SCIENTIFIC ARTICLE

Colonoscopy sedation: clinical trial comparing propofol and fentanyl with or without midazolam

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Abstract Colonoscopy is one of the most common procedures. Sedation and analgesia decrease anxiety and discomfort and minimize risks. Therefore, patients prefer to be sedated when undergoing examination, although the best combination of drugs has not been determined. The combination of opioids and benzodiazepines is used to relieve the patient's pain and discomfort. More recently, propofol has assumed a prominent position. This randomized prospective study is unique in medical literature that specifically compared the use of propofol and fentanyl with or without midazolam for colonoscopy sedation performed by anesthesiologists. The aim of this study was to evaluate the side effects of sedation, discharge conditions, quality of sedation, and propofol consumption during colonoscopy, with or without midazolam as preanesthetic. The study involved 140 patients who underwent colonoscopy at the University Hospital of the Federal University of Juiz de Fora. Patients were divided into two groups: Group I received intravenous midazolam as preanesthetic 5 min before sedation, followed by fentanyl and propofol; Group II received intravenous anesthesia with fentanyl and propofol. Patients in Group II had a higher incidence of reaction (motor or verbal) to the colonoscope introduction, bradycardia, hypotension, and increased propofol consumption. Patient satisfaction was higher in Group I. According to the methodology used, the combination of midazolam, fentanyl, and propofol for colonoscopy sedation reduces propofol consumption and provides greater patient satisfaction.
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Sedação para colonoscopia: ensaio clínico comparando propofol e fentanil associado ou não ao midazolam

Resumo A colonoscopia é um dos procedimentos mais feitos. Sedação e analgesia diminuem a ansiedade e o desconforto e minimizam riscos. Em razão disso, os pacientes preferem que o exame seja feito sob anestesia, embora não tenha sido determinada a melhor combinação de fármacos. A associação de benzodiazepínicos com opioides é usada para aliviar a dor e o desconforto do paciente. Mais recentemente, o propofol assumiu posição de destaque. Este estudo, prospectivo e randomizado, é único na literatura médica e especificamente comparou o uso do propofol e fentanil associado ou não ao midazolam na sedação para colonoscopia feita por anestesiologistas. Os objetivos do estudo foram avaliar os efeitos colaterais da sedação, as condições de alta, a qualidade da sedação e o consumo de propofol durante a colonoscopia, com ou sem o midazolam como pré-anestésico. Envolveu 140 pacientes submetidos à colonoscopia, no Hospital Universitário da Universidade Federal de Juiz de Fora. Os pacientes foram dividi-dos em dois grupos. O Grupo I recebeu, por via endovenosa, midazolam como pré-anestésico, cinco minutos antes da sedação, seguido do fentanil e propofol. O Grupo II recebeu, por via endovenosa, anestesia com fentanil e propofol. Os pacientes do Grupo II apresentaram maior incidência de reação (motora ou verbal) à introdução do colonoscópio, bradicardia, hipotensão arterial e maior consumo de propofol. A satisfação dos pacientes foi maior no Grupo I. De acordo com a metodologia empregada, a associação de midazolam ao propofol e fentanil para sedação em colonoscopia reduz o consumo de propofol e cursa com maior satisfação do paciente.

Introduction

Colonoscopy is one of the most common procedures in the world. Sedation and analgesia are considered key components, as they reduce anxiety and discomfort and therefore improve the procedure tolerability and patient satisfaction, minimize risk of complications and provide better conditions for the examination.[1,2] Colonoscopy pain results from mesenteric traction maneuvers and colonic distension by gas insufflation and the device frequent winding inside the intestine, which requires correction maneuvers.[3–6] As a result, many patients prefer the examination done under sedation and analgesia.[7]

Although the goal of sedation is to facilitate colonoscopy, patients may have varying degrees of impairment in their cognitive function, with a consequent delay in discharge and restrictions in various daily activities. The combination of benzodiazepines with opioids has been used since 1980 in colonoscopy procedures to alleviate patient's pain and discomfort. More recently, propofol has taken a prominent position.[4–7]

Propofol may be used alone or in combination with opioids (fentanyl 25–75 μg, meperidine 25–50 mg), and/or benzodiazepines (midazolam 0.5–2.5 mg), but there is no clear evidence that the combination of propofol with other drugs leads to reduction of side effects.[8] The use of propofol alone requires higher doses, which may lead to increased incidence of side effects. However, the risks and benefits of adding analgesic and sedative to propofol are controversial, and the selection of drugs is a crucial factor in determining the outcomes.[9] Regardless of the drug used, the anesthesia for colonoscopy is related to complications such as hypoxia, respiratory depression, apnea, hypotension, and cardiac dysrhythmia.[6,7,10,11]

Based on surveys, only two studies evaluated the use of propofol and fentanyl combined with midazolam for colonoscopy. However, both studies used propofol alone as the basis for comparison with the other three groups: fentanyl and propofol, midazolam and propofol, and propofol with fentanyl and midazolam.[9,12] In the study by Padmanabhan et al., although sedation has been made by anesthesiologists, the objective of the studies was to evaluate only the cognitive function of patients post-sedation, without any mention of the parameters related to the endoscopic procedure.[9] In turn, in the survey conducted by Rex and Vannatta, although variables similar to ours have been evaluated, the sedation was made by registered nurses and supervised by endoscopists.

Our study is unique in the literature that specifically compared, prospectively, the use of propofol and fentanyl associated or not with midazolam in sedation for colonoscopy performed by anesthesiologists.

Methods

A prospective, randomized, double-blind study, involving 140 patients undergoing colonoscopy at the University Hospital (HU/CAS) of the Federal University of *Juiz de Fora* (UFJF), from December 2010 to December 2011. The study was approved by the Research Ethics Committee.

The study included men and women, aged between 18 and 60 years, ASA I-II, referred to the Digestive Endoscopy Unit of HU/CAS of UFJF for a diagnostic colonoscopy. Patients invited to participate in the study signed the informed consent, and the study primary objectives were to evaluate the side effects of sedation, discharge conditions from the post-anesthesia care unit (PACU), and quality of sedation in the opinion of the endoscopist and patient. Secondarily, we evaluated the total consumption of propofol.

The exclusion criteria were patients with chronic use of drugs such as benzodiazepines, neuroleptics, and anticonvulsants for more than 30 days; hypersensitivity reactions to drugs used in the study; those undergoing abdominal laparotomy; body mass index above 35 $kg\,m^{-2}$; psychiatric patients; inadequate preparation conditions, defined as those preventing or hindering the examination; patients with clinical suspicion of intestinal subocclusion or stenotic colon tumors; using drugs that interfere with the heart rate; requiring complex therapeutic procedures set during diagnostic colonoscopy, such as polypectomy of larger polyps, flat lesion mucosectomy, and multiple polypectomy (>3).

In total, 140 patients were allocated randomly into two groups. A third doctor, responsible for randomization, prepared the syringe with premedication (midazolam) and placebo (distilled water), so that both the endoscopist and the anesthesiologist in charge of sedation were blind to the allocation of patients.

All patients were monitored with pulse oximetry, continuous ECG, and noninvasive blood pressure assessed every 5 min. The groups consisted of 70 patients each (Group I and Group II). In Group I, patients received intravenous (IV) midazolam ($0.05\,mg\,kg^{-1}$) as a pre-anesthetic 5 min before sedation, followed by IV fentanyl ($1\,\mu g\,kg^{-1}$) and propofol ($1\,mg\,kg^{-1}$).

In Group II, patients received anesthesia with IV fentanyl ($1\,\mu g\,kg^{-1}$) and propofol ($1\,mg\,kg^{-1}$). In both groups, anesthesia was induced with propofol, and the total loading dose was applied slowly, within 60 s, or limited to the drooping eyelid with loss of corneal-palpebral reflex. The maintenance dose of $0.5\,mg\,kg^{-1}$, was repeated whenever there were signs of discomfort (motor or verbal reaction, tachycardia and/or hypertension). In both groups, supplementary oxygen was offered with nasal catheter ($3\,L\,min^{-1}$).

Endoscopic examination was performed by two experienced endoscopists using a Fujinon 4400 video system and colonoscopy tubes of the series 490.

During procedures, age, weight, and height of patients; indication for colonoscopy; reactions (motor or verbal) to the introduction of the colonoscope; time to colonoscope introduction into the cecum; total examination time; dose of propofol induction; total propofol consumption; cardiovascular disorders: hypertension and tachycardia, defined as elevated blood pressure and heart rate levels greater than 20% above preanesthetic values; hypotension and bradycardia, defined as a loss greater than 20% above preanesthetic values, and changes in the levels of peripheral hemoglobin oxygen saturation. In cases where hypoxia lasted for more than 30 s or the drop reached levels below 80%, ventilation was started with a face mask.

After 30 minutes in the PACU, the patients with a score ≥ 9 according to the Aldrete–Kroulik modified index were considered fit for discharge.[13] Finally, we evaluated the satisfaction of the endoscopist and patient using a visual analog scale (0 = dissatisfied and 10 = extremely satisfied).

Statistical analysis was performed and initially we evaluated the data normality using the Kolmogorov-Sminorv test. Then we chose to use non-parametric tests because the data did not reach normal distribution. To compare the means of the two groups, we used the Mann–Whitney test, and to compare proportions we used the chi-square test. All analyzes were performed using the Graph Pad Prism version 5.01 software, and a p-value <0.05 was considered statistically significant.

Results

Table 1 shows a summary of all the research data, including general data related to colonoscopy, cardiovascular and hemoglobin saturation changes, sedation, and anesthetic recovery.

All patients underwent a complete colonoscopy examination. Regarding the examination, patients in Group II had a higher incidence of reaction (motor or verbal) to the colonoscope introduction ($p < 0.04$).

Regarding cardiovascular changes, Group II had a higher frequency of hypotension, although this difference did not reach statistical significance ($p = 0.121$), and a greater number of episodes of bradycardia ($p = 0.04$). Only one episode of mild hypoxemia was seen in each group.

The mean dose of propofol used for induction was similar between both groups. However, the total consumption of propofol was higher in Group II, and this difference reached statistical significance ($p < 0.001$).

The assessment of patients in the PACU with the use of Aldrete–Kroulik modified scale and the satisfaction of endoscopists and patients are shown at the end of Table 1. When comparing these three variables, only pacient satisfaction was significantly higher in Group I ($p = 0.006$).

Discussion

Colonoscopy is a procedure often performed for prevention, diagnosis, and treatment of a variety of symptoms and diseases of the lower digestive tract,[9,14] and sedation or anesthesia should be considered as an important tool to increase its effectiveness.[15]

Sedation or anesthesia is intended to decrease anxiety and discomfort, increase tolerance and satisfaction with the procedure, reduce risks of complications, and promote satisfactory conditions for the examination.[2,5,15]

The dose and the depth of sedation should be individualized according to the needs of each patient.[2] Gastrointestinal endoscopic procedures are often complex and require endoscopist's attention. Patient cooperation and anesthesiologist participation help to improve the procedure,[2,16,17] increase the detection of polyps, and facilitate therapeutic procedures.[7,16]

There are several anesthetic techniques available for colonoscopy.[2] Traditionally, the combination of narcotics and benzodiazepines has been used and, more recently,

Table 1 Study data.

	Group I	Group II	p
n	70	70	–
Sex (male/female)	35.7/64.3	38.5/61.4	–
Mean age (years)	48.4 ± 9.7	48 ± 10.8	0.996
Weight (kg)	71.1 ± 13.2	69.8 ± 13.2	0.670
Height (m)	1.7 ± 0.1	1.7 ± 0.1	0.849
Colonoscopy data			
RCI	3/70 (4.3%)	14/70 (20%)	<0.04
MTIC	6.9 ± 3.5	6.3 ± 3.0	0.590
TET	19.4 ± 6.4	20.2 ± 5.6	0.191
Cardiovascular and SpO$_2$ data			
Arterial hypertension	1/70 (1.4%)	0/70 (0%)	0.315
Arterial hypotension	14/70 (20%)	22/70 (31%)	0.121
Tachycardia	0/70 (0%)	0/70 (0%)	1.000
Bradycardia	0/70 (0%)	4/70 (5.6%)	0.04
SpO$_2$	1/70 (1.4%)	1/70 (1.4%)	1.000
Sedation data			
MDI (mg)	70.6 ± 13.4	71 ± 14.6	0.890
TCP (mg)	153 ± 60.3	206 ± 79.2	<0.001
Anesthetic recovery data			
AKI > 9	70/70 (100%)	70/70 (100%)	>0.05
ESR	9.7 ± 0.7	9.6 ± 0.7	0.432
PSR	9.8 ± 0.5	9.4 ± 1.0	0.006

Sex, data expressed as a percentage; age, weight and height: data expressed as mean and standard deviation; RCI, reaction to colonoscope introduction; n, no of cases/no of patients (%); MTIC, mean time of device introduction to the cecum in minutes; TET, total examination time (mean in minutes); MDI, mean dose of propofol induction; TCP, total consumption of propofol; AKI, post-anesthetic recovery according to the modified Aldrete–Kroulik index; ESR, endoscopist satisfaction ratings (mean and standard deviation); PSR, patient satisfaction ratings (mean and standard deviation).

propofol occupies a prominent place.[1,2,7,16–18] The pharmacokinetic model of propofol presents a safe agent for colonoscopy because it has an amnesic effect and a 4-min half-life, which provides fast recovery and awake even after prolonged administration.[19] However, the analgesic effect of propofol is limited and, when used as a single agent, higher doses are required which increases the risk of deep sedation. The bolus administration associated with a short half-life of propofol facilitates the occurrence of ''sedation waves'', in which deep sedation peaks and respiratory depression may alternate with episodes of superficiality and risk of agitation during colonoscopy.[9] The use of continuous infusion pump minimizes this problem, but increases the cost of the procedure.

It also should be considering that, because propofol has a very narrow therapeutic window, which leads easily from a state of moderate to deep sedation or general anesthesia,[2] and because there is no reversal agent, propofol should only be administered by an anesthesiologist or doctor with proven experience in airway management.[9]

To reduce these mentioned risks, sedation with propofol in colonoscopy has its administration often associated with fentanyl and/or midazolam, which, in small doses, usually produce moderate sedation.[4,16,18] Some studies reported

that patients receiving combined sedation were discharged more quickly and reported greater satisfaction.[4,20,21]

Our results showed that patients who did not receive midazolam (Group II) had a higher frequency of reaction to the colonoscope introduction (Table 1). We believe that the addition of midazolam to propofol and fentanyl, at the doses used in the research (minimum recommended doses), provides a more adequate level of sedation to the device introduction.

The similarity between the two groups regarding the rectum-cecum time and the total examination time (Table 1) shows that procedures were technically similar in both groups, and thus comparable.

Another important finding in our study was the total consumption of propofol significantly lower in Group I. This finding is consistent with the literature, in which the reduced propofol dose is associated with the combined use of opioids and benzodiazepines.[4,6,9,21] The combination of propofol and fentanyl and/or midazolam reduces the consumption of propofol and decreases the risk of deep sedation, without prolonging the recovery.[22] A smaller consumption of propofol is usually expected in combined sedation.[12,16] Similarly to our study, two other studies reported lower consumption of propofol in combination with

midazolam and fentanyl.[12,16] Reduction in propofol consumption is an important technical aspect because the drug has no specific antidotes or antagonists, which can be considered a limiting factor for its use.[14,19]

Sedation can prolong recovery and discharge time and increase costs and the possibility of cardiopulmonary complications. Heart rate, blood pressure, and pulse oximetry should be routinely monitored, and some protocols suggest supplemental oxygen administration,[8] because the practice of sedation for colonoscopy exposes patients to increased mortality and morbidity. In our study, we found a higher frequency of hypotension in Group II (Table 1). Although this difference did not reach statistical significance, the higher frequency of hypotension in Group II patients is likely due to the increased consumption of propofol in this group, a known hypotensive agent. Also in Group II, we noticed an increased frequency of bradycardia, which may be explained by the possibility of myocardial depression. The interaction of propofol with muscarinic cholinergic receptors is concentration-dependent and may induce bradycardia.[23]

Regarding the peripheral hemoglobin oxygen saturation, we observed in both groups only one patient with temporary reduction of SpO_2, without requirement for ventilation with a face mask. Our data support the fact that both techniques are safe and have small risk of cardiopulmonary adverse events, as reported in the literature.[12,16]

The possibility of early discharge from PACU is an important aspect in the care of outpatients, and it generates improved service and lower costs.[1] Although our study does not focus on PACU discharge time, our results showed that regardless of the sedation technique used, all 140 patients were discharged with an Aldrete–Kroulik modified index >9 after 30 min.

The endoscopist assessment showed no difference between the groups, demonstrating that anesthesia, regardless of the combination of drugs used, facilitates colonoscopy. Patients in Group II had a higher incidence of reaction to the colonoscope introduction, which may be related to the decreased satisfaction with the technique and confirms that the addition of midazolam improves comfort.

Conclusion

According to the methodology used, the combination of midazolam, propofol, and fentanyl for sedation in colonoscopy reduces the total consumption of propofol and is associated with greater patient satisfaction.

Conflicts of interest

The authors declare no conflicts of interest.

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