



Original Article

Safety degree assessment of drugs used in conscious sedation for colonoscopy in patients that develop respiratory depression[☆]



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ABSTRACT

Objective: To analyze the safety degree of drugs used in colonoscopy during conscious sedation in patients developing respiratory depression.

Methods: Cross-sectional observational study that evaluated 1120 patients who underwent colonoscopy between February 2015 and February 2016. Physical characteristics, surgical history and previous colonoscopies, indication and conditions of the current examination, fentanyl and midazolam doses and subsequent complications were analyzed. Level of significance: $p < 0.05$. Chi-square test was used for association of categorical variables, whereas Student's *t* test was used to compare means and Spearman's coefficient for correlation.

Results: There were 661 female (59%) and 459 (41%) male patients, with a mean age of 54.90 (20–87) years and BMI of 27.00 (14.5–45.4). Of the 1120 patients, only 2 (0.2%) had respiratory depression, reversed with lanexat. Patients who had complications were of both genders, with a body mass index of 21.25 and 28.7. There was a correlation between the required dose of fentanyl and age ($p < 0.001$ to -0.121 Spearman's coefficient), as well as midazolam ($p < 0.001$ – Spearman's coefficient -0.452) and increasing age was associated with a lower dose of the drug.

Conclusion: The number of patients with complications was 0.17%. The age of the patient showed an inverse association, i.e., the older the patient, the lower the required dose of medication. The drugs used in colonoscopy show a high degree of safety, corroborating their frequent use for superficial/conscious sedation in this procedure.

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Avaliação do grau de segurança dos fármacos utilizados na sedação superficial na colonoscopia em pacientes que desencadeiam depressão respiratória

R E S U M O

Palavras-chave:

Colonoscopia, Sedação consciente, Complicação, Sedação, Depressão respiratória

Objetivo: Analisar o grau de segurança dos fármacos utilizados na colonoscopia sob sedação superficial em pacientes que desencadeiam depressão respiratória.

Métodos: Estudo observacional transversal, que avaliou 1.120 pacientes que realizaram colonoscopia entre Fevereiro de 2015 e Fevereiro de 2016. Analisaram-se características físicas, histórico cirúrgico e colonoscopias prévias, indicação e condições do exame atual, dose de fentanil e midazolam e complicações apresentadas. Nível de significância adotado: $p < 0,05$. Utilizou-se teste Qui-quadrado para associação de variáveis categóricas, teste t de Student para comparação de médias e coeficiente de Spearman para correlação.

Resultados: Foram 661 pacientes do sexo feminino (59%) e 459 (41%) do sexo masculino, com média de idade de 54,90 (20-87) anos e IMC de 27,00 (14,5-45,4). Dos 1120 pacientes, apenas 2 (0,2%) exibiram depressão respiratória revertida com lanexate. Os pacientes que apresentaram complicação eram de sexos diferentes, com índices de massa corpórea de 21,25 e 28,7. Houve correlação entre a dose necessária de fentanil e a idade ($p < 0,001$ - coef Spearman - 0.121), assim como a de midazolam ($p < 0,001$ - coef Spearman - 0.452), sendo que com o aumento da idade se correlacionou com uma menor dose utilizada de medicamento.

Conclusão: O número de pacientes que apresentaram alguma complicação foi 0,17%. A idade do paciente tem associação inversa, quanto maior a idade do paciente, menor é a dose necessária de medicamentos. Verifica-se alto grau de segurança dos medicamentos utilizados na colonoscopia, corroborando sua utilização frequente para a sedação superficial/consciente neste procedimento.

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Introduction

Colonoscopy is a safe endoscopic examination, which provides information that common radiological tests may not be able to disclose. Colonoscopy has the advantage of being used both for the diagnosis and treatment of some colorectal diseases.¹

Despite its importance, patients undergoing colonoscopy frequently have many questions and concerns about the procedure. Because it is an invasive procedure, it may have its performance hindered by factors such as patient anxiety and discomfort, who in addition to fear of pain, also must face the possibility of diagnosis of a severe illness.²

Several factors are associated with increased likelihood of feeling discomfort during colonoscopy, which can be inherent or not to the patient. Being very young or of older age, female gender, low body mass index (BMI), previous abdominal or pelvic surgery, inadequate colon preparation, inadequate sedation, kinking, high pressure of the air blown for colon distention are some of these factors.³ An experienced endoscopist, adequate colon preparation, patient compliance and effective analgesia and sedation are required for an effective and good-quality examination.²⁻⁴

The best type of sedation/analgesia for gastrointestinal endoscopic procedures has yet to be defined,⁵ although, it is believed that sedation administration before the procedure

is safer for the patient and the endoscopist.^{6,7} Both deep sedation and superficial sedation and analgesia are options for colonoscopies. When deeper sedation is desired, usually an anesthesiologist is called to follow the examination. Conscious sedation allows patients to give verbal responses or respond to tactile stimulation and allows control of respiratory and cardiovascular functions.⁵

Therefore, the most adequate medication for sedation during colonoscopy is that with an immediate effect and that lasts only for the duration of the examination, resulting in a rapid patient recovery and cause few or no side effects.⁸ Benzodiazepines are routinely used associated with opioids. Midazolam is a benzodiazepine that reduces anxiety and is used in patient sedation. It has an onset of action of 1-2 min after intravenous administration of 5 mg and has a quick recovery. Fentanyl is a short-acting opioid, of which effect takes place within 2 min after the intravenous administration of 1-2 mg/kg and is responsible for anesthesia and pain reduction during the examination.⁹

The examination starts with the patient placed in left lateral decubitus, after adequate colon preparation and sedation by peripheral venous access, monitored by pulse oximetry. The perianal and anal region are inspected for the presence of lesions, and digital rectal examination is performed for dilation of the anal sphincter and evaluation of possible tumor masses. If general anesthesia is not being used, the patient

may experience cramping or severe pain, resulting from tube movement and can also feel the urge to evacuate.

The colonoscopy should evaluate the mucosa of all colon segments, both at the introduction and the withdrawal of the device. Some landmarks are used by the endoscopist to better locate the colonoscope during the procedure. The bluish shade of the spleen, seen by transparency, identifies the splenic flexure. The second shade, more extensive, consists of the liver and identifies the hepatic flexure. The appendicular ostium is located in the center of the triangle formed by the convergence of teniae coli, in the cecum. The ileal papilla can be identified through a bilabiate fold located in the transition between the ascending colon and the cecum. The examination is considered complete when the examiner can identify the cecum, ileal papilla and appendicular ostium and the colonoscope must be introduced in the ileal papilla to evaluate the terminal ileum.²

The colonoscopy performance may lead to complications arising from the preparation, sedation and diagnostic and/or therapeutic procedures. These events, which are relatively common, have a morbidity rate of around 1% and are usually transient and underreported. Among the complications related to the drugs used for sedation are local reactions, such as superficial phlebitis at the site of benzodiazepine injection and localized itching due to use of opioids.⁵ Systemic reactions caused by the drugs are more significant and potentially more dangerous, with most of them being cardiorespiratory-related. The most common are: hypoventilation, hypertension, hypotension, hypoxia, tachycardia, bradycardia. Some may be potentiated by the pain and discomfort of patients, requiring higher doses of sedatives.⁶

The aim of this study is to analyze the safety degree of the drugs used in colonoscopy procedures in patients under superficial sedation, identify possible complications resulting from the drug doses, correlating them with the presence of complications.

Methods

This was an observational study with a cross-sectional design, which was approved by the Research Ethics Committee of Universidade do Sul de Santa Catarina under opinion n. 875,131, CAAE 49379915.5.0000.5369, according to the standards of the National Health Council for research involving human subjects, resolution 466/2012.

Patients treated on an outpatient basis between February 2015 and February 2016 were evaluated at the Endoscopy and Colonoscopy Service at Clínica Pró Vida, in the municipality of Tubarão, state of Santa Catarina, Brazil. Based on the number of monthly consultations at the service, of approximately 100 consultations/month, it was estimated a sample of 1000 patients.

The study included all patients submitted to colonoscopy at the Endoscopy and Colonoscopy Service at Clínica Pró Vida in Tubarão, Santa Catarina, from February 2015 to February 2016. Patients who required emergency examinations or who were submitted to deep sedation were excluded from this study.

All patients received a diet without residues on the day before the examination, followed by a 12-h fasting. On the

day of the colonoscopy, colon preparation was performed with a balanced polyethylene glycol solution, 1000 mL administered orally 3 h before the examination, associated with the antiemetic drug ondansetron, 8 mg orally.

Midazolam at a dose of 0.1 mg/kg of weight and intravenous fentanyl, 1 mcg/kg, were used for patient sedation and analgesia, immediately before the examination. In patients older than 70 years, the initial dose of midazolam was 0.05 mg/kg. Drugs were administered simultaneously and a second dose of midazolam was administered in cases where the patient expressed pain, usually half of the initial one, 0.05 mg/kg.

Monitoring of vital signs was carried out with pulse oximetry and, when necessary, oxygen supplementation was provided with a mask. The criterion used for respiratory depression was a respiratory rate <8–10 bpm or decreased oxygen saturation (SpO₂) recorded in pulse oximetry. Patients with oxygen saturation ≤70% were treated for respiratory depression. Sedation and monitoring were performed by the endoscopists participating in the study, all of which were professionals with more than 10 years of experience. The devices used for the colonoscopy were Pentax® EPK 1000 Series.

Data were collected through a Medical Record for Analysis, containing age, gender, weight, height, BMI, indication (diagnostic or therapeutic) and reason for colonoscopy (which disease was to be investigated and/or treated or what type of treatment was used), if there was prior abdominal and/or pelvic surgery and previous colonoscopy examinations, time of examination, adequate or inadequate colon preparation, complete or incomplete examination, dose of fentanyl and midazolam used and subsequent complications, if any.

The drugs used for sedation and analgesia during the examination are the ones routinely used in procedures at the Endoscopy and Colonoscopy Service of Clínica Pró Vida, in all patients submitted to colonoscopy. The study did not require the signing of the free and informed consent form and used only a justification for not using the Term of Informed Consent in cases of research using medical records.

Data were recorded in a spreadsheet using the EpiInfo® program, version 3.5.4 and analyzed with the program SPSS, version 20.0. The significance level was set at less than 5% ($p < 0.05$). The description of the variables was performed using means and standard deviations for numerical variables and relative frequencies for categorical variables. The chi-square test was used for the association of categorical variables, while Student's t test was used for the comparison of means and the correlation of variables used Spearman's correlation coefficient, with rho (ρ) between -1 and +1.

Results

Of the 1120 patients evaluated, 661 were females (59%) and 459 (41%) males, with a mean age of 54.90 (20–87) years. The mean BMI of the patients was 27 (14.5–45.4), with a mean height of 163 cm and mean weight of 67.38 kg.

Table 1 shows the characteristics of patients in relation to gender, age, BMI, number (%) of patients submitted to prior colonoscopy, how many had adequate colon preparation and how many patients had a complete examination. Patients with

Table 1 – General aspects of patients submitted to colonoscopy under conscious sedation in a private clinic in Tubarão (SC).

Characteristics	Number (%)
Gender	
Female	661 (59.0%)
Male	459 (41%)
Age (mean)	
<54.87 years	478 (42.7%)
≥54.87 years	642 (57.3%)
BMI	
<18.5	15 (1.3%)
≥18.5 < 25.0	372 (33.3%)
≥25.0 < 30.0	463 (41.3%)
≥30.0	270 (24.1%)
Previous colonoscopy	
Yes	252 (22.5%)
No	868 (77.5%)
Colon preparation	
Adequate	1102 (98.4%)
Inadequate	18(1.6%)
Complete examination	
Yes	1077 (96.2%)
No	43 (3.8%)

BMI, body mass index.

Table 2 – Indications for colonoscopy under conscious sedation in a private clinic in Tubarão (SC).

Indication	Frequency (%)
Abdominal pain	316 (28.2%)
Intestinal bleeding	229 (20.5%)
Change in bowel habit	160 (14.3%)
Familial screening	150 (13.4%)
History of colorectal cancer/polyposis	49 (4.4%)
Indication not mentioned	36 (3.2%)
Anemia	33 (3%)
Intestinal inflammatory disease	40 (3.6%)
Oncologic follow-up	40 (3.6%)
Follow-up post-polypectomy	29 (2.5%)
Weight loss	16 (1.5%)
Proctalgia/tenesmus	12 (1.1%)
Endometriosis	3 (0.3%)
Pre/Postoperative procedure	3 (0.3%)
CEA ^a level alteration	2 (0.2%)
Portal hypertension	1 (0.1%)
Altered rectal digital examination	1 (0.1%)
Total	1120 (100%)

^a Carcinoembryonic antigen.

complications had adequate colon preparation and a complete examination.

Table 2 shows patients' indications for the colonoscopy. Of the total number of patients, 1092 (97.5%) had a diagnostic colonoscopy indication and 28 (2.5%) had a therapeutic indication. Patients with complications had an indication for diagnostic colonoscopy, one of them due to abdominal pain and another due to change in bowel habits.

Table 3 – List of doses and means of drugs in mg used in colonoscopy under conscious sedation in a private clinic in Tubarão (SC).

Medication	Total	Minimum	Maximum	Mean
Fentanyl dose	1120 patients	0	0.25	0.05
Midazolam dose	1120 patients	1	11	5.19

The mean number of prior pelvic and abdominal surgeries was 1.06 per person; 508 (45.35%) had not been submitted to any type of surgical procedure, while 612 (54.64%) had undergone some type of surgery. Of the patients with complications, both had undergone some type of surgical intervention.

Regarding medications, 210 patients received additional doses of midazolam. The mean midazolam dose administered to patients without complications was 5.19 mg (minimum dose of 1 mg and maximum dose of 11 mg), while the mean fentanyl dose was 0.05 mg (minimum dose of 0 mg and maximum dose of 0.25 mg). The mean dose used in the two patients with complications was 20 mg of midazolam and 0.05 mg of fentanyl (Table 3).

There was a correlation between the necessary dose of fentanyl and age ($p < 0.001$ – Spearman's coefficient of -0.121). The negative Spearman coefficient shows an inverse association, with increasing age correlating with a lower dose of fentanyl. There was also a correlation between the necessary dose of midazolam and age ($p < 0.001$ – Spearman's coefficient of -0.452). The negative Spearman coefficient shows an inverse association, with increasing age correlating with a lower dose of midazolam. There was no significant correlation between the dose of fentanyl and the dose of midazolam with BMI.

Of the 1120 patients, 1118 (99.8%) did not have any complications, while 2 (0.2%) had respiratory depression reversed with lanexat. Patients who had complications were of different genders, with a BMI of 21.25 (male gender – 1.68 m and 60 kg) and 28.7 (female gender – 1.56 m and 70 kg).

The mean weight in patients without complications was 73.39 kg/BMI 26.51, and in cases with complications was 65 kg/BMI 24.97. The mean age in the cases of respiratory complications was 72 years, whereas in those with no complications was 54.87 years (Table 4).

According to the analysis, no significant association was verified between age, weight, BMI, dose of fentanyl and midazolam with the observed complications. The mean duration of the colonoscopy in the patients was 7.47 min. It was observed that even with a longer colonoscope insertion time, corresponding to the time elapsed since the unit was introduced until it reached the cecum, it was not associated with respiratory depression observed in two patients, in whom the mean duration of the examination was 9 min.

Discussion

Colonoscopy is an examination of utmost importance in coloproctology and associated specialties. Even though the patient may feel some discomfort in several situations, it is still one of the safest examinations to be performed with a low complication rate.

Table 4 – Correlation between complications and other variables observed in patients submitted to colonoscopy under conscious sedation.

	Age (years)	Weight (kg)	BMI (kg/m ²)	Fentanyl dose (mg)	Midazolam dose (mg)
With complication (2 patients)	72	65	24.97	0.05	20.00
No complications (1118 patients)	54.87	73.39	26.51	0.05	5.19
p value	0.084	0.669	0.875	1	0.185
Total	54.9	73.38	27	0.05	5.21
	1120	1120	1120	1120	1120

There are several indications for a colonoscopy. Contraindications are increasingly restricted and most of them are only relative ones. The most frequent indications in this study were abdominal pain ($n=316$; 28.2%), intestinal bleeding ($n=229$; 20.5%) and change in bowel habits ($n=160$; 14.3%). According to the study by Silva et al.,¹⁰ there are reports of similar indications such as diarrhea, anal bleeding and abdominal pain. Although it is a routine examination, it has a non-negligible morbidity, whether regarding the preparation, sedation, the examination or the therapy. The examination is often required in the elderly and/or patients with comorbidities, which contributes to increased morbidity.

Most scientific studies related to complications inherent to colonoscopy aim to study complications such as perforation and bleeding. The present study assessed the complications related to the drugs used in colonoscopy, emphasizing respiratory depression. It is noteworthy that, even though there was associated morbidity, colon preparation in this study was classified as adequate in most patients ($n=1102$; 98.4%). After all, as reported in the study of Habr-Gama et al.,¹¹ this variable is of utmost importance in this examination and possible resulting complications.

The colonoscopies were performed under conscious sedation with benzodiazepines and opioid analgesics, administered concomitantly to enhance sedation. Midazolam has a limited effect on the cardiovascular and respiratory systems, causing little change in blood pressure (BP) and only a transient depression. Its most prominent and easily quantifiable action is the central nervous system (CNS) depression. Respiratory depression remains one of the most feared adverse effects during anesthesia with opioids. Its incidence in adults described in the literature varies widely, mainly due to the different definitions used by the authors.² Commonly, studies consider a respiratory rate lower than 8–10 bpm or decreased oxygen saturation (SpO₂) recorded in pulse oximetry.³ In this study, patients with oxygen saturation $\leq 70\%$ were treated for respiratory depression.

In addition to the side effects associated to preparation and sedation, the examination also has the potential to cause complications due to the air insufflation in the digestive tract, mesocolon traction and pain experienced by the patient, triggering or worsening complications such as increase or decrease in BP, bradycardia, asystole or leading to the need for higher doses of hypnotics and hypoanalgesics. Mean doses of 5.19 mg of midazolam and 0.05 mg of fentanyl were used, with a maximum dose of each drug, of 11 mg and 0.25 mg, and a minimum dose of 1 mg and 0 mg, respectively.

Due to the sedation/examination, of 1120 patients, two had respiratory depression as a complication. This alteration

occurred in a minority of patients and was easily resolved with the use of lanexat (flumazenil), with both patients receiving oxygen supplementation through a mask, with no need for orotracheal intubation. The criteria used for respiratory depression included all patients with oxygen saturation $\leq 70\%$, who required intervention. Lanexat is indicated in the complete or partial reversal of the central sedative effects of benzodiazepines. Therefore, it is used in anesthesia and intensive care units. The drug aims to counteract the sedative effects of benzodiazepines for short-duration diagnostic and therapeutic procedures, reestablishing spontaneous respiration and consciousness to avoid intubation and subsequent extubation.

BP monitoring throughout the examination is crucial to prevent possible worsening of morbidities. The importance of using pulse oximetry during the examination is well-established, aiming to diagnose and promptly correct decreased oxygen saturation, tachycardia or bradycardia, especially in the elderly and/or in patients with comorbidities. The depressed level of consciousness entails a reduction in oxygen saturation.

The present study demonstrated that regardless of all the factors that can contribute to complications during colonoscopy, of the total 1120 patients enrolled in the study, 1118 (99.82%) tolerated the examination very well, without any complications or decompensation events.

Regarding the increasing age of patients undergoing the examination and the complications, it was observed that with increasing age, lower doses were required for conscious sedation.¹² As mentioned in the literature, it is noteworthy the direct association between increased cardiovascular risks and other complications after colonoscopy due to increased age.¹³ The mean weight in patients without complications was 73.39 kg/BMI 26.51, and in cases with complications was 65 kg/BMI 24.97. There was no significant association between the doses of fentanyl and of midazolam with BMI. However, previous studies with a larger number of cases of patients with complications observed that the higher the BMI, the higher the doses used in patients for conscious sedation.⁷

Another parameter that determines the progress and effectiveness of the examination is colon preparation. This illustrates the fundamental importance of good colon preparation, customizing it for each patient, aiming to reduce the complications that arise from inadequate preparation. The dirtier the colon, the more difficult is the examination and the colonic mucosa may be only partially visualized, which can hinder the diagnosis of lesions (polyps and flat lesions, mainly) and there is a greater chance of complications. In our study, there was no direct association between colon

preparation and complications. Both patients had adequate colon preparation and a complete examination was attained.

As for the association between gender and complications, although it was not found in this analysis, there are articles that suggest an increased risk of complications in women due to gynecologic surgeries that contribute to the lower tolerance of women to colonoscopy.¹⁴ It is believed that colonoscopy is more difficult in these patients due to the formation of adhesions, common in patients with previous abdominal-pelvic surgeries.

Very often, the technical difficulty is not associated with any patient-related factor, but to the examiner's experience. It is known that more experienced endoscopists have fewer technical difficulties when performing colonoscopy,¹⁴ therefore, patients with risk factors for complications should be examined by them, while patients with an easier examination profile should be examined by endoscopists with less experience.¹⁵ All endoscopists participating in the study have more than 10 years of experience.

Colonoscopy can be performed without any analgesia; however, because it is an invasive procedure and many patients have anxiety and fear of pain, most endoscopy services use some type of conscious sedation, through the association of benzodiazepines and opioids.

Midazolam is a benzodiazepine that reduces anxiety and is used in patient sedation and fentanyl is a short-acting opioid, responsible for analgesia during the examination. Both have an onset of action of approximately 2 min after the intravenous administration and fast recovery,¹⁶ respecting the principles of conscious sedation. It was observed that 210 patients received extra doses of midazolam in addition to the initial one, but the mean administered dose in patients who had complications was not significantly higher than that administered to patients who did not receive them. Thus, the group that did not show alterations received a mean dose of midazolam of 5.19 mg and the minority with complications received a dose of 20 mg. The mean fentanyl dose was 0.05 mg, both for patients with and without complications.

A third study, after comparing two groups of patients, one using only midazolam and the other using only fentanyl, showed that the group receiving fentanyl showed a higher level of satisfaction and shorter recovery time. In this study, during the examination, patients in the fentanyl group required fewer decubitus changes, none had mental confusion and the duration of the procedure was significantly shorter.¹⁵ Thus, sedation and analgesia should be more customized, by previously researching the biophysical and psychological profile of the patient. Patients with risk factors such as female gender, anxious patients, those with low BMI could receive a more intense sedation. Respiratory depression, regardless of the opioid administration route, does not occur abruptly. It is a complication that is always accompanied by other central nervous system depression signs, such as sedation. Analgesia precedes sedation, which in turn, precedes the respiratory depression. Still, the low rate of complications observed in the study demonstrated the high degree of safety of the drugs used during colonoscopy, corroborating their frequent use for superficial/conscious sedation for this procedure.

Conclusion

Colonoscopy is a safe examination when performed under conscious sedation, as even though several factors contribute to the emergence of possible complications, in this study the number of patients with complications was 0.17%, with respiratory depression. Patient age showed an inverse association, i.e., the older the patient, the lower the required dose of medication. The low rate of complications in the study demonstrated the high degree of safety of the drugs used during colonoscopy, corroborating their frequent use for superficial/conscious sedation for this procedure.

Conflicts of interest

The authors declare no conflicts of interest.

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