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Propofol-ketamine versus propofol-tramadol sedation in children undergoing gastrointestinal endoscopy

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ABSTRACT

Numerous combinations of drugs are used for sedation in upper gastrointestinal endoscopies. The aim of this study was to compare the quality of two sedation regimens in upper gastrointestinal endoscopy performed on pediatric patients. After the study approval by the local ethics committee of Ondokuz Mayıs University Hospital, written informed consent was obtained from parents. Eighty patients between the ages of 1 and 18 were randomized into two groups. Group K (n=40) received propofol 1 mg/kg + 1 mg/kg ketamine intravenously. Group T (n=40) received propofol 1 mg/kg + 1 mg/kg tramadol intravenously. In both groups, additional propofol (0.5 mg/kg) was administrated when a patient showed signs of discomfort, in order to maintain a Ramsey Sedation Scale of 4 to 5. In Group K, additional propofol requirements were significantly lower compared to Group T (p=0.003). Group K had significantly higher sedation scores than Group T at 3rd min. (p=0.028) and 20th min. (p=0.015). Recovery time increased significantly in Group K (p=0.002). Although there was no difference between two groups concerning the propofol consumption, both groups required additional propofol and tramadol resulted in a shorter recovery time compared to ketamine.

1. Introduction

Increasing numbers of gastrointestinal endoscopic procedures are being performed outside the operating room (Kuzhively and Pandit, 2019).

Gastrointestinal endoscopies (GIE) are the most useful procedures for diagnosing and treating gastrointestinal tract disorders (Van Beek and Leroy, 2012). This procedure requires moderate/deep sedation as described by the American Society of Anesthesiologists (ASA) (American Society of Anesthesiologists, 2002). Although at least moderate sedation is necessary to maintain spontaneous ventilation, some children undergoing endoscopy require deep sedation. As levels of sedation can change rapidly, maintaining spontaneous ventilation and patient safety is quite difficult. The most commonly used medications for pediatric sedation are barbiturates, benzodiazepines, propofol, ketamine, and opioids (Van Beek and Leroy, 2012). This study was aimed to compare the clinical efficacy and safety of a propofol–ketamine combination and of a propofol–tramadol combination in children undergoing GIE.

2. Materials and methods

After approval of the study by the local ethics committee of Ondokuz Mayıs University Hospital (OMU-KAEK 2012-113, 30.11.2012), written informed consent was obtained from parents. Eighty ASA physical status I–II patients, ages 1 to 18 who were scheduled for upper gastrointestinal endoscopies (UGIE), were randomized using a sealed envelope assignment. Patients were excluded from the study if they had a history of allergic reactions to the study drugs, eggs, or soybeans; a history of behavioral problems and neurological impairment; preexisting respiratory conditions and previous difficult intubations.

The patients, pediatric endoscopist, and anesthesiologist were blinded to the study groups. Another anesthesiologist administrated the study drugs and monitored the patient. No sedative premedication was administered, and patients fasted for at least 6 h before the intervention.

Patients were divided into two groups. The ketamine group (Group K, n=40) received propofol (propofol-lipuro; 10 mg/mL, Braun, Philippines) 1 mg/kg + 1 mg/kg ketamine (ketalar; 50 mg/mL ketamine hydrochloride, Pfizer USA) intravenously (IV), while the tramadol group (Group T, n=40) received propofol 1 mg/kg + 1 mg/kg tramadol (contramal; 100 mg/ampul, Abdi İbrahim, Turkey) IV. Patients in both groups received 1 mg/kg propofol for sedation induction. In both groups, additional propofol (0.5 mg/kg) was administrated when a patient showed signs of discomfort in order to maintain a RSS of 4 to 5. The heart rate (HR), mean arterial pressure (MAP), peripheral oxygen saturation (SpO_2), respiratory rate (RR), and Ramsay sedation scores (Ramsay et al., 1974) of all patients were recorded at baseline, after induction, and every five min thereafter during the procedure by an anesthesiologist blinded to the study.

The following data were recorded for each patient: Age, sex, weight, duration of the procedure (defined as the time from oral insertion of the endoscope to its withdrawal), recovery time (defined as the time to reach a Steward Recovery score (Steward, 1975), number of patients who needed additional propofol, and adverse effects during and after the procedure.

Adverse events included laryngospasm [wheezing, stridor, seizure (generalized tonic-clonic activity) and dyspnea], changes in the MAP and HR of at least 20% from baseline, oxygen desaturation with SpO_2 of < 90% for more than 15s, increased secretions (which require suction), nausea, vomiting, and agitation. After the end of procedure, during the recovery period agitation was evaluated by four-point scale (Watcha et al., 1992); 1= calm, quite, 2= crying, but can be consoled, 3= crying, cannot be consoled, and 4= agitated and thrashing around. Children with an agitation score of 3 or 4 were classified as agitated.

Statistical analysis was performed using Statistical Package for Social Sciences, version 20.0 (SPSS Inc., Chicago, IL, USA). Between-group comparisons of numerical data were analyzed using the Mann–Whitney U Test or a t-test. Adverse events and additional propofol required were analyzed using Fisher's exact test and Pearson's chi-square test respectively. A repeated measures analysis of variance was used to evaluate respiratory rate and hemodynamic data. Statistical significance was reached when the $p < 0.05$.

3. Results

Eighty patients ranging in age from 1 to 18 successfully completed the procedure. There were no statistically significant differences between groups with respect to age, sex, weight, duration of the procedure, agitation score, or adverse events.

Compared to Group T, Group K had significantly lower additional propofol requirements (p=0.002, Table 1) and significantly higher sedation scores at the 3th min (p=0.028) and 20th min (p=0.015) (Fig. 1). The recovery time was significantly higher in Group K than Group T (p=0.002, Fig. 2).

Table 1. Number of patients required one or more additional propofol boluses (p=0.002).

	Group K (n=40)	Group T (n=40)	P value
Additional propofol required	21 (52.5%)	34 (85%)	0.002

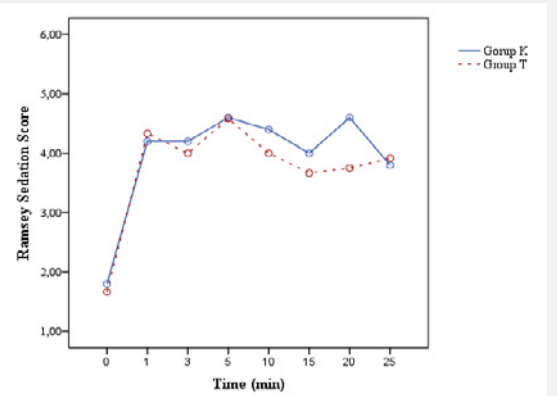

Fig. 1. Ramsey sedation scores in both groups. Significantly higher sedation scores 3th min (p=0.028) and 20th min (p=0.015) in group K.

Comparisons of the groups' HR, MAP, RR, SpO_2, duration of the procedure and number of adverse events did not reveal any statistical significance. One patient in each group experienced an adverse respiratory event. Respiratory depression requiring bag-valve-mask ventilation, occurred in one patient in each group. Other adverse events for ketamine group included tachycardia (4), nausea (1), laryngospasm (1), and increased secretions (1). As for the tramadol group bradycardia and hypotension occurred in 1 patient, but

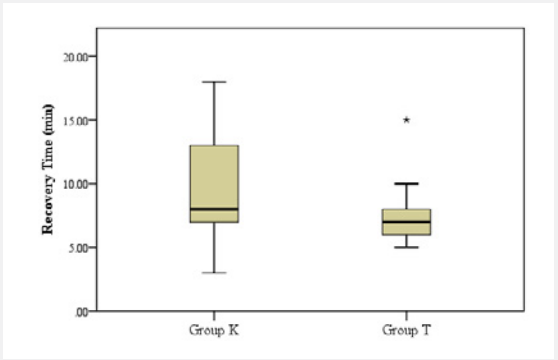

Fig. 2. Recovery times in both groups. The recovery time was significantly higher in Group K than Group T (p=0.002).

there were no significant differences between the study groups (Table 2). We observed emergence agitation only in one patient in Group K.

Table 2. Type and frequency of adverse events (p>0.005).

	Group K	Group T
Hypotension	-	1 (2.5%)
Bradycardia	-	1 (2.5%)
Tachycardia	4 (10%)	
Decrease in SpO2	1 (2.5%)	1 (2.5%)
Laryngospasm	1 (2.5%)	-
Increase in secretions	1 (2.5%)	-
Nausea	1 (2.5%)	-
Vomiting	-	-
Agitation	1 (2.5%)	-

4. Discussion

The aim of this study was to evaluate the effects of a propofol–ketamine combination and a propofol–tramadol combination on hemodynamics, quality of sedation, recovery profile and adverse events in pediatric patients undergoing UGIE. Endoscopic procedures are frequently performed outside the operating room. While medical centers perform different approaches, there is no ideal protocol for sedation in children during endoscopic procedures (Chung and Lightdale, 2016). The ideal sedative agent for endoscopic procedures should have a rapid onset and a short duration of action (Stogiannou et al., 2018). Propofol is commonly used for sedation outside the operating room. Beyond its sedative hypnotic effect, though, propofol has no analgesic properties. Therefore, it is frequently combined with analgesic drugs, especially opioids. The combination of propofol and ketamine has been associated with effective sedation and analgesia during UGIE.

Ketamine has many advantages. First, in addition to its analgesic effects, it acts as an anxiolytic and amnesic drug while protecting airway reflexes. It has a short duration of action and allows rapid recovery, (Roelofse, 2010). Sharieff et al. reported the patient receiving single dose 0.5:1 ratios of ketamine: propofol showed rapid recovery. In contrast, prolonged recovery was associated with continuous infusions, especially 1:1 ratio of propofol ketamine mixture (Sharieff et al., 2007; Kramer et al., 2012; Finn et al., 2014). In our study 1:1 ratio of propofol:ketamine combination was probably associated with prolonged recovery in group K. Besides its advantages, ketamine is associated with laryngospasm, hypersalivation, emergence delirium. Brecelj et al. reported potentially dangerous laryngospasm and hypersalivation in 5% of patients in both study groups (Brecelj et al., 2012). Incidence of laryngospasm was relatively higher (13.9%) in preschool-age children (< or =6) than school-age children (3.6%) (Green et al., 2001). In our study, laryngospasm occurred in one patient who was six years old and sedated with ketamine - propofol (2.5%). It is reported that using propofol and ketamine as combination may lead to lower rates of adverse events. Likewise, hypersalivation occurred in only one child who was also sedated with ketamine – propofol (Alletag et al., 2012). Another important adverse event is the emergence agitation, common undesired effects of ketamine, are significantly decreased with the addition of propofol (Alletag et al., 2012). Thus, we observed emergence agitations in only one patient who did not need any treatment.

Many studies have evaluated vomiting during pediatric procedural sedation. In three different studies in which the effects of sedation with ketamine were investigated, the frequency of vomiting among children was 17%, 19.4% and 18.9%, respectively (Wathen et al., 2000; Langston et al., 2008; Brecelj et al., 2012). In the present study, we observed nausea in only one patient in the ketamine group and none in the tramadol group. We did not observe any vomiting. This result may be related to the antiemetic property of propofol.

Combinations of drugs use lower doses of each agent and might reduce their hemodynamic effects. In our study, there were no differences in hemodynamic instability between the study groups. It was recommended a combination of ketamine–propofol, rather than fentanyl–propofol, for hemodynamic stability (Guit et al., 1991). UGIEs are among the most common outpatient procedures, and the most frequent adverse events during procedural sedation are respiratory (Van Beek and Leroy, 2012). Therefore, we used tramadol to avoid respiratory adverse events such as hypoxia and laryngospasm. In addition to a weak opioid analgesic effect, tramadol has less sedation potency, respiratory depression, and minimal

gastrointestinal dysfunction compared opioid drugs. In our study, the number of patients with additional propofol requirement were significantly higher in the tramadol group than the ketamine group. In addition, the tramadol group had significantly lower sedation scores than the ketamine group. In our opinion, these findings are related to the weak sedative property of tramadol. Thus, recovery time was significantly shorter in the tramadol group than the ketamine group. Rare adverse effect profile and shorter recovery time improving patient safety and lowering costs, reducing length of hospital stay can release capacity in the system (including beds and staff time) and enabling the hospital to serve more patients.

Our study has some limitations. First, we do not know whether patients experienced unpleasant dreams and hallucinations after the procedures. Different doses could be compared in larger patient groups undergoing UGIE. Finally, these regimens might not suitable for longer procedures.

The present study demonstrated that, combination of tramadol-propofol result in a faster recovery without increase the rate of adverse effects. However, patients required additional propofol due to insufficient sedation, so tramadol should be considered for short procedures.

Acknowledgments

Ethical approval

The experimental protocol of this study was reviewed and approved by the Clinical Research Ethical Committee of Ondokuz Mayis University, Samsun, Turkey (Ethical Committee Number: OMU-KAEK 2012-113, 30.11.2012).

Informed consent

Parental permission consent document was obtained from both parents/legal guardians in this study.

Conflict of interest

The authors declare that they have no conflict of interest.

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