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Comparison of post-anesthesia recovery time in sedated patients for colonoscopy using midazolam or fentanyl associated with propofol

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ABSTRACT

Objective: Comparison of post-anesthesia recovery time in sedated patients for colonoscopy using two drug combinations: midazolam and propofol or fentanyl and propofol.
Method: Fifty patients ASA I and II, from 18 to 65 years of age, candidates for elective colonoscopy under sedation administered by an anesthesiologist, were randomized in two groups: Group A (midazolam and propofol) and Group B (fentanyl and propofol). Each patient was evaluated as for the length of the exam (Exam length), length of stay in the post-anesthesia care unit 1 and 2 (LSPACU1 and LSPACU2) and hospital discharge. Episodes of awakening, and of movement, drop in SpO2 < 90%, need for mechanical ventilation, propofol consumption, heart rate (HR) and mean blood pressure (MBP) were also evaluated.
Results: Patients of group B had a recovery time in LSPACU1 statistically shorter than that for those in group A. In both groups, LSPACU1 was considered inversely proportional to LSPACU2. Hospital discharge time was similar between groups. Patients of group B had a significant decrease in MBP during and at the end of the exam, when compared to the initial measurement and that during sedation. Nevertheless, this variation was lower than 20%. No adverse event was observed. All patients were discharged on the same day, with no unexpected hospitalization.
Conclusions: The combined use of fentanyl and propofol for colonoscopy sedation had a post-anesthesia recovery time in LSPACU1 shorter than that with the combination of midazolam and propofol. Nevertheless hospital discharge time was similar between groups.

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Comparação do tempo de recuperação pós-anestésica em pacientes sedados para colonoscopia usando midazolam ou fentanil associados a propofol

R E S U M O

Palavras-chave:
Colonoscopia
Anestesia
Midazolam
Fentanil
Propofol

Objetivo: Comparar o tempo de recuperação pós-anestésica de pacientes sedados para colonoscopia usando duas combinações de fármacos: midazolam e propofol ou fentanil e propofol.

Método: Cinquenta pacientes ASA I e II, entre 18 e 65 anos, candidatos a colonoscopia eletiva sob sedação administrada por anestesiologista, foram randomizados em dois grupos: Grupo A (midazolam e propofol) e Grupo B (fentanil e propofol). Cada paciente foi avaliado quanto ao tempo de realização do exame (TExame), tempo de permanência na sala de recuperação pós-anestésica 1 e 2 (TSRPA 1 e TSRPA2) e a alta domiciliar. Episódios de despertar, movimentação, queda de $SpO_2 < 90\%$, necessidade de assistência ventilatória, consumo de propofol, frequência cardíaca (FC) e pressão arterial média (PAM) também foram avaliados.

Resultados: Pacientes do grupo B apresentaram tempo de recuperação na SRPA1 inferior estatisticamente ao grupo A. Em ambos os grupos o TSRPA1 foi considerado inversamente proporcional ao TSRPA2. O tempo de alta domiciliar foi semelhante entre os grupos. Pacientes do grupo B apresentaram redução significativa na PAM no tempos exame e final, em relação ao inicial e sedação. Entretanto, essa variação foi inferior a 20%. Não foram observados eventos adversos. Todos os pacientes evoluíram com alta domiciliar no mesmo dia, sem ocorrência de internação não prevista.

Conclusões: O uso combinado de fentanil e propofol para sedação em colonoscopia produziu tempo de recuperação pós-anestésica na SRPA1 inferior a combinação midazolam e propofol. No entanto, o tempo de alta domiciliar foi semelhante entre os grupos.

Introduction

In Brazil, colorectal cancer is the fourth most prevalent type according to the estimate for the 2020−2020 period.[1] Colonoscopy is the standard procedure for the detection of colorectal cancer and treatment of precancerous lesions, because, in addition to allowing an accurate diagnosis, it allows the removal of these lesions. It can be performed under mild to deep sedation, varying according to cultural aspects and resources available in different health systems.[2]

The use of sedation during colonoscopy facilitates the procedure by the endoscopist and also has higher patient satisfaction rates. However, the costs and risks of adverse events increase, since patients can show varying degrees of cognitive function impairment, with a consequent delay in hospital discharge and restrictions in several daily activities.[2–6] In general, a benzodiazepine and/or short-acting opioid is used, associated or not with propofol, a fast-acting hypnotic with rapid recovery, but with a high potential for cardiorespiratory depression.

The use of propofol alone requires the utilization of larger doses, which can lead to an increased incidence of side effects.[6] This association of drugs, on the other hand, allows dose reduction and consequent adverse reactions. Opioids, such as fentanyl, provide analgesia, while benzodiazepines, such as midazolam, promote a synergistic effect.[7–11] Both

are currently used in colonoscopy, as they produce moderate sedation, relieve the patient's pain and discomfort during the performance of the procedure and provide a short recovery time.[6,12] However, there is still no consensus in the literature about which drug alone, or combination of drugs, is best to safely achieve the desired level of sedation, with minimal adverse effects and that will allow the patients to return quickly to their daily activities. Thus, the aim of this study was to compare the post-anesthetic recovery time in sedated patients undergoing colonoscopy, using midazolam and propofol or fentanyl and propofol. Moreover, other parameters were analyzed in order to identify the best combination of drugs, such as consumption of propofol, exam length and hospital discharge time, variation in mean blood pressure (MBP) and heart rate (HR), possible complications during the procedure and post-anesthetic recovery, and the unexpected hospitalization rate.

Methods

The present study is a prospective, randomized, double-blind study, carried out in the outpatient exam department at Hospital Luxemburgo in Belo Horizonte, state of Minas Gerais, Brazil, with patients eligible for elective colonoscopy, from March to June 2018. The project was approved by the institutional Research Ethics Committee

(CCAE 56538616.2.3001.5121) and registered on the website https://clinicaltrials.gov/ (NCT02769390).

The inclusion criteria used were age between 18 and 65 years, Body Mass Index (BMI) between 18 and 30, and healthy patients or those with clinically controlled comorbidities (classification of physical status by the American Society of Anesthesiology - ASA I and II). The exclusion criteria were allergy to any substance used in the procedure, cognitive impairment, psychiatric disorder, pregnancy, lactation and chronic use of opioids.

The sample size was calculated according to Hong et al., totaling two groups of 25 individuals, with a standard deviation of ±7.5; power of 90% and level of significance of 5%.[13]

As shown in Fig. 1, 62 patients were initially assessed for eligibility, but 10 did not meet the inclusion criteria and two patients decided not to participate in the study. After excluding these patients, the others (n = 50) were randomly divided into two groups of 25 individuals each, through a randomization sequence previously generated by the website www.random.org. Group A patients received 3 mg of midazolam and Group B received 50 mcg of fentanyl, both associated with propofol (initial dose of 50 mg + 20 mg increments). All patients who agreed to participate in the study signed the free and informed consent form.

The endoscopist, the anesthesiologist, the patient and the technicians at the post-anesthetic recovery room were blinded as to which drug (midazolam or fentanyl) was administered before propofol.

In the exam room, the patients received standard monitoring and oxygen through a nasal catheter at 4 L/min. The syringes were previously prepared with 3 mg of midazolam or 50 mcg of fentanyl and bidistilled water, up to five milliliters of clear solution. A resident of anesthesiology who did not participate in the research drew the lots and informed the nursing technician to which group each patient belonged. The technician then delivered the syringe to the anesthesiologist according to the patient's allocation. The anesthesiologist in charge administered the clear solution intravenously, without knowing its contents. Then, 50 mg of propofol was administered in increments of 20 mg until the patient reached level 4 of sedation according to Ramsay's scale: patient asleep and with no reaction to verbal command, when the endoscopist was then authorized to introduce the colonoscope.[14] The patient was maintained in this sedation plan through new increments of 20 mg of propofol, administered according to the anesthesiologist's subjective evaluation. The time between the introduction of the colonoscope and its removal was defined as the examination time (Exam length).

Episodes of awakening, movement, drop in SpO2 < 90% and need for ventilatory assistance were recorded. Additionally, Heart Rate (HR) and Mean Blood Pressure (MBP) were recorded at the following times: initial (patient arrival in the procedure room), sedation (administration of midazolam or fentanyl), examination (Ramsay stage 4, endoscopist authorized to start the exam) and final (last measurement, end of the procedure). The data obtained in the initial period and during the exam were used to determine the relative variation of HR and MBP, using the following formula: [(exam data - initial data) / initial data] × 100.

At the end of the procedure, the patient was referred to the Post-Anesthetic Recovery Room 1 (PARR1), where monitoring and supplemental oxygen were maintained, and where patients were assisted by a different nursing team than the one that helped with the colonoscopy. The patients remained until a recovery criterion compatible with a score on the Aldrete scale □ 9 was reached.[15] This time was defined as Length of Stay in the Post-Anesthesia Care Unit 1 (LSPACU1). Subsequently, the patients were transferred to the Post-Anesthetic Recovery Room 2 (PARR2) where they remained without monitoring and supplemental oxygen until they were able to walk, change themselves and drink water, so they could be discharged to home. This period was recorded as Length of Stay in the Post-Anesthesia Care Unit 2 (LSPACU2). The time until discharge to home was determined as the sum of LSPACU1 and LSPACU2.

For the statistical analysis, quantitative variables were submitted to the Shapiro-Wilk normality test. Parametric data were submitted to Student's t test. Nonparametric data were analyzed using the Mann-Whitney test. Pearson's test was used to assess whether there was a correlation between the times evaluated in the study (Exam length, LSPACU1, LSPACU2 and discharge to home), in each group. The collected data were tabulated and analyzed using the Graphpad Prism® program, version 5.0 for Windows, with $p < 0.05$ being considered statistically significant.

Results

The patients' characteristics and their comorbidities are described in Table 1. The groups showed to be homogeneous, and most patients were females, with a median age of 57 years. The median weight was 69 kg for patients in Group A and 74 kg for Group B. Only the presence of clinically controlled comorbidities was statistically higher in patients who received fentanyl (Group B) compared to those who received midazolam (Group A) (p = 0.0047). In both groups, Systemic Arterial Hypertension (SAH) was the most frequent comorbidity in the patients.

Group A patients received a median dose of midazolam of 0.04 mg/kg (minimum 0.03 mg/kg – maximum 0.08 mg/kg), while in Group B the median dose of fentanyl was 0.68 mcg/kg (minimum 0.58 mcg/kg – maximum 0.96 mcg/kg). Regarding the consumption of propofol, despite a higher consumption in Group A patients, both regarding the total dose and dose/kg, there was no significant difference between the groups (Table 2).

The analysis of the recovery time in the PARR1 showed that the patients in Group B had a statistically shorter recovery time than that observed in Group A patients (p = 0.0380) (Fig. 2). Regarding the duration of the exam (Exam Length), LSPACU2 and discharge to home care, there was no significant difference between the groups.

Throughout the procedure, patients were monitored for HR and MBP. Fig. 3 shows the kinetics of HR and MBP obtained during the analyzed periods (initial, sedation, during exam and final). There were no significant differences in HR between patients in Groups A and B (Fig. 3A) or between the different times analyzed within each group (Fig. 3 B and C). Regarding
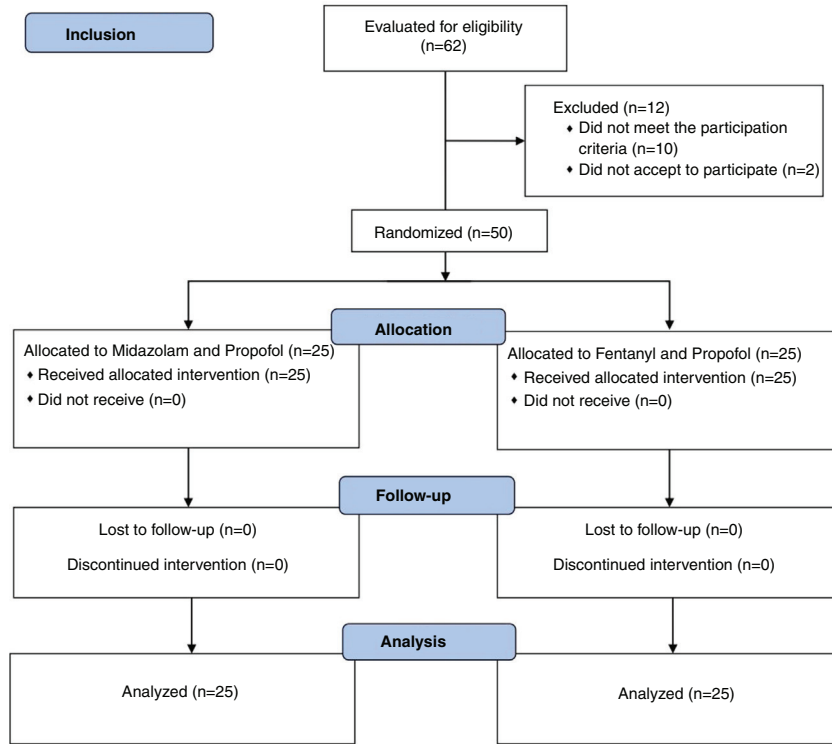
Fig. 1 – Sample and application of the inclusion and exclusion criteria.
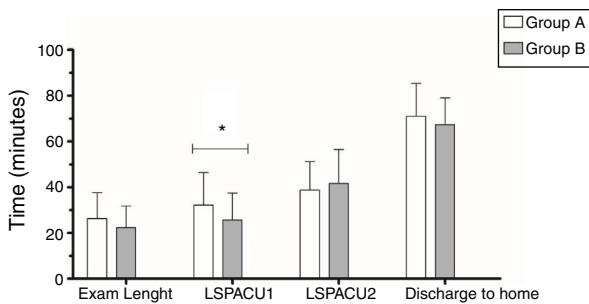
Fig. 2 – Comparative analysis between Exam Length, LSPACU1, LSPACU2 and Discharge in patients of Group A (midazolam and propofol) and Group B (fentanyl and propofol). The values presented herein represent the means obtained and the bars indicate the standard deviation (*p < 0.05).

the MBP, patients in Groups A and B did not show significant differences regarding the initial, exam and final periods (p> 0.05). However, during the sedation period, the MBP values of Group B were significantly higher than those of Group A (p = 0.0051) (Fig. 3E). In the analysis within each group, a significant variation was observed in Group B in relation to the following analyzed times: the initial and the sedation periods showed a statistically higher MBP than the exam length and final periods (p < 0.0001). There was no significant difference between the analyzed times in group A (Fig. 3 F and G).

The relative variation rates in HR and MBP obtained after propofol administration are shown in Figs. 3 D and H. No sig-

nificant difference was observed between the mean values observed in Groups A and B (p > 0.05).

During the exam and the post-anesthetic recovery period, there were no episodes of agitation, bradycardia (HR < 60 bpm), ventilatory depression (SpO2 < 90%) and/or maneuvers for ventilation, pain, nausea or vomiting. All patients had a good evolution and were discharged to home on the same day, with no unexpected hospitalizations.

The correlation analysis demonstrated that in both groups the recovery time in the PARR1 showed a negative correlation with the recovery time in the PARR2 (Group A: r = -0.4198 and p = 0.0367; Group B: r = -0, 6345 and p = 0.0007). Therefore, the LSPACU2 will be increasingly shorter as the patient stays longer in the PARR1, and vice versa. Regarding the discharge to home, in Group A the time of discharge showed a positive correlation with the LSPACU1 (r = 0.617 and p = 0.001) and LSPACU2 (r = 0.456 and p = 0.022) times. In Group B patients, this correlation was observed only in relation to LSPACU2 (r = 0.630 and p = 0.001). The other variables showed no correlations with each other (p > 0.05).

Discussion

Colonoscopy is considered the gold standard for detecting polyps and pre-malignant lesions, which contributes to reducing the incidence of colorectal cancer. Although it is a safe procedure, it is not free from complications such as bleeding, intestinal perforations, cardiorespiratory alterations and other side effects associated with the use of sedatives.[16] Therefore, it is essential that it be performed under a safe anesthetic technique, which allows for quick

Table 1 – Characterization of the study population regarding gender, age (years), weight (Kg) and presence of comorbidities.

	Group A		Group B		p-value
Gender	ƒ	%	ƒ	%	
Female	17	68.00	15	60.00	0.5557
Male	8	32.00	10	40.00	
Age (years)	Group A		Group B		
Median	57 years		57 years		0.4836
P25−P75	48–61		52–61		
min−max	34–64		27–64		
Weight (Kg)	Group A		Group B		
Median	69 kg		74 kg		0.3125
P25−P75	62–74		64.5–79.0		
min−max	39–103		52–86		
	Group A		Group B		
Comorbidities	ƒ	%	ƒ	%	
Total of patients with some comorbidity	9	36.00	18	72.00	0.0047[a]
	Group A		Group B		p-value
N. of comorbidities per patient	ƒ	%	ƒ	%	
One comorbidity	7	77.78	9	50.00	–
Two comorbidities	2	22.22	6	33.33	
Three comorbidities	–	–	3	16.67	
	Group A		Group B		p-value
Type of comorbidity	ƒ	%	ƒ	%	
Controlled cardiac arrhythmia	0	–	1	3.45	–
Breast cancer	0	–	1	3.45	
Rectal cancer	1	9.09	2	6.90	
Diabetes mellitus	1	9.09	6	20.69	
Dyslipidemia	0	–	2	6.90	
SAH	7	63.64	13	44.83	
Hypothyroidism	0	–	3	10.34	
Osteoporosis	1	9.09	0	0.00	
Smoking	1	9.09	1	3.45	
Total of comorbidities/group	11		29		–

ƒ, Frequency values; %, Percentage values; SAH, Systemic Arterial Hypertension.

[a] Represents a statistically significant difference ($p < 0.05$), according to Student's *t* test.

Table 2 – Consumption of propofol (total dose – mg, and per patient weight – mg/kg), according to the sedation scheme.

|	Total dose (mg)			Patient weight (mg/kg)		
	Group A	Group B	p-value	Group A	Group B	p-value
Mean	152	144.80		2.24	2.03	
SD	40.62	37.54	0.485	0.56	0.54	0.195
min−max	100–260	100–240		1.37–3.59	1.16–3.16	

SD, Standard Deviation.

recovery, decreases the patient's length stay in the hospital environment and reduces the costs associated with the procedure.[10,11]

This study differs from the others as it standardizes the level of sedation used in each patient and measures an objective clinical parameter of recovery: the post-anesthetic recovery time. Previous studies used different levels of sedation or combinations of drugs or objectives.[6,7,13,17–22]

In the present study, the analyzed population showed similar social characteristics in both groups, except for the presence of comorbidities, which was more frequent in patients of Group B. Regarding the sedative dose used, fixed concentrations of midazolam and fentanyl were administered, aiming at standardizing the level of sedation and also facilitating the preparation of the syringes. The dose used, when calculated based on the patient's weight, is in accordance with the literature.[6,7,12,17,19,20,23]

The consumption of propofol was not statistically significant. However, a greater consumption of propofol was observed in patients of Group A, both in relation to the total dose and in the dose per kilo of the patient. The reduction in the consumption of propofol is an important aspect to be considered in clinical practice, due to the absence of specific antidotes or antagonists to this drug, as well as its hypotensive effect and its capacity to generate ventilatory depression.[6,12] The absence of a significant difference between the groups may have occurred due to the small sample size for this inference. Previous studies that demonstrated the reduction in
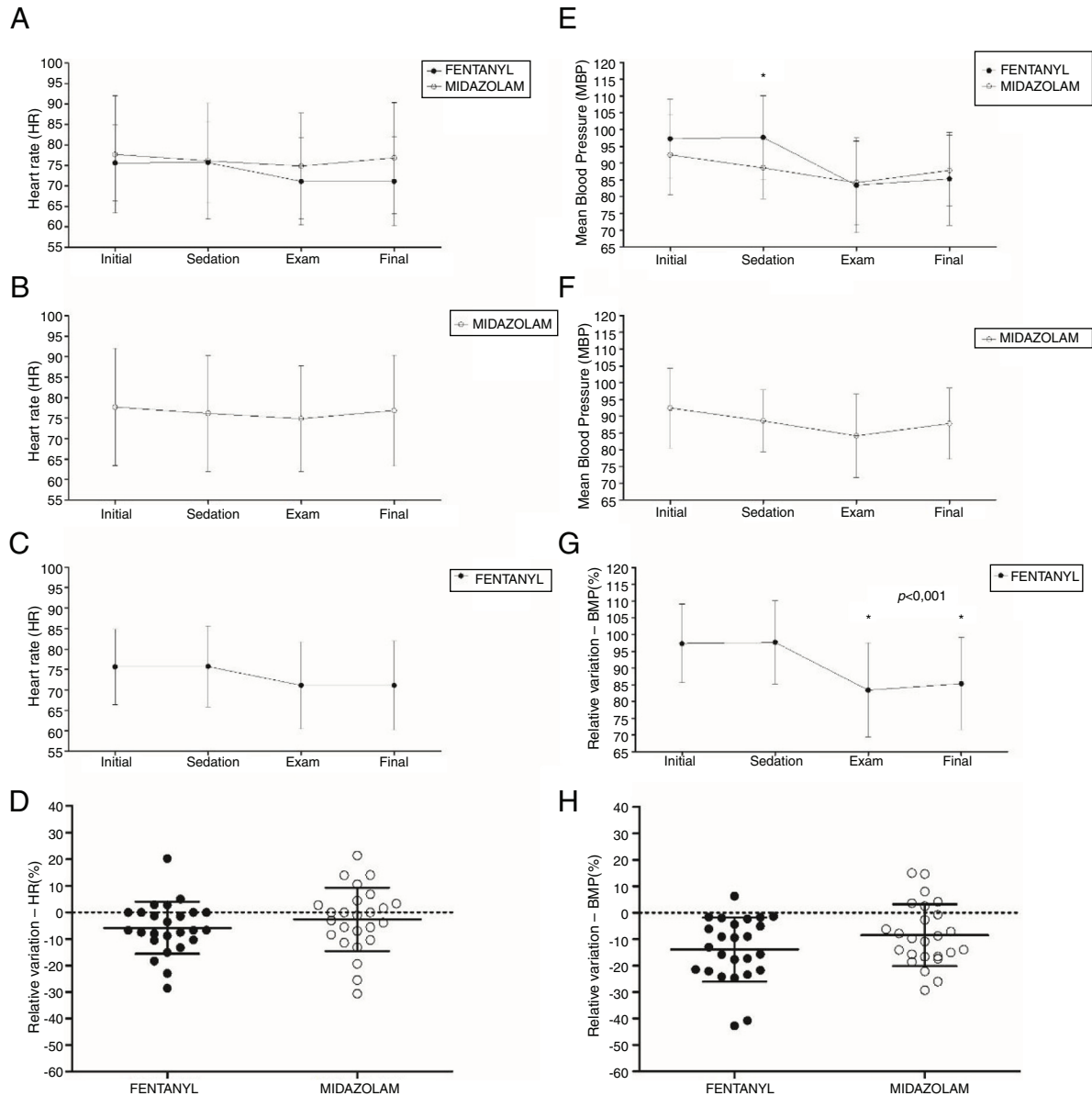
Fig. 3 – Kinetics of Heart Rate (HR) and Mean Blood Pressure (MBP) observed in the different assessed times (initial, sedation, exam and final). (A) Mean HR observed in the Fentanyl and Midazolam groups, (B) only in the Midazolam group, (C) only in the Fentanyl group, (D) Mean relative HR variation in both groups, (E) Mean observed MBP in the Fentanyl and Midazolam groups, (F) only in the Midazolam group, (G) only in the Fentanyl group, (H) Mean relative variation in MBP in both groups. The bars represent the standard deviation values. *Statistically significant difference (p <0.05).

propofol consumption used a larger sample than the one used in the present study. However, the total dose of propofol was within the average observed in those studies, despite the great variability between them.[7,12,17–22]

The colonoscopy exams were performed due to several indications, including polypectomy, which may justify the higher mean exam length (Exam Length) in relation to other studies.[6,17,20,23] As for the recovery time, it was observed that patients sedated with fentanyl and propofol (Group B) had a shorter recovery time in PARR1 when compared to those who received midazolam and propofol (Group A). These data corroborate those by Turk et al.,[20] in which they demonstrated that the association of fentanyl and propofol

resulted in shorter post-anesthetic recovery time when compared to the association between alfentanil and propofol. In another study, of which objective was to compare the recovery time of propofol use alone with other drug associations, the midazolam-propofol and fentanyl-propofol groups had similar recovery times between themselves after moderate sedation.[6]

In both groups, the recovery time in the PARR1 was considered inversely proportional to the time in the PARR2. In this sense, the longer the patient remains in the PARR1, the shorter the recovery time in the PARR2, and vice-versa. This similar correlation observed in Groups A and B contributed for the time of discharge to home to be similar in the study

patients. Despite this similarity between the groups, the discharge to home in Group A was directly related to recovery times in the PARR1 and PARR2, while in Group B the discharge time was correlated only with the LSPACU2. This result corroborates the data demonstrated in this study, where, despite showing a reduction in LSPACU1, patients in Group B remained in the PARR2 for as long as Group A, leading to an increase in the time of discharge. Thus, the longer the LSPACU2, the longer the period for the patient to be discharged from the hospital. This result suggests that the evaluation of discharge parameters be carefully analyzed by the team, as a tendency to keep the patient in the recovery room for a minimum period in demonstrated, even when the patient has already clinical conditions to be discharged.

The MBP analysis during the sedation period showed a statistical significance between the groups. However, this increase observed in Group B in comparison to Group A can be justified by the initial data observed in these patients. It is observed that in Group B the initial MBP values are similar to those obtained during sedation. Therefore, there was no change in this parameter after the administration of fentanyl. In contrast, in Group A there was a slight reduction in MBP during the sedation period, when compared to the initial one. Although this reduction was not significant in patients who received midazolam, it was sufficient to determine the difference between the two groups. In the intragroup analysis, Group B showed a significant variation in MBP between the different moments of the procedure (initial × exam/final and sedation × exam/final). However, the variation was less than 20%, which does not characterize hypotension.

The absence of complications during the exam and in the post-anesthetic recovery period is compatible with the low frequency of these events and the profile of the patients selected for the present study. Transient hypoxemia is the most frequent complication described in the literature. However, the administration of supplemental oxygen to all patients and the small sample size may explain why this complication was not observed.[3,17,20,22,24–26] Although no questionnaire about pain or nausea was applied, none of the patients had these complaints during the recovery period.

The limitations of this study include the small sample size, lack of information about the exams (indication, preparation, polypectomy, quality) and level of satisfaction of the patients and endoscopists. Further studies, with greater diversity and number of participants, are necessary to identify complications, differences in relation to the consumption of propofol and to indicate the most appropriate adjuvants in specific populations.

Conclusion

Based these data, it is possible to conclude that the fentanyl combination resulted in shorter post-anesthetic recovery time in the PARR1 than the midazolam and propofol combination in adult patients, healthy or with controlled comorbidities. However, the time of discharge to home was similar in both groups.

Conflicts of interest

The authors declare no conflicts of interest.

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