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Comparison of propofol-based sedation regimens administered during colonoscopy

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ABSTRACT

***Background**: The ideal sedative agent for endoscopic procedures should allow a rapid modification of the sedation level and should not have any adverse effects.* ***Aim:** To evaluate and compare the efficacy, safety, cost and patient satisfaction of some propofol-based sedation regimens administered during colonoscopy.* ***Material and Methods**: One hundred twenty one patients scheduled for elective outpatient colonoscopy with conscious sedation were randomized to four groups to evaluate the administration of dexmedetomidine, sufentanil, meperidine and midazolam in combination with propofol to maintain sedation during the procedure. Evaluated outcomes were efficacy, safety, cost and patient satisfaction of sedation procedures.* ***Results**: Patients receiving dexmedetomidine achieved a higher degree of sedation when compared with the other groups ($p < 0.05$). The lapse to recover protective reflexes and motor function, was significantly shorter in groups receiving dexmedetomidine or sufentanil than in groups receiving meperidine or midazolam ($p < 0.05$). There were no differences between groups in pre-sedation and post-sedation neurophysiologic performance, measured by the Trail Making A and B tests.* ***Conclusions:** Sedation for endoscopy can be safely and effectively accomplished with low doses of propofol combined with dexmedetomidine, intranasal sufentanil, IV meperidine and IV meperidine with midazolam.*

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***Key words:** Colonoscopy; Conscious sedation; Dexmedetomidine; Midazolam; Propofol; Sufentanil.*

Comparación de protocolos de sedación basados en propofol para obtener sedación durante endoscopias

***Antecedentes:** El protocolo de sedación ideal para procedimientos endoscópicos es aquel que permita efectuar modificaciones rápidas del nivel de sedación y no tenga efectos secundarios.* ***Objetivo**: Comparar la eficacia, seguridad, costos y satisfacción del paciente con protocolos de sedación basados en propofol, durante colonoscopias.* ***Material y Métodos:** Ciento veinte pacientes programados para una colonoscopia fueron aleatorizados en cuatro grupos en que se evaluó la administración de dexmedetomidina, sufentanil, meperidina y midazolam en combinación con propofol, para mantener la sedación durante el procedimiento. Se evaluó la eficacia, seguridad, costo y satisfacción del paciente con los diferentes protocolos de sedación.* ***Resultados**: Los pacientes que recibieron dexmedetomidina, alcanzaron un mayor nivel de sedación que el resto de los grupos. El lapso necesario para recuperar reflejos*

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y funciones motoras protectoras, fue significativamente menor en los grupos que recibieron dexmedetomidina o sufentanil comparado con los grupos que recibieron meperidina o midazolam (p < 0,05). No hubo diferencias entre los grupos en la capacidad neuro-cognitiva, medida con los Tests de Reitan A y B, antes o después de la sedación. ***Conclusiones****: Se puede obtener una buena sedación para endoscopia combinando dosis bajas de propofol con dexmedetomidina, sufentanil intranasal, meperidina endovenosa con o sin midazolam.*

Colonoscopy is an important diagnostic and therapeutic method and usually regarded as an invasive procedure that cannot be tolerated by most patients without sedation. Recently, endoscopic procedures are generally performed under sedation. Sedation is generally described as a continuum ranging from minimal sedation through to general anesthesia. The term 'conscious sedation' is used for sedation for therapeutic or diagnostic procedures, which corresponds to moderate level of sedation that enables the patient to respond to verbal and tactile stimulations and preserves cardiovascular and respiratory systems. Conscious sedation during colonoscopic procedures provides a high level of patient and physician satisfaction[1,2].

The ideal sedative agent should allow for rapid modification of the sedation level by modifying the dosage and should not have any adverse effects. It should be cheap and have rapid onset and short duration of action without cumulative effects. The metabolites of the sedative agents should be inactivated at the end of the procedure, so that hospitalization is not prolonged. Because no such an ideal sedative agent exists; opioids, benzodiazepines, barbiturates, propofol and antipsychotics can be administered in combinations with each other[3,4].

Combinations of agents such as propofol, benzodiazepines, opioids or dexmedetomidine, provide more advantages by acting synergistically[5-7] and may have advantages over the use of a single agent[4,8,9].

Data about sedation with low dose propofol in combination with dexmedetomidine, intranasal sufentanil, meperidine or midazolam + meperidine during gastrointestinal endoscopic procedures are very limited. The purpose of this study was to evaluate and compare these propofol-based sedation regimens administered during colonoscopy regarding their efficacy, safety, cost and patient satisfaction.

Material and Methods

We conducted a single-centered, single-blinded randomized controlled trial in which we compared efficacy, safety and cost of four different propofol-based sedation regimens. The study protocol was approved by the Local Hospital Ethics Committee and all patients provided written informed consent forms.

A hundred twenty one patients, aged 18-70 years with *American Society of Anesthesiologists (ASA)* physical classification status of I-II, scheduled for elective outpatient colonoscopy with conscious sedation were recruited from the practices. Patients were randomized into four groups.

Patients with limited access to air (inability to open mouth, jaw problems), history of sleep apnea, neuropsychiatric, cardiac, respiratory and renal disorders, hypotension (mean arterial pressure (MAP) < 60 mmHg), hypertension (MAP > 105 mmHg), bradycardia (heart rate (HR) < 45 beats/min), tachycardia (HR > 115 beats/min), dysrhythmia, in a pregnant state, and those who used opioids, sedatives and βblockers, intolerant or with an allergy to the study drugs, egg and soya oil were excluded. There is no patient for postoperative control colonoscopy.

Oral intake was allowed until 8 hours before the colonoscopic procedure and on the day before the procedure, only a liquid dominant oral intake was allowed. We preferred sodium phosphate enema and phospho-soda in combination for the total colon preparation.

On arrival in the endoscopy room, intravenous access was obtained and each patient received isotonic saline at a rate of 8 ml/kg/h. All patients were monitored with continuous pulse oximetry, electrocardiogram, and noninvasive arterial blood pressure measured at 5-min intervals, and oxygen 3 L/min was administered by nasal cannula.

There are several brain function monitors based on the processed electroencephalogram (EEG)

or evoked potentials to assess anesthetic depth. The most widely used is the bispectral index (BIS) monitor that processes a single frontal EEG signal to calculate a dimensionless number that provides a measure of the patient's level of consciousness as values 100 to 0 reflecting the awake state to absence of brain activity respectively[10]. BIS was monitored throughout the procedure.

Ramsay sedation score (RSS) was defined as a scale from 1 to 6 as from anxious, agitated to asleep, no response respectively[11,12]. RSS was used in the sedation scale of these patients along with BIS. A sedative agent was administered by nurses with intermittent boluses to obtain the sedation level targeted at a BIS score from 65 to 75. Frequency and dose were titrated to keep the patient at the same level of sedation and the level of sedation was designed to maintain the patient at a score of 3 or 4 in the RSS.

Patients' age, sex and body mass index, used dose of anesthetic agents, total sedation time, patient and physician satisfaction, sedation scores, recovery time, total cost and adverse effects were recorded. Patients' periprocedural risk was classified according to ASA classification[13]. Complications were categorized as respiratory (decrease in oxygen saturation to < 90% for > 120 sec.), hemodynamic (decrease in systolic blood pressure to < 90 mmHg or decrease in heart rate to 50/min for >120 sec).

Neurophysiologic performance was evaluated before sedation and 20 min after recovery using the Trail Making A and B tests[14]. The Trail Making Test is one of the most popular neuropsychological tests and provides information on visual search, scanning, speed of processing, mental flexibility and executive functions[15].

All colonoscopic procedures were conducted by the same endoscopist while the drugs were administered by the same anesthesiologist throughout the study. The indications for colonoscopy were common such as population monitorization for malignancy or benign disorders such as inflammatory bowel diseases.

Anesthetic regimens and study drug administration:

There were four groups of randomized patients and the used drug protocols are as follow, according to groups: Group I (n = 30) received 0.2 mcg/kg/h of dexmedetomidine. Group II (n = 30) received intranasal 0.1 mcg/kg of sufentanil. Group III (n = 31) received intravenous 0.4 mg/kg of meperidine. After 10 min, 1 mg/kg bolus of propofol was administered, followed by infusion of propofol with a dose range of 0.5-3 mg/kg/h. Group IV (n = 30) received intravenous 0.4 mg/kg of meperidine. After 10 min, intravenous midazolam 0.03 mg/kg was administered, followed by infusion of propofol (0.5-3 mg/kg/h). The procedure was begun after the level of sedation was maintained at the score of 3 or 4 in the RSS. The patient's clinical level of sedation was monitored by using BIS.

Patients were transferred to the recovery room (RR) after anesthesia when vital signs (MAP, HR and oxygen saturation (SpO_2)) stabilized. During RR monitoring, a nurse with the anesthesiologist determined if the patients reached the Aldrete score of 8 or higher, pre-procedure scores, are fully conscious and able to be discharged[16].

Statistical analysis

Various indicators were summarized with descriptive statistics. Mean and standard deviation were used for quantitative variables and the frequencies for qualitative variables. Kolmogorov-Smirnov test was used to test normality of the distribution. Quantitative variables were compared using Pearson chi-square test. Normally distributed qualitative variables were compared with independent samples t-test and non-normally distributed qualitative variables with Mann-Whitney U-test. One-way ANOVA with Tukey test was used to compare qualitative variables in more than 2 groups with normal distribution and Kruskal-Wallis with Mann-Whitney U-test to compare qualitative variables in more than 2 groups with non-normal distribution. Variables in the same group with normal distribution were compared with repeated measures with ANOVA Bonferroni correction whereas variables in the same group with non-normal distribution were compared with Wilcoxon signed-rank test. $p < 0.05$ was considered statistically significant with 95% confidence interval.

Results

All patients completed the study; no patient was excluded. There were no observed severe events requiring assisted ventilation or hemodynamic support; the procedure-associated mortality

was 0%. Minor complications were observed in a total of 6 patients with no significancy (group 1: one dry mouth, group 2: one dry mouth, group 3: one dry mouth, one agitation and nausea, group 4: one dry mouth, one agitation and nausea). The colonoscopic examinations were defined as suboptimal in 8 patients due to inadequate bowel preparation but the procedure was fully completed in all patients.

There were no significant differences according to age, body mass index (BMI), gender, ASA physical status of patients and overall procedure time between the four groups (Table 1). The mean doses of used propofol were as 88.2 mg (1.12 ± 0.25 mg/kg) in dexmedetomidine group; 87.6 mg (1.07 ± 0.43 mg/kg) in sufentanil group and 88.2 mg (1.10 ± 0.17 mg/kg) in meperidine group. There was no difference between these groups in terms of consumption of propofol. In meperidine + midazolam group, the mean dose of propofol used was 61.3 mg (0.71 ± 0.25 mg/kg). The propofol consumption was significantly lower in group 4 than in the other groups ($p < 0.00$) (Table 1). When we examined the HR and SpO_2 of patients, there were no statistically significant differences intragroup and intergroup ($P > 0.05$) (Figures 1 and 2). The MAPs at 5, 10, 15, 20, 25 and 30 min following induction were significantly lower than that at induction (Figure 3). The decrease was most significant in group 1 and least in group 4. No patient in any group required bolus ephedrine or atropine.

Table 1. Patients' Characteristics, Dosage of Propofol and Duration of The Procedure

	Group 1		Group 2		Group 3		Group 4		p
	mean	SD ±	mean	SD ±	mean	SD ±	Mean	SD ±	
Age (year)	46,467	12,317	46,267	12,160	52,903	11,193	50,667	11,106	0,075
Weight (kg)	78,633	9,423	77,033	11,857	76,935	10,699	79,333	9,408	0,275
Lenght (cm)	165,967	4,499	167,600	7,238	165,355	8,220	165,200	4,852	0,453
BMI	24,887	3,002	27,373	3,272	28,235	4,820	25,417	3,301	0,321
Duration of endoscopy (min)	25.324	3,003	24.123	2,678	25.121	3,432	26.432	2,325	0.369
Total propofol doses (mg)	81,2	8,03	79,6	9,31	80,2	9,41	61,3	9,54	**0,000**
ASA	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**p**
I	21	70	22	73,3	24	77,4	18	60	0,492
II	9	30	8	26,7	7	22,6	12	40	

SD: standard deviation.

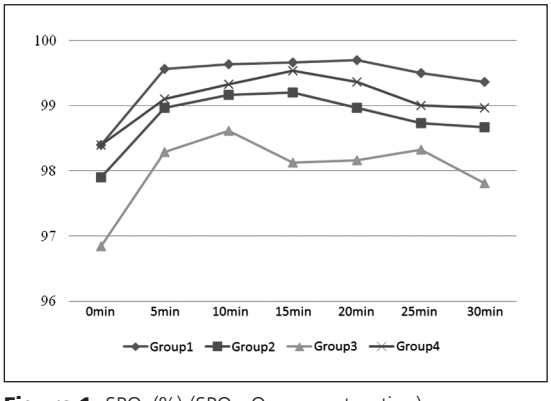

Figure 1. SPO_2 (%) (SPO_2: Oxygen saturation).

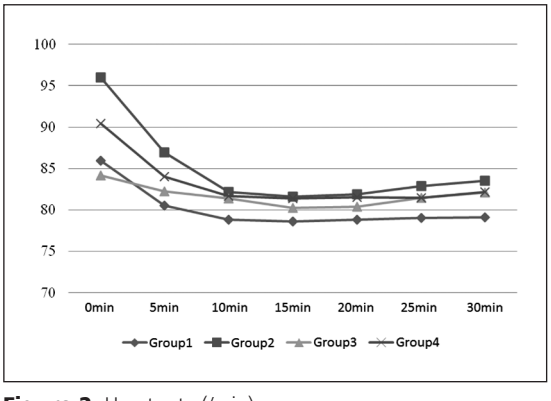

Figure 2. Heart rate (/min).

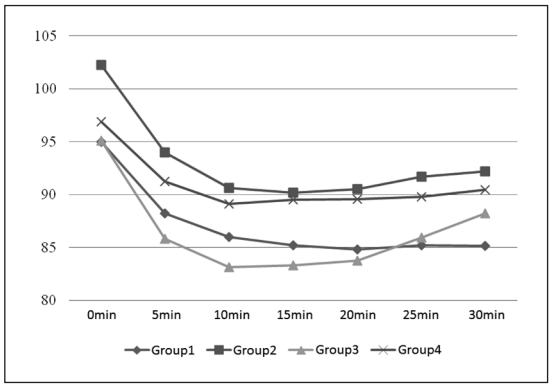

Figure 3. Mean Arterial Pressure (mmHg).

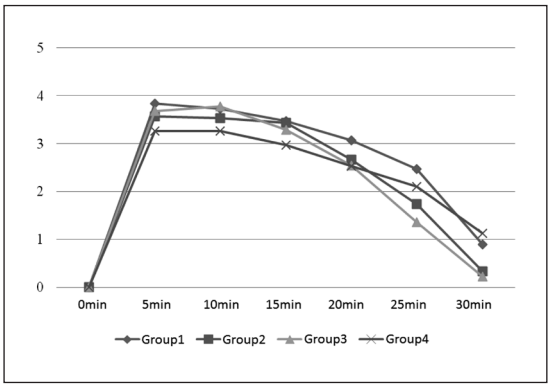

Figure 4. Ramsey Sedation Scores.

Table 2. Aldrete Scores (min)

Time to Achive Aldrate 10	Group 1		Group 2		Group 3		Group 4		p
	mean	SD ±	mean	SD ±	mean	SD ±	mean	SD ±	
Min	4,533	1,484	4,732	1,760	6,000	2,082	6,767	1,478	0,000**

Table 3. Satisfaction Findings

		Group 1		Group 2		Group 3		Group 4		p
		n	%	n	%	n	%	n	%	
Endoscopist overall satisfaction	no	0	% 0	0	% 0	0	% 0	1	% 3,3	0,383
	yes	30	% 100	30	% 100	30	% 100	29	% 96,7	
Patient overall satisfaction	no	2	% 6,7	2	% 6,7	2	% 6,5	5	% 16,7	0,428
	yes	28	% 93,3	28	% 93,3	29	% 93,5	25	% 83,3	

The patients in group 1, in which dexmedetomidine was administered, were significantly more sedated compared with the other groups ($p < 0.05$). Likewise, the RSS scores at 5 and 25 min following the induction were significantly higher in group 1 than in the other groups ($p < 0.05$). On the other hand, the RSS scores at 5, 10, 15 and 20 min were significantly higher in group 2 than in group 4. RSS scores at 25 and 30 minutes in group 2 and 3 were significantly lower than in group 4 ($p < 0.05$) (Figure 4).

The BIS readings in each case remained above 65. The lowest BIS value recorded was 68, occurring in one patient in group 1. Time to achieve Aldrete's score to 10 was significantly shorter in group 1 and 2 than in group 3 and 4 ($p < 0.05$) (Table 2). Patient and physician satisfaction showed no significant differences among the groups (Table 3) ($p > 0.05$).

The average time to full recovery was found to be similar between the groups ($p = 0.235$). Mean times to full recovery were 10 ± 5 min, 10 ± 5 min, 12 ± 5 min, 12 ± 6 min, in groups 1 to 4, respectively. There was no difference between the groups for recovery at the 10th, 15th and 20th min.

No patient required emergency intervention (mask ventilation, orotracheal intubation or cardiopulmonary resuscitation procedure). There was no difference between the groups in pre-sedation and post-sedation neurophysiologic performance, measured by the Trail Making A and B tests. However, the post-sedation test scores were significantly higher than pre-sedation test scores in all groups

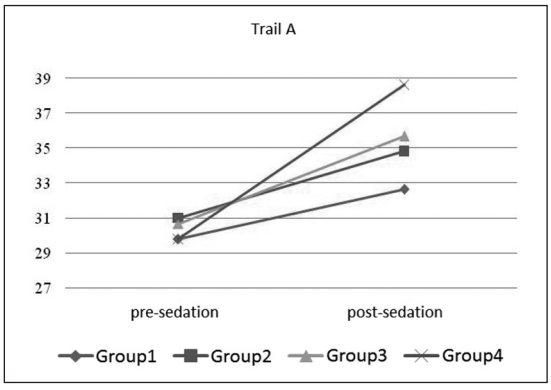

Figure 5. Trail A.

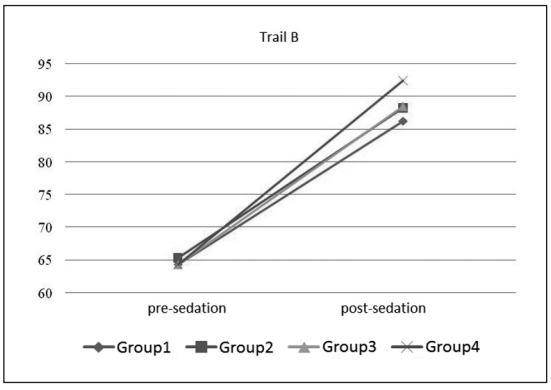

Figure 6. Trail B.

Table 4. Cost Findings (as USD)

	Group 1		Group 2		Group 3		Group 4		p
	mean	SD	mean	SD	mean	SD	mean	SD	
Cost (USD ($)	6,858	0,951	1,901	0,241	1,105	0,163	0,919	0,190	0,000

($p < 0.05$) and this difference was greatest in group 4 (Figures 5 and 6).

In this study, overall cost in group 1 was significantly greater than in the other groups ($p < 0.05$) and lowest in group 4 ($p < 0.05$). Furthermore, cost in group 3 was greater than in group 2 ($p < 0.05$) (Table 4).

Discussion

Colonoscopy plays a crucial role in the diagnosis of colorectal pathologies and colonoscopic therapeutic procedures have also increased over the recent decades. Although conscious sedation is the ideal method used to reduce anxiety in patients undergoing endoscopy, the choice of agent or combination of agents is still controversial.

Propofol alone or in combination with midazolam and/or fentanyl is one of the most widely used agents for sedation during endoscopic procedures[17-21]. Adding adjuvant sedatives or analgesics to propofol may provide some benefits, along with additional risks. Theoretically, adjuvants may increase patient's comfort during the procedures but they could also delay return to normal consciousness[8,22,23].

This study demonstrates the safety of propofol combined with IV dexmedetomidine, intranasal sufentanil, IV meperidine or IV midazolam + meperidine, without causing any discomfort during colonoscopy.

Jalowiecki et al[7], evaluated the safety of dexmedetomidine during outpatient colonoscopy. They suggested that the use of dexmedetomidine was limited due to its distressing side effects, such as hemodynamic instability, prolonged recovery, and a complicated administration regimen. However, fentanyl supplementation was required in 47% of 19 patients in the dexmedetomidine group to achieve a satisfactory level of analgesia, which caused vertigo in five patients, nausea and vomiting in five patients, ventricular bigeminy in one patient.

It has been reported that dexmedetomidine provides more efficient hemodynamic stability, higher RSS, higher satisfaction scores and lower numeric rating scale (NRS) scores than midazolam during colonoscopic procedures[24]. Dexmedetomidine was also reported to be associated with delayed recovery room discharge due to lower HR and MAP values and cardiovascular depression, which could be explained by the decreased sympathetic outflow[25-27]. There are conflicting reports on the respiratory effects of dexmedetomidine. Hsu et al[28], have reported a significant increase in respiratory rate with dexmedetomidine, whereas

Belleville et al[29], reported a significant decrease. It is proposed that this conflict may result either from the physiologic reactions due to arousal phenomenon or from the fact that boluses were used in these studies that may have resulted in sustained and higher concentrations.

In our study, sedation in group 1, in which dexmedetomidine was administered, was more efficient and the RSS scores between 5 and 25 minutes following the induction were significantly higher than the other groups. We suggest that the efficacy of dexmedetomidine is related to its synergistic effects with propofol. Aldrete's scores were significantly lower in groups 1 than in groups 3 and 4 and no respiratory depression was noted during the procedure.

In all groups, a significant reduction in the MAP values was observed during the procedure when we compared the pre-sedation MAP with post-sedation MAP values. In dexmedetomidine group, MAP values were moderately lower than the baseline values and no severe bradycardia or hypotension requiring intervention occurred. In group 3 and 4 MAP values were found significantly higher than in the other groups. The results of this analysis may be related to administration of midazolam instead of bolus propofol and so that low dose propofol consumption.

Intranasal opioid analgesia is an effective and practical alternative to intravenous analgesia with fewer adverse effects[30,31]. In group 2, propofol with intranasal sufentanil was a suitable option and it provided adequate conscious sedation and did not prolong the recovery period. Patient and physician satisfaction and adverse effects were not different than in the other groups. In previous studies, adequate analgesia and sedation was provided by intranasal administration of anesthetic agents including sufentanil[32,33].

Cohen et al[8] showed that endoscopy could be performed at a moderate level of sedation by combining a low dose of propofol with a narcotic agent and/or benzodiazepine, and that the combination of propofol with a small dose of a narcotic agent and midazolam does not prolong patient recovery. Paspatis et al[5] found that a low dose of midazolam combined with propofol provided superior patient recovery and shorter recovery times than the combination of midazolam and the opioid pethidine during colonoscopies. Likewise, Vargo et al[34] reported that propofol improved the recovery to baseline activity significantly more effectively than a combination of midazolam/meperidine. Additionally, they observed 54 episodes of apnea/disordered respiration in 28 patients in the midazolam/meperidine group (mean duration 70.8 s). In this study, no patient required emergency intervention (mask ventilation, orotracheal intubation) due to respiratory failure or O_2 desaturation. This may have been related to the initial and maintenance low dose given as an infusion and over a much longer time (10 min).

In this study, time to achieve an Aldrete's score of 10 was shorter in the dexmedetomidine and intranasal sufentanil group than in the meperidine and midazolam meperidine groups (Table 2). Group 1 had a greater depth of sedation and faster recovery of consciousness than groups 3 and 4. Sipe et al.[6] found the recovery time of 14 minutes by using the psychometric tests to assess recovery in 40 patients sedated with propofol during colonoscopy. In other studies of propofol for endoscopy, recovery times have ranged from 15 to 20 min[8,19,35]. In this study, the time to full recovery was between 10 ± 5min and 12 ± 6 min by using the Trail Making A and B tests. There was no difference between the groups in pre-sedation and post-sedation neurophysiologic performance, measured by the Trail Making A and B tests. However, the post-sedation test scores were significantly higher than pre-sedation test scores in all groups ($p < 0.05$) and the greatest difference was found in group 4, in which midazolam was administered as a co-induction anesthetic agent. Post-sedation psychomotor and psychometric functions may be affected by the duration of the procedure and the age of the patient but in our study there was no difference in these parameters between the groups (Table 1).

During endoscopic procedures, the frequency of serious adverse events due to anesthesia was reported as 2.5 per 1,000 (0.25%)[8]. There are only few studies on endoscopic examinations performed with low -dose propofol, in which no serious adverse events have been reported[5,20,36]. Likewise, we did not observe any serious adverse events in our study groups.

In the current study, patient and endoscopist satisfaction rates were 83,3-93,3% and 96,7-100%, respectively. In the present study, satisfaction after the procedure was considerably good in all groups (Table 3). The cost analysis revealed that the mean

cost was maximum in group 1 and minimum in group 4 (Table 4).

This study shows that propofol combined with dexmedetomidine, intranasal sufentanil, meperidine or meperidine + midazolam provides effective sedation during colonoscopy with rapid recovery, minimal adverse effects, and it is safe. However, it is remarkable that dexmedetomidine increases the cost significantly.

In conclusion, the present study demonstrates that sedation for endoscopy can be safely and effectively accomplished when using drug regimens that perform synergistic sedation as low doses of propofol combined with dexmedetomidine, intranasal sufentanil, IV meperidine and IV meperidine with midazolam. The use of low doses of propofol combined with dexmedetomidine or a narcotic agent and the combination with midazolam do not retard patient recovery. It is our belief that all sedation protocols assayed by us provided shorter recovery time, are well tolerated, safe, with no major side events and they provide high patient and physician satisfaction. They also are economic alternatives to traditional-based sedoanalgesia.

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