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Safety of midazolam-propofol combination for sedation in pediatric patients undergoing gastrointestinal endoscopy

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Abstract
In recent years, the number of pediatric gastrointestinal procedures with anesthesia has increased. Purpose of this study is to evaluate the safety and efficacy of midazolam and propofol combination used in pediatric patients by anesthesiologists for upper and lower gastrointestinal system endoscopy and determine whether there is any difference in the sedation complications and recovery of anesthesia between age groups. The records of 273 patients aged between 3 and 17 who underwent upper and/or lower gastrointestinal system endoscopies were analyzed retrospectively. Complications, vital signs and modified Aldrete recovery scores were recorded. The patients were grouped as those under and over 5 years of age for comparison. There was no significant difference in the rate of complications between age groups (p =0.42, p=0.72). The rate of attained recovery for patients under 5 years of age and over 5 years of age were statistically significant at the 5th (p=0.014). The present study demonstrates that deep sedation with propofol and midazolam combination for pediatric elective esophagogastroduodenoscopies are provided safely by anesthesiologist with close monitoring. Patients under 5 years of age tend to recover more slowly from the drug effects. Thus, we recommend closer follow-up for children under 5 years of age in post-procedure period.

Keywords: Propofol, midazolam, pediatrics, endoscopy

Introduction

Endoscopic interventions in pediatrics have become more common in recent years. Performing endoscopic interventions without sedation is a difficult and stressful experience for pediatric patients, while it also increases the time required to complete the procedures, as well as the potential for complications associated with the procedures [1]. For these reasons, providing sedation and anesthesia is important and valuable in pediatric endoscopy.

Gastrointestinal endoscopic procedures are challenging due to extensive anxiety and non-cooperation in the pediatric age groups. For this purpose, opioids (eg, fentanyl or meperidine) benzodiazepines (eg, midazolam or diazepam) and hypnotic agents (eg, propofol) are used alone or in combination. Benzodiazepines and opioids are usually used for mild sedation, whereas propofol, an ultra-short-acting anesthetic, is used for moderate or deep sedation [2]. Although there are many studies related to procedural sedation with drug combinations in adult patients, this issue is still limited and a significant debate prevails regarding the efficacy and safety of anesthetic agents used for these purposes in pediatric populations [3]. One such combination is midazolam used as premedication prior to the procedure and propofol for deep sedation [4]. These combination offers synergistic anesthesia effects, allowing for the use of lower doses and increased sedation comfort [5,6].

The purpose of this study is to evaluate the safety and efficacy of midazolam and propofol combination, which is pediatric sedation protocol of our Anesthesiology clinic, used in pediatric patients for upper and lower gastrointestinal system (GIS) endoscopy and share our experiences with the literature. We also determined whether there is any difference in the sedation complications and recovery of anesthesia between age groups.

Material and Methods

This study was carried out in procedural sedation data of Pediatric Gastroenterology Department between September 2011 and

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September 2015 using the data of patients who were sedated with propofol and midazolam for upper and lower gastrointestinal endoscopy by anesthesiologists. This sedation protocol is our standard of care for pediatric gastrointestinal procedures. The records of 273 patients aged between 3 and 17 who underwent upper and/or lower GIS endoscopy for diagnosis and treatment were analyzed retrospectively.

Approval from our hospital Local Ethics Committee was obtained prior to the study (No: 50687469-1771-13/1648.4-1932). Patients' guardians provided two separate written consents, one for anesthesia and one for endoscopy procedures prior to interventions. Intravenous lines were placed using 22–24 gauge angiocaths in the premedication room by anesthesiologists. Just before the patients were carried to the procedure rooms, midazolam (Dormicum; Deva, F. Hoffmann, Fontenay, France) was given intravenously (dose: 0.05 mg/kg, max. 2.0 mg/kg). Vital signs such as heart rate, oxygen saturation and non-invasive blood pressure was monitored and 2 L/minute oxygen via nasal cannula was administered throughout the procedure. Propofol (Propofol; Fresenius Kabi, Uppsala, Sweden) was administered by 20 mg repeated doses by anesthesiologists at two minutes intervals followed by 5.0 ml normal saline flush for to provide the desired sedation level at the dose of 1–2 mg/kg until the eyelash reflexes and extremity movements disappeared. If patient movements and gag reflexes were observed during the procedures, additional doses of propofol at 0.5 mg/kg were given. All the endoscopy and anesthesia procedures were performed by the same experienced pediatric endoscopist and anesthesiologist. Patients were moved to the recovery room where they were monitored by an experienced nurse in the lateral position with supplemental oxygen provided after the procedure.

Hemodynamic variables, total drug doses, procedure duration, adverse effects and complications were recorded before, during, and after the procedures. Hypoxia [SpO2 < 90%], bradycardia [20% less than the initial value], tachycardia [20% more than the initial value], hypotension [20% less than the initial systolic value], hypertension [20% more than the initial systolic value]) laryngospasm, apnea, local allergic reaction and anaphylaxis were defined as adverse effects and complications. Modified Aldrete recovery scores at 5, 10 and 60 minutes, as well as the entry and exit times to the recovery room were also recorded. Those who had modified Aldrete scores of eight and above and who were fully awakened were transferred to the pediatric gastroenterology ward for further observation of 6–10 hours. Patients who developed no contraindication at the end of the observation period were discharged from the hospital.

As the airway management would be more difficult due to anatomical differences and have more tend to come up complication under the age of 5 years patients were evaluated in different group. We compared complication rates, duration of the procedure and rate of recovery at consecutive time points between two groups.

The data obtained for the study were analyzed using the Statistical Package for Social Sciences (SPSS) version 15.0 (SPSS Inc., Chicago, IL, USA). A chi-square test was used to compare categorical variables. The continuous variables were given as "average ± standard deviation." The normality of the data was tested using the Kolmogorov-Smirnov test. Comparisons were made with the Kruskal-Wallis and Mann Whitney-U tests. A p-value less than 0.05 was considered statistically significant.

Results

The study population was consisted of 116 (42.4%) males and 157 (57.6%) females. Thirty-two of the patients were ≤5 years (Group I) while 241 were ≤5 years (Group II). Of the 273 patients, 203 had only upper GIS endoscopies, 34 had lower GIS endoscopies, while 36 had both upper and lower GIS endoscopies (Table 1). The average duration for the upper GIS endoscopy was 7.59±4.46 min, while it was 19.44±8.39 min for the lower GIS endoscopy, and 25.93±9.65 min for the combined upper and lower GIS endoscopies.

The difference of complication rate during or after the procedures between age groups was evaluated. The complication rates during the procedure for Group I was 15.6% (5/32) while it was 18.6% (45/241) in Group II. Similarly, the complication rates after the procedures for Group I was 6.2% (2/32), while it was 4.1% (10/241) for Group II (Table 2). There were no significant differences between the two groups in terms of complications rates during or after the procedures (p=0.42, p=0.72). The average duration of UGSE, LGSE and U&LGSE procedure durations were 7.59±4.46, 19.64±7.86, 25.92±9.13 minutes respectively.

Among the groups, recovery rate for consecutive time points are presented in Table 3. Patients under the age of 5 required longer time to recover. The difference was significant mainly at 5 minutes after the procedures. Patients in both age groups recovered enough to be sent to the wards one hour after the procedures.

The average time spent in the recovery room was 39.76±17.2 minutes.

Table 1. Demographics data. (Group I: 5 years and under 5 years of age, Group II: older than 5 years of age.)

Age Distribution	Group I (n: 32)			Group II (n:241)		
Gender	20 males (7.4%)		12 females (4.4%)	96 males (35.1%)		145 females (53.1%)
Type of the Procedure	UGE (n:18)	LGE (n:8)	U&LGE (n:6)	UGE (n:185)	LGE (n:26)	U&LGE (n:30)

(UGE: Upper Gastrointestinal System Endoscopy, LGE: Lower Gastrointestinal System endoscopy, U&LGE: Upper and Lower Gastrointestinal System Endoscopy, min: minutes)

Table 2. List of indications for endoscopy procedures

Upper GIS endoscopy	Indications
	Dysphagia and dispeptic complaints
	Upper abdominal or chest pain
	Known or suspected ingestion of a caustic material
	Unexplained iron deficiency anemia
	Gastrointestinal tract bleeding
	Malnutriusion
	Nausea and vomiting
	Diarrhea
	Dilation
	Removal of foreign body
	Follow-up of selected ulcers or mucosal abnormality
Lower GIS endoscopy	Lower abdominal pain
	Unexplained gastrointestinal bleeding
	Diarrhea
	Evaluation of inflammatory bowel disease
	Polypectomy
	Removal of foreign body
	Malignancy screening

Table 3. Complication rates during and after the procedures in Group I and Group II.

	Group I	Group II	p
Total Complication Rates During The Procedures	15.6 % (5/32)	18.6 % (45/241)	0.42
Total Complication Rates During The Procedures	6.2 % (2/32)	4.1 % (10/241)	0.72

Table 4. Level of consciousness of patients under and over 5 at the 0th, 5th, 10th, 30th, and 60th minutes after the procedures (Aldrete score of 8 and above is considered conscious)

Post-procedure time	Aldrete score of 8 and above in Group I	Aldrete score of 8 and above in Group II	p
0th minute	15.4	34	0.22
5th minute	23.1	63	0.014
10th minute	53.8	88	0.06
30th minute	72.7	96.7	0.24
60th minute	100	100	1

Discussion

In the present study, we evaluated the complication rates and recovery times for children who were deeply sedated with propofol-midazolam combination for endoscopic gastrointestinal procedures. Intraoperative and postoperative complication rates were similar between children under and over 5 years of age. Children below 5 years of age were tended to recover slower compared to older ones, particularly significant at 5th minute postoperatively.

Anesthetic agents can be used alone or combined for sedation in pediatric GIS procedures [7]. Drug combinations are preferred for procedural sedation because this may reduce individual drug doses to attain desired effects and limit adverse effects while potentiating the individual drug effects [8-11]. In pediatrics, the two most commonly used anesthetic agents are propofol and ketamine [12-13]. Vardi et al. [14] compared propofol and ketamine in pediatric patients and found that both agents were provided effective sedation but while patients who received propofol recovered from anesthesia sooner and spent less time in the recovery room, propofol was caused temporary respiratory depression and hypotension. In another study Kapklein et al. [15] indicate that the recovery time for patients who received propofol was nearly half of those who received ketamine; however, while the propofol group required more respiratory support and experienced greater variances in blood pressure, ketamine group more often experienced hallucinations and discomfort during recovery from anesthesia.

A common drug combination used for sedation in pediatrics is midazolam and propofol, which creates synergistic effects. Midazolam is a safe and reliable anesthetic agent that can be use alone in a variety of conditions, including upper GIS endoscopy in pediatrics but it has adverse effects, such as respiratory depression, dysphoria, nystagmus, diplopia, and hiccups. Propofol is also an effective anesthetic agent that has quicker onset and faster recovery time compared to other anesthetic agents [16-18]. However, propofol may cause cardiac and respiratory depression, apnea, and hypotension compared to other sedatives [19, 20]. Propofol in combination with midazolam significantly reduced the total dosage of propofol and ease of the procedure with minor side effects [21]. It was reported that when midazolam used as a premedication agent at a dose of 0.05 mg/kg intravenously with a maximum of 0.2 mg/kg and propofol for inducing and maintaining deep sedation, is a safe and effective option for endoscopic procedures in pediatrics [22]. If propofol was used as the sole anesthesia agent in pediatrics undergoing upper GIS endoscopy, the complication rate, including tachycardia, apnea, and desaturation, was reported as 19%, while the same rate was only 6% when midazolam was added as a combination drug [21].

In the present study, the rate of minor complications during the procedures, such as desaturation, apnea, bradycardia, tachycardia, hypotension, and hypertension, was 18.3%. All of these adverse effects disappeared once the procedures were complete. Complications rate after the procedure was 4.4%. There was no major adverse effects or complications observed during or after the procedures. Tachycardia was the most common (13.3%, n=36), while desaturation that reflecting respiratory depression was the least common complication (1.8%, n=5) observed in the current study. Of the five desaturated patients, only one required ventilation support while the remaining four patients' saturation levels improved spontaneously (SpO_2 > 90%) following simple repositioning of the airways. None of the patients required endotracheal intubation. The results of the present study support the use of midazolam and propofol in combination for sedation and anesthesia purposes in pediatrics undergoing upper and lower GIS endoscopies.

Younger children (under 5 years of age) are more prone to laryngospasm and apnea due to their larger tongues and narrower tracheas. So, they should be more closely monitored during and after procedures such as endoscopies. In the present study, there was not revealed any significant difference between the age of the patients and the rate of complications resulting from sedation during or after the upper and/or lower GIS endoscopy. However,

recovery time for the patients under five was significantly longer compared to those over five. While the complete recovery rates were similar for both age groups at the 0th, 10th, and 30th minutes, significant differences were observed at the 5th minute ($p<0.05$). At the 60th minute, the recovery rates were 100% in both groups ($p=1$). These findings indicate that it takes longer for younger children to recover from anesthesia drugs; thus, they must be monitored closely after the procedures.

There are several limitations in our study, for example number of the patients under 5 years old is less than number of the patients above 5 years old. This significant difference has reduced the power of the comparison between the two groups. Also, total dose of the drugs used throughout the procedure is a strong predictor for recovery time and these data is missing.

Conclusion

The findings of the present study showed that the synergistic effects attained by the combined use of midazolam and propofol in patients undergoing upper and lower GIS endoscopy are safe and applicable. Patients under 5 years of age tend to recover more slowly from the drug effects. Thus, we recommend closer follow-up for children under 5 years of age in post-procedure period.

Conflict of interest
The authors declare that there are no conflicts of interest.

Financial Disclosure
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Ethical approval
Consent of ethics was approved by the local ethics committee.

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