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Original Scientific Article

USE OF BISPECTRAL INDEX (BIS) FOR MONITORING OF SEDATION AND TOTAL INTRAVENOUS ANESTHESIA (TIVA) IN PEDIATRIC PATIENTS UNDERGOING COLONOSCOPY

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Abstract. *The objectives of this study were to determine whether there was a correlation between bispectral index (BIS) and Ramsey Sedation Scale (RSS) in regard to the type of sedation and total intravenous anesthesia (TIVA) during colonoscopy procedures in children, and to assess the utility of ketamine and propofol combination (ketofol) for this kind of procedures at children's age. In our prospective study, 40 ASA I-II patients, 3 to 17 years of age, were randomly divided into two groups of 20 patients each. After premedication with atropine and midazolam, sedation was induced with propofol and fentanyl in Group PF, whereas in Group PK propofol and ketamine were used for induction. Both groups were further divided into two subgroups depending on whether anesthesia was maintained with intermittent doses or continuous infusion of propofol. Ketamine and/or fentanyl were administered as bolus doses. Heart rate (HR), peripheral oxygen saturation (SpO2), RSS and BIS values of all patients were recorded every 5 minutes throughout the colonoscopy procedures. The strongest degree of correlation between RSS and BIS existed when sedation or TIVA was maintained by the boluses of propofol and fentanyl. The use of ketamine significantly reduced the doses of propofol and fentanyl. BIS can be monitored in all pediatric patients in whom sedation and TIVA are administered during colonoscopy, but the effect of different anesthetics on the EEG signal should be considered in order to adequately assess the depth of sedation and anesthesia*.

Key words: awareness, monitoring, child, anesthetics, endoscopy

INTRODUCTION

Awareness during anesthesia is a serious complication with potentially long-term psychological consequences. In practice, about 95% of the cases of consciousness are blamed on human error, the wrong anesthetic technique, or the malfunction of the anesthesia machine [1,2].

Monitoring of the bispectral index (BIS) enables the reduction of the incidence of awareness during sedation or general anesthesia. It is considered a valuable monitor of sedation levels and loss of consciousness for a wide range of anesthetics, such as propofol, midazolam and sevoflurane. BIS monitoring has also become a helpful tool to titrate hypnotic agents and reduce drug consumption, therefore allowing faster recovery while avoiding side effects such as hemodynamic instability [3].

The efficacy of BIS monitoring during sedation and total intravenous anesthesia (TIVA) for colonoscopy in children is debated for two reasons. In the first place, the influence of different anesthetics applied during sedation and anesthesia should be considered, eg ketamine can lead to a transient increase in BIS values due to activation of electroencephalogram (EEG), etomidate-induced myoclonus also transitory increases the BIS value [4]. Another important question that arises is whether BIS can be equally applied to children who are subjected to colonoscopy in

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the same way as it is used in adults? Children cannot be expected to participate in volunteer studies involving sedation and general anesthesia. Estimates that depend on the response to the verbal command or memory function are unreliable in this population. And in the waking state, from infant to adulthood, EEG amplitude decreases and the frequency of brain activity increases. In addition, EEG during anesthesia, especially in infants, differs from adults because the maturation of the brain tissue and the formation of synapses occurs in the first months of life [5-7].

The objectives of this study were to 1) determine whether there was a correlation between BIS and Ramsey Sedation Scale (RSS) in regard to the type of sedation and total intravenous anesthesia (TIVA); 2) assess the utility of ketamine and propofol combination (ketofol); 3) compare doses of drugs when used in different combinations for colonoscopy procedures in children.

PATIENTS AND METHODS

In our prospective study, after obtaining the Ethics Committee approval (No 5343/15, March 1, 2016, according to the Article 12 Rules of Procedure of the Ethics Committee Clinical Centre Nis) and written informed consent from the parents, 40 ASA I-II patients, 3 to 17 years of age, were randomly divided into two groups of 20 patients each. After premedication with atropine (Atropina solfato S.A.L.F.®; Laboratorio Farmacologico, Bergamo, Italy) and midazolam (Dormicum®; Roche, Basel, Switzerland), sedation was inducted with 1 mg/kg propofol (Propofol 1% Fresenius®; Fresenius Kabi, Graz, Austria) + 1 mcg/kg fentanyl (Fentanyl Panpharma®, Rotexmedica, Trittau, Germany) in Group PF, and 1 mg/kg propofol + 1 mg/kg ketamine (<20 kg BW) or 0.5 mg/kg ketamine (>20 kg BW), (Ketamine hydrochloride®; Rotexmedica, Trittau, Germany), in Group PK. Both groups were divided into two subgroups. In PF1 Group, deep sedation was maintained with boluses of propofol and fentanyl, whereas in Group PF2 sedation was maintained with continuous infusion of propofol (3 mg/kg) with intermittent boluses of fentanyl and propofol. In PK1 Group deep sedation was maintained with intermittent boluses of propofol, ketamine, and fentanyl, while in Group PK2 sedation was maintained using continuous infusion of propofol (3 mg/kg) with intermittent boluses of ketamine and fentanyl.

Heart rate (HR), peripheral oxygen saturation (SpO2), RSS (Table 1) and BIS values (BIS VISTA™ monitoring system, Aspect Medical Systems, Inc., the Netherlands) of all patients were recorded throughout the colonoscopy procedures. The observer who assessed sedation using RSS did not communicate his assessment to those who administered the drugs and recorded BIS values.

Table 1 Ramsay Sedation Scale

Definition	Score
Patient is anxious and agitated or restless, or both	1
Patient is cooperative, oriented and calm	2
Patient responds to commands only	3
Patient exhibits brisk response to light glabellar tap or loud auditory stimulus	4
Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus	5
Patient exhibits no response	6

Colonoscopy duration included the overall time of the endoscopy procedure. The recovery time was related to the fall of the RSS score to 2. The discharge time was referring to the transfer of a patient from the post anesthesia care unit (PACU) to the pediatric gastroenterology unit. Pediatric gastroenterologist's satisfaction was scored on a visual analogue scale (VAS) from 1 to 10.

Statistical analysis

Statistical analysis of data was performed with SPSS 15.0 statistic software package (SPSS, Chicago, IL, USA). Continuous variables were presented as arithmetic mean ($\overline{X}$), standard deviation (SD) and median (Me). The qualitative characteristics of the examined variables were presented as frequency (n) and percentage value (%). The regularity of the distribution of the continuous variables, depending on the sample size, was examined by the Shapiro-Wilk test. The Student's t-test was used for normally distributed parameters, whereas for non-normally distributed variables, the Mann–Whitney U-test was used to compare the two groups. A value of $p < 0.05$ was considered significant. As a measure of the linear relationship between two continuous variables Pearson correlation coefficient was used for normally distributed variables whereas nonparametric Spearman's rank correlation coefficient provided a measure of a monotonic relationship between variables that were not normally distributed.

RESULTS

There were no significant differences between the groups in age, weight, gender, American Society of Anesthesiologists (ASA) Score and the duration of colonoscopy (Table 2).

Table 2 Demographic characteristics of the patients and duration of colonoscopy

		PF1	PF2	PK1	PK2
Age (years)		12.20 ± 4.73 (14.00)	12.20 ± 4.34 (13.00)	11.50 ± 4.77 (12.00)	12.60 ± 5.66 (15.00)
Weight (kg)		52.70 ± 21.95 (60.50)	43.10 ± 9.50 (43.00)	41.60 ± 12.02 (41.50)	41.80 ± 15.26 (49.00)
Colonoscopy duration (min)		53.00 ± 10.06 (57.50)	56.50 ± 5.30 (60.00)	52.00 ± 10.33 (55.00)	55.30 ± 7.59 (60.00)
Gender	M	5 (50.00%)	6 (60.00%)	5 (50.00%)	6 (60.00%)
	F	5 (50.00%)	4 (40.00%)	5 (50.00%)	4 (40.00%)
ASA	1	4 (40.00%)	4 (40.00%)	4 (40.00%)	5 (50.00%)
	2	6 (60.00%)	6 (60.00%)	6 (60.00%)	5 (50.00%)

Notes: Continues variables are given as means ± SD (medians) and categorical variables as absolute number and in percentages (%)
Abbreviations: ASA, American Society of Anesthesiologists Score

Figure 1 shows that in most of the observed periods the highest SpO_2 values were in the PK1 Group (intermittent boluses of propofol, ketamine, and fentanyl), where these values were statistically significantly higher in relation to PF2 (continuous infusion of propofol with intermittent boluses of fentanyl and propofol) in the 1st and 25th minute ($p < 0.05$), as well as in relation to PF2 and PK2 (continuous infusion of propofol with intermittent boluses of ketamine and fentanyl) in the 40th and 45th minute ($p < 0.01$). In the 40th minute, the value in the PF1 Group (boluses of propofol and fentanyl) was higher than in the PF2 and PK2 Group ($p < 0.01$).

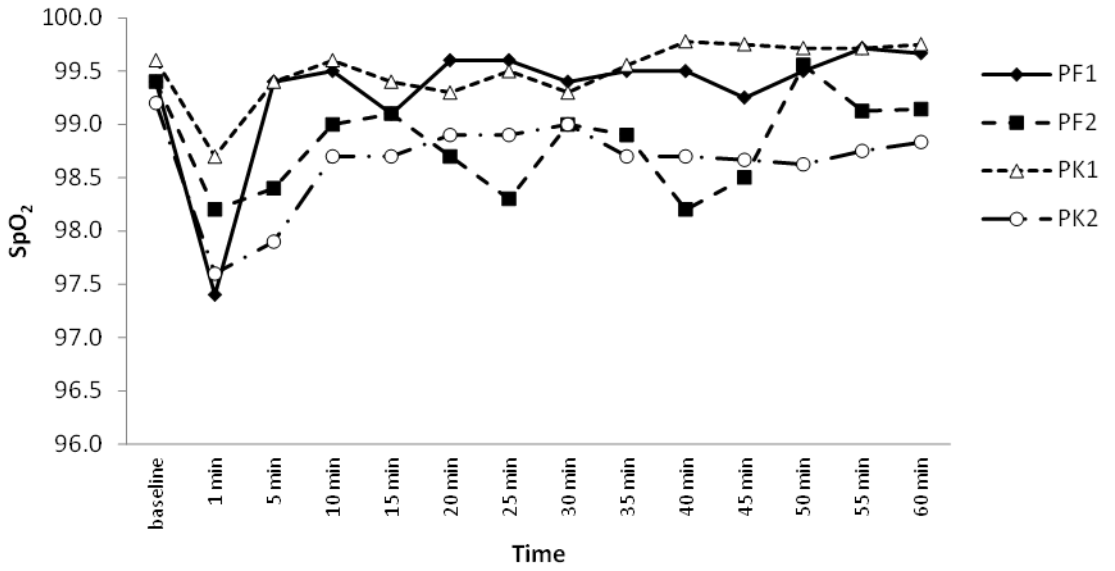

Fig. 1 SpO_2 values recorded during colonoscopy procedure.
Abbreviations: SpO_2, peripheral capillary oxygen saturation; PF1, boluses of propofol and fentanyl; PF2, continuous infusion of propofol (3 mg/kg) with intermittent boluses of fentanyl and propofol; PK1, boluses of propofol, ketamine, and fentanyl; PK2, continuous infusion of propofol (3 mg/kg) with intermittent boluses of ketamine and fentanyl.

By analyzing the data in Figure 2, it is evident that, except in the 30th and 60th minute, the heart rate (HR) values were the highest in the PK2 Group, while the values in both PF Groups were lower, which was most pronounced in the PF1 Group. Compared to the PF1, the HR values were statistically higher in the PK1 Group at 5, 10. 15, 20 and 30 minutes, the same applied to the PK2 Group in the 1st and 5th minute ($p < 0.05$).

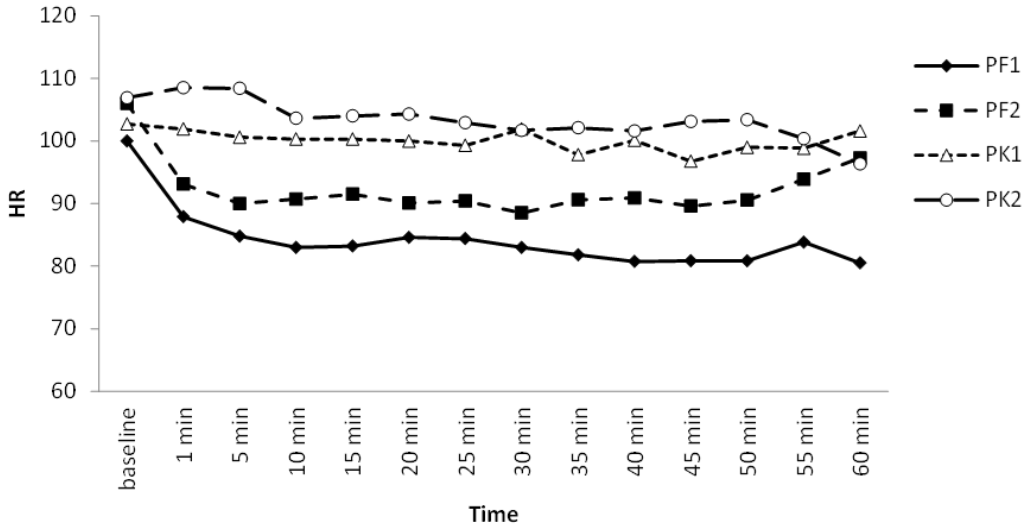

Fig. 2 HR values recorded during colonoscopy procedure.

Abbreviations: HR, heart rate; PF1, boluses of propofol and fentanyl; PF2, continuous infusion of propofol (3 mg/kg) with intermittent boluses of fentanyl and propofol; PK1, boluses of propofol, ketamine, and fentanyl; PK2, continuous infusion of propofol (3 mg/kg) with intermittent boluses of ketamine and fentanyl.

Figure 3 shows the RSS values for the investigated groups. The values of this parameter were relatively close among the groups, and only in 5th minute significantly higher RSS was noticed in the PF2 Group compared to the PK2 Group ($p < 0.05$).

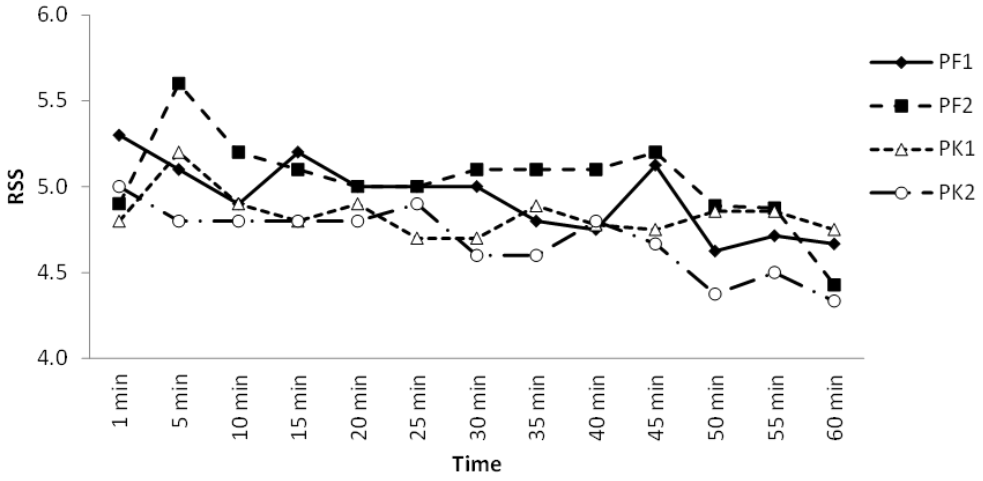

Fig. 3 RSS monitored during colonoscopy procedure.

Abbreviations: RSS, Ramsay Sedation Scale; PF1, boluses of propofol and fentanyl; PF2, continuous infusion of propofol (3 mg/kg) with intermittent boluses of fentanyl and propofol; PK1, boluses of propofol, ketamine, and fentanyl; PK2, continuous infusion of propofol (3 mg/kg) with intermittent boluses of ketamine and fentanyl.

The data presented in Figure 4 indicate that BIS values in the PK1 Group were statistically significantly higher in relation to the PF2 Group in 5, 10 and 15 minutes ($p < 0.05$), as well as in the 25, 30 and 40 minutes ($p < 0.01$), the same pattern repeated in relation to the PF1 Group at 15, 20, 25, 30, 35 and 40 minutes ($p < 0.05$). The BIS values were higher in the PK2 Group compared to the PF2 group in 5 ($p < 0.01$), 10 and 15 minutes ($p < 0.05$), and in relation to the PF1 Group at 20 and 30 minutes ($p < 0.05$). Generally, the values were lower in the PF1 and PF2 Groups. In 1st minute, BIS in PF1 was statistically significantly lower compared to all three other groups ($p < 0.05$).

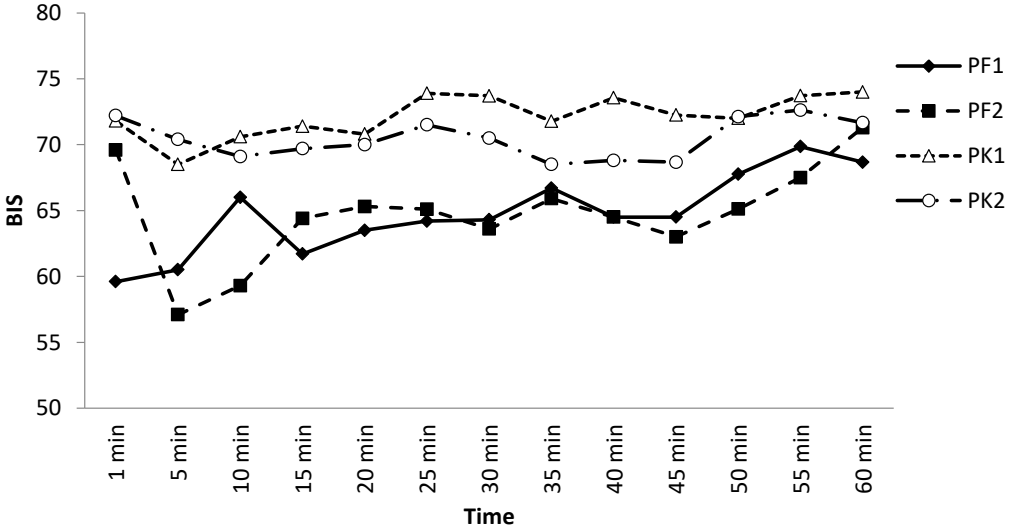

Fig. 4 BIS values measured during colonoscopy procedure.

Abbreviations: BIS, bispectral index; PF1, boluses of propofol and fentanyl; PF2, continuous infusion of propofol (3 mg/kg) with intermittent boluses of fentanyl and propofol; PK1, boluses of propofol, ketamine, and fentanyl; PK2, continuous infusion of propofol (3 mg/kg) with intermittent boluses of ketamine and fentanyl.

Correlations between RSS and BIS values for all examined periods and groups are presented in https://doi.org/10.22190/FUMB220413003B. As expected, due to the fact that the higher value of RSS means that the patient sleeps deeper, and the lower BIS means that anesthesia is deeper, in all periods of observation correlations were negative. It is also evident that patients within the PF1 Group had the largest number of such correlations.

Table 3 Correlations between RSS and BIS values

	PF1	PF2	PK1	PK2
1 min	-0.87 **	-0.81 **	-0.70 *	-0.46
5 min	-0.76 *	-0.71 *	-0.86 **	-0.57
10 min	-0.76 *	-0.70 *	-0.82 **	-0.44
15 min	-0.92 ***	-0.28	-0.52	-0.57
20 min	-0.96 ***	-0.55	- 0.18	-0.51
25 min	-0.77 **	-0.86 **	-0.58	-0.64 *
30 min	-0.87 **	-0.81 **	-0.70 *	-0.51
35 min	-0.85 **	-0.81 **	-0.48	-0.42
40 min	-0.51	-0.66 *	-0.74 *	-0.81 **
45 min	-0.79 *	-0.83 **	-0.76 *	-0.91 ***
50 min	-0.69	-0.40	-0.62	-0.77 *
55 min	-0.88 **	-0.50	-0.62	-0.87 **
60 min	-0.93 **	-0.67	-0.77	-0.83 *

Notes: * – $p<0.05$, ** – $p<0.01$, *** – $p<0.001$

Abbreviations: PF1, boluses of propofol and fentanyl; PF2, continuous infusion of propofol (3 mg/kg) with intermittent boluses of fentanyl and propofol; PK1, boluses of propofol, ketamine, and fentanyl; PK2, continuous infusion of propofol (3 mg/kg) with intermittent boluses of ketamine and fentanyl.

The mean total propofol dose in mg/kg (Table 4) was significantly lower ($p<0.001$) in PK1 Group (1.86) than in PF1, PF2 and PK2 Groups (4.06, 4.99 and 3.95, respectively). The mean fentanyl dose (mcg/kg) was the highest ($p<0.01$) in PF2 Group (2.06) in comparison to PF1, PK1 and PK2 Groups (1.60, 1.46 and 1.39, respectively). No significant difference was noted in mean ketamine dosage (mg/kg) between PK1 and PK2 Groups (1.24 and 1.33, respectively). Recovery time (min) was significantly shorter in PF1 Group (14.20) and in PF2 Group (14.40) in comparison with PK1 and PK2 Groups (17.30 and 16.50, respectively). Discharge time (min) was significantly longer in PK1 and PK2 Groups (49.10 and 50.00) in comparison to PF1 and PF2 Groups

(34.30 and 36.80). Only in the PK1 Group we did not note transitory respiratory depression. No other adverse events were noted in any of the investigated groups.

Table 4 Distribution of propofol, fentanyl and ketamine doses, rate of complications, recovery and discharge times and colonoscopist satisfaction score

	PF1	PF2	PK1	PK2
Total propofol dose (mg)	204.00 ± 81.13 (205.00)^{c***}	212.90 ± 53.32 (220.00)^{c***}	76.50 ± 24.04 (72.50)	160.60 ± 52.56 (184.00)^{c**}
Propofol dose (mg/kg)	4.06±1.03 (3.61)^{c***}	4.99±0.97 (5.13) ^{c***d**}	1.86±0.28 (1.83)	3.95±0.50 (3.97) ^{c***}
Total fentanyl dose (mcg)	85.00 ± 42.82 (87.50)^{d*}	88.50±34.32 (75.00)^{c*d**}	58.50±16.67 (57.50)	47.20±20.29 (42.50)
Fentanyl dose (mcg/kg)	1.60 ± 0.58 (1.43)	2.06 ± 0.66 (1.86)^{acd**}	1.46 ± 0.44 (1.35)	1.39 ± 0.64 (1.20)
Total ketamine dose (mg)			49.00±8.76 (50.00)	47.20±20.29 (42.50)
Ketamine dose (mg/kg)			1.24±0.34 (1.22)	1.33±0.80 (1.33)
Complications	2 (20.00%)	2 (20.00%)	0 (0.00%)	2 (20.00%)
Recovery time (min)	14.20±2.30 (14.00)	14.40±2.41 (15.00)	17.30±1.64 (17.00)^{ab**}	16.50±2.59 (15.00)^{a*}
Discharge time (min)	34.30±3.92 (33.50)	36.80±7.45 (34.50)	49.10±5.82 (47.00)^{a***b**}	50.00±7.36 (49.00)^{a***b**}
Gastroenterologist satisfaction	9.90±0.32 (10.00)	9.80±0.42 (10.00)	9.90±0.32 (10.00)	9.90±0.32 (10.00)

Notes: Continues variables are given as means ± SD (medians) and categorical variables as absolute number and in percentages (%); a – vs PF1, b – vs PF2, c – vs PK1, d – vs PK2; * – $p<0.05$, ** – $p<0.01$, *** – $p<0.001$.
Abbreviations: PF1, boluses of propofol and fentanyl; PF2, continuous infusion of propofol (3 mg/kg) with intermittent boluses of fentanyl and propofol; PK1, boluses of propofol, ketamine, and fentanyl; PK2, continuous infusion of propofol (3 mg/kg) with intermittent boluses of ketamine and fentanyl.

DISCUSSION

A colonoscopy is uncomfortable for the patient because of its long duration and many factors affecting abdominal pain.[5] In children, colonoscopy presents an even greater challenge. Achieving and maintaining an adequate level of sedation is difficult, therefore, it is important to set an objective indicator for monitoring the patient sedation level during colonoscopy [8-10].

The bispectral index algorithm was developed by recording and retrospectively analyzing EEG data of healthy adults, who suffered a repeated transition between a conscious and unconscious state using several different anesthetic regimens. BIS monitor generates a number on an uninterrupted scale from 0 to 100, where 100 represents normal cortical electrical activity, 90-60 sedation, 60-40 general anesthesia, 40-20 deep anesthesia and 0 represents the absence of any activity. The precondition for the correct interpretation of BIS changes is the knowledge of the specific effects of anesthetic agents on the EEG [4,11]. Meta-analyses conducted by Park et al [12] showed that the total propofol consumption was significantly lower in the BIS group than in the non-BIS group, although mean propofol consumption was not significantly different. In the pediatric population, the ability of the BIS to accurately follow variations in anesthetic agent concentration and evaluate depth of anesthesia remains controversial. Tirel et al [13] found the large variation of BIS values at 2 mcg/ml target-controlled plasma propofol concentration and explained that it could be mainly due to the influence of age. The effect of fentanyl on the BIS value was described as minimal, although its administration is associated with clinical evidence of increased sedation [14]. In the present study, fentanyl was administered along with other drugs such as midazolam, propofol or ketamine and so we cannot comment on the effect of fentanyl alone on the BIS values. Ketamine, in the doses of 0.25 to 0.5 mg/kg, can block the response capacity of patients, but it does not reduce the BIS [15]. Vereeke et al [16] found that BIS values increased significantly between 3 and 8 minutes after administration of ketamine bolus followed by a subsequent decrease for the rest of the study period. Faraoni et al [17] concluded that during stable propofol-remifentanil anesthesia low doses of ketamine (0.2 mg/kg) had no effect on BIS.

Without any doubt, the depth of sedation should primarily be monitored on the basis of clinical criteria [18] so studies were conducted to determine the correlation between different sedation scores and BIS values.

Sadhasivam et al [14] described a significant correlation between BIS and Observer's Assessment of Alertness/Sedation (OAA/S) as well as between BIS and University of Michigan Sedation Scale (UMSS). The authors excluded children requiring sedation with ketamine. In our study, although BIS values were higher in patients who received ketamine, we found correlation between BIS and RSS in all investigated groups. This could be in line with the study of Vereecke et al [16] who concluded that when used during sedation in combination with propofol, ketamine increased hypnosis without affecting BIS levels. Our results showed that the strongest degree of correlation between RSS and BIS existed when TIVA was maintained by the boluses of propofol and fentanyl.

We would like to emphasize the importance of propofol and ketamine combination ("ketofol") for a comfortable performance of colonoscopy and to give our own contribution regarding its use in pediatric patients. Ketamine stimulates the cardiorespiratory system, as it was also observed in our study because the increased heart rate was recorded in patients in whom ketamine was administered. It also increases cardiac output, arterial blood pressure, heart rate and central venous pressures. However, psychomimetic activity, emergence delirium and other adverse events have been shown to be dose related. In contrast, propofol is a sedative, hypnotic and anesthetic agent and it can improve sedation scores but it has a narrow therapeutic range and increases the risks of cardiovascular depression and airway compromise [19,20]. Combining these two agents for colonoscopy may preserve sedation efficacy while minimizing their respective adverse effects. Although popular for short procedural sedation and analgesia in pediatric patients [21] it is surprising that yet neither the optimal combination nor infusion rate of ketofol is known. Coulter et al [22] suggested an optimal ratio of racemic ketamine to propofol of 1 : 5 for 30-min anesthesia and 1 : 6.7 for 90-min anesthesia. Tosun et al [23] investigated propofol-ketamine for sedation during pediatric upper gastrointestinal endoscopy (PK Group received 1 mg/kg ketamine + 1.2 mg/kg propofol with additional propofol (0.5–1 mg/kg) when a patient showed discomfort) and concluded that this combination resulted in stable hemodynamics and deeper sedation but caused more side effects (eg vomiting, dizziness, diplopia). Türk et al. [24] investigated the use of ketofol (prepared at a ratio of 1:2) compared with an opioid-propofol combination in colonoscopic procedures. They reported that ketofol provides better hemodynamic stability and better quality of sedation-analgesia than alfentanil-propofol in elective colonoscopy. In our study, the use of ketamine did not affect the trends of BIS values to the extent that it could lead to a wrong assessment of the clinical depth of sedation or anesthesia, while significantly reducing the doses of propofol and fentanyl. Higher doses of propofol when it was administered as continuous infusion suggested why most gastroenterologists prefer the flexibility of the bolus approach [25]. Only in the group of patients who received appropriate bolus doses of propofol, ketamine and fentanyl (Group PK1) we did not note transitory respiratory depression. No other adverse events were noted in any of the investigated groups. Recovery time was slightly prolonged in patients who received propofol-ketamine combination.

CONCLUSION

BIS can be monitored in all pediatric patients in whom sedation and TIVA are administered during colonoscopy, but the effect of different anesthetics on the EEG signal should be considered in order to adequately assess the depth of sedation and anesthesia.

The combination of ketamine and propofol for use in procedural sedation has received significant attention during the last few years. Based upon the results of our study, we may conclude that a combination consisting of appropriate doses of propofol, ketamine and fentanyl can be safely used for colonoscopy sedation or TIVA in children.

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