect.[6] However, PSA among the children is a difficult task since the sedation risk is higher in pediatric population.[7] The anatomic differences in the airway like smaller airway diameter, longer and floppy epiglottis, and the physiologic differences in drug metabolism between children and adults could predispose the former to a higher risk for adverse events related to sedation. In addition, the various pathological states affecting the airway, breathing, circulation, and neurological function elevates the risk during PSA.[8] Ketamine and midazolam are two agents commonly used for procedural sedation in the emergency setting.[9] A recent meta-analysis reveals the safety of Propofol and Ketamine for PSA among the pediatric population.[10] However the studies related to the safety profile of ketamine-midazolam is limited and in India the studies are scarce in PICU. In this backdrop, the present study was carried out to evaluate safety profile of a PSA protocol, ketamine-midazolam when implemented by Paediatric Intensivists in a tertiary PICU with a varied set of procedures being performed in patients with significant underlying morbidity.

Materials and methods

This was a prospective and retrospective hospital based observational study performed in PICU in a tertiary healthcare institute, Surya Children's Medicare Pvt. Ltd, Mumbai, from May 2015 to October 2017.The study was conducted after the formal approval from Institutional Ethics committee and patients were recruited after informed consent.

Sample Size calculation

In a large study by Grunwell et al.[8] it was estimated that adverse event rate in children undergoing PSA was 7.26%. For a 95% Confidence Interval and a margin of error (difference >or =3%) and the estimated sample size was found to be 287.

Inclusion criteria

PICU admitted patients requiring PSA for performing painful diagnostic or therapeutic procedures.

Children with age range 1 month to 18 years.

Patient's guardians providing the informed consent for the study participation

Exclusion Criteria

Patients with additional epidural analgesia/regional block/regional analgesia, mechanically ventilated patients and patients with contraindication for any of the study drugs were excluded from the study.

Procedure

After screening the patients based on eligibility criteria, a detailed clinical history of the patients for pre assessment was obtained such as hemodynamic variables and ASA status. All procedures requiring PSA were done in the PICU, all emergency equipment and drugs appropriate for the pediatric patient were available with

continuous cardiac monitoring along with electrocardiogram, pulse oximetry, noninvasive blood pressure.

PSA was given by trained PICU intensivists or Paediatric resident fellow under direct supervision of the Intensivists. Patients were given the drug in titrated aliquots according to a weight- based dosing schedule. The procedure was commenced when the sedating physician believed that an adequate depth of sedation had been achieved as observed by absence of wincing or withdrawal to painful stimulus. Vital signs will be recorded on the study proforma form every 10 minutes, most adverse value during the interval between two recordings would be noted until completion of the procedure and the reestablishment of clear verbal contact with the patient.

Post completion of procedure, the occurrence of adverse events and interventions, as well as procedural success, was recorded in study proforma. After recovery, patients were monitored for recovery agitation, hallucinations and other adverse events.

Outcome measures

Primary outcome measure - occurrence of one or more of the adverse events defined as - hypoxia/ desaturation (SpO2 <93%), hypoventilation (respiratory rate <8 breaths/min), apnea, laryngospasm, airway obstruction or aspiration (persistent hypoxia plus infiltrates on chest radiograph), cardiac arrest, convulsion variation in heart rate or blood pressure (heart rate/systolic blood pressure –variation of >20 %), nausea, vomiting, occurrence of emergence delirium, cough and increased secretions. Apnea, laryngospasm, airway obstruction or aspiration (persistent hypoxia plus infiltrates on chest radiograph), cardiac arrest and convulsion were defined as serious adverse events.

Secondary outcome measures- Identification of risk factors associated with increased odds for adverse events - ASA grading, age, cumulative doses of Ketamine and Midazolam.

Statistical Analysis

The data was represented as mean ± standard deviation (SD) for normally distributed quantitative parameters and median with inter-quartile range for non-normally distributed quantitative parameters. The categorical parameters were expressed as proportions for their incidence in the study groups. Adverse events were represented as proportion rates. Odds ratio was calculated to identify risk factors associated with increased risk of primary outcome events. P value <0.05 was considered as statistically significant.

Results

The mean age of the study population was 2.92±0.76 years and majority of the children were at the age range ≤ 6 months, which constitute about 29.9%. Among the children, 158 (53.7%) were males and 136 (46.3%) were females. The main indication for PSA was diagnostic 192 (65.3%), followed by therapeutic in 102 (34.7%) children. Further, the Lumbar puncture (Diagnostic and therapeutic) was the main indication for PSA in 181 children (61.6%). In this study, majority of the patients 113 (38.4%) were from ASA grade II.

The overall outcome of the PSA procedure 99.5%. The mean cumulative dose used was 1.306 ± 0.4920 mg/kg for ketamine and 0.137 ± 0.0456 mg/kg for midazolam. The mean duration of the procedure was 23.9 ± 5.52 minutes. Supplemental oxygen was required by 98 (33.33%) patients which was delivered at a median rate of 2 liters/min with range from 0.5 to 6 liters/min. Further, 56 patients out of a total of 294 patients (19.04%) had a primary outcome event as defined in the study outcomes criteria. The total number of individual components of these events was 67.

The individual components of primary outcome events were described in the table 1.The most commonly encountered adverse event was change in blood pressure (>20 of baseline). All these events were decrease in blood pressure and this was observed in 19 (6.5%) patients. Events when

patients developed decrease in heart rate > 20% of baseline were 16 (5.4%). Twelve patients (4.1%) patients developed hypoxia/ desaturation and all these 12 patients were provided rescue intervention with supplemental O2. 2 patients (0.7%) experienced laryngospasm and were rescued with mechanical ventilation. Out of 56 patients, 14 experienced adverse events requiring rescue intervention. Increased secretions were observed during 9 (3.1%) PSAs. Seven (2.4%) patients developed nausea and vomiting, out of which nausea was reported in all 7 patients and none of the patients developed vomiting in the observation period. One patient (0.3%) developed emergence reaction in the form of hallucination in recovery period.

Table 1: Distribution of Individual Components of Primary outcome events (N=56 patients, 67 individual components of primary outcome events)

Events	No of adverse events	Proportion
Any Adverse Events		
Hypoxia/Desaturation	12/294	4.1%
Airway Obstruction/Aspiration/Apnea	0/294	0.0%
Change in blood pressure (>20%)	19/294	6.5%
Change in heart rate (>20%)	16/294	5.4%
Nausea	7/294	2.4%
Vomiting	0/294	0%
Emergence reaction(hallucination)	1/294	0.3%
Cough(new/worsened)	0/294	0.0%
Increased secretions	9/294	3.1%
Serious Adverse Events		
Laryngospasm	2/294	0.7%
Convulsion	1/294	0.3%

Out of 56 primary outcome events, 3 events were serious AEs (4.5%). These included 2 events of laryngospasm during the procedure and one event of convulsion (accompanied by desaturation) after the procedure. 2 of these patients had a baseline ASA physical status grade of Vand1of these patients had ASA physical status grade of 2. The patients of laryngospasm were treated with mechanical ventilation as the rescue measure. The patient with convulsion was provided supplemental oxygen in view of desaturation and was provided anti convulsant treatment appropriate for the age and weight based on institutional practice. Out of 56 patients, 14 experienced a primary outcome event requiring rescue intervention. Further, 12 patients were rescued with supplemental oxygen (mask or hood delivery) and 2 patients required mechanical ventilation. The results were showed in table 2.

Table 2: Rescue intervention among the Study Population

Type of rescue analgesia	No of Patients	Patient type
Supplemental O2	12	Hypoxia/desaturation = 11 Convulsion with desaturation = 1
Ventilation	2	Laryngospasm = 2

Meanwhile, a subgroup analysis was done to find the association between PSA agent used and primary outcome events. The rate of occurrence of primary outcome event in the patients with cumulative dose less than or equal to Ketamine 2mg/kg + Midazolam 0.2 mg/kg was 18.7% while the same was 25% in the higher dose group and it was not significant (p=0.59). The results were shown in table 3.

Table 3: Effect of the Cumulative Doses of Midazolam and Ketamine on Occurrence of Primary Outcome Events

Cumulative Dose	Primary outcome event (n=56)	No of primary outcome event	No of patients	Odds Ratio, 95% Confidence interval and P value
Ketamine ≤ 2mg/kg + Midazolam ≤ 0.2mg/kg	53(18.7%)	230	283	0.69, (0.18 to 2.64) p=0.59
Ketamine >2.0 mg/kg + Midazolam >0.2 mg/kg	3(25 %)	8	11	

The incidence of primary outcome events was 33% in the patients of age 1 year or younger, 11.62% in the patients of age group 1-5 years and 18% in the patients more than 5 year old. Odds ratio was calculated taking age group1-5years as baseline. Patients in the age group of less than1year old had significant chance of higher primary outcome events (p=0.04). The results were shown in table 4.

Table 4: Effect of Age Distribution on Occurrence of Primary Outcome events

Age group	Primary outcome events (n=56)	No primary outcome events	Total No of patients	Odds Ratio, 95% Confidence interval and P value
≤ 1year	33(22.14%)	116	149	2.16,(1.0 9 to 4.64), P=0.048
1 to 5 years	10(11.62%)	76	86	1, (0.39 to 2.54) ,P=1
>5years	11(18.3%)	49	60	1.70, (0.67 to 4.32) , P=0.26

In addition, another subgroup analysis was done to identify if ASA physical status of the patient affected the primary outcome events. The incidence of primary outcome events was 17.3%, 12.38%, 17.46%, 33.9% and 40% in the ASA grades I to V respectively. Odds ratio was calculated taking ASA Grade I as baseline. None of the results were statistically significant. The incidence of SAE was 1.02% - among 2 patients with ASA physical status grade V and 1 patient with ASA grade II. The results were shown in table 5.

Table 5: Effect of ASA Status on Occurrence of Primary Outcome Events

ASA status	Primary outcome event	No of primary outcome event	Total No of Patients	Odds Ratio, 95% Confidence interval and P-value
I	9(17.3%)	43	52	1, (0.36 to 2.76), P=1
II	14(12.38%)	99	113	0.67, (0.27 to 1.68), P=0.40
III	9(17.46%)	54	63	0.8, (0.29 to 2.18), P=0.66
IV	18(33.9%)	38	56	2.26,(0.91 to 5.63), P= 0.08
V	4(40%)	6	10	3.18,(0.74to 13.64), P=0.12

Discussion

Procedural sedation in pediatric patients is employed in the various medical procedures such as radiology, dentistry, emergency department and nuclear medicine. Neonates and infants may not express the pain verbally and depend on the care takers or physicians and it can be recognized only by their behavioral and physiological responses. Development of novel pharmacological agents or any non invasive monitoring technique is used for the administration of short acting sedative by ensuring the safety of children.

Previous reports show that synergistic use of opioids and benzodiazepines elicits marked sedation but imposes significant risk of respiratory depression in children.[11] Midazolam, a short acting benzodiazepine, is routinely used in the pediatric protocols for procedural sedation and elicits good amnesia and anxiolytic properties. Ketamine is a dissociative anesthetic and produces excellent analgesia, amnesia and sedation for painful procedures in children. [12]

In our study, mean age of study population was 2.92±0.76 years and majority of the children are under the age less than 6months. Meanwhile in a study done by Agarwal et al.[13] the mean age of the children is 5.90 years which is slightly higher when compared to the present study. In the present study, lumbar puncture (Diagnostic and therapeutic) was the main indication for PSA in encompassing 61.6%. Similar to our report, Borkar et al.[14] used PSA for therapeutic lumbar puncture in 78.18% of children.

The overall procedure success rate in the present study is 99.5%, with a failure in one children aged 1.5 months with meningitis and ASA grade III and PSA could not be completed as a result of traumatic tap. Similarly, in a study done by Brown et al.[15] the PSA success rate was 96.82% using ketamine and midazolam in autism children. In another study done by Borker et al.[14] 100 % procedure success rate was documented using combination of Midazolam and Ketamine.

The incidence of adverse events in our study is 19.04%. In a study done by Grunwell et al.[8] the incidence was 7.3%, whereas most other studies reported an AE rate in the range of 12.9% - 27%.[14,16] The incidence of SAE in our study is 1%, which is in line with the study done by Grunwell et al.[8] with SAE rate of 1.77% .The serious AEs included 2 episodes of laryngospasm and one episode of convulsion. Patients with two of these SAEs had higher ASA grade (grade 5) whereas 1 of them had ASA grade 2.

In our study hypoxia/desaturation was reported in 4.1% of patients and all these patients were rescued with supplemental oxygen. Miqdady et al.[17] reported desaturation in 12.3% patients. Further, change in blood pressure >20% of baseline observed in 19 patients. In a study done by Khutia et al. [18]the incidence of hemodynamic events (variation in blood pressure) was reported as 14.6%. Increased secretions were observed in 9 (3.1%) patients. In a study done by Grunwell et al.[8] the incidence of increased secretions was 0.7%. Nausea was reported in 7 (2.4%) patients and similarly Grunwell et al.[8] reported an incidence of 1.1%.

The mean dose of ketamine and midazolam used in the study population was 1.306 ± 0.492 mg/kg and 0.137 ± 0.045 mg/kg respectively. One of the studies which included higher doses of ketamine (≥2.5 mg/kg initial dose or ≥5 mg/kg total dose) for analysis by Green et al.[19] observed that these higher doses were the predictors of higher airway events. In the study by Grunwell et al.[8] the total IV dose of more than 5mg/kg was associated with significant increase in adverse events and SAEs, while total IV dose of 2.5mg/kg was associated with increase in adverse events.In the present study, that the incidence of primary outcome events higher in ASA grade VI and V with 33.9% and 40% respectively. Previous reports shows that, children in ASA classes III and IV are at increased risk of adverse events if subjected to sedation, especially moderate or deep sedations.[20]

Conclusion

The ketamine and midazolam combination provided close to 100% success rate in PSA with a clinically favorable safety profile. The study results are in alignment with the existing literature for similar objectives and pharmacological interventions.

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