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Sedation with Midazolam, Fentanyl and Propofol in Gastrointestinal Endoscopy Procedures: A Systematic Review

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Abstract

Introduction: *Gastrointestinal endoscopy plays an important role in gastroenterology. Sedation in this type of examination reduces the risks of physical damage to the patient, increases patient comfort and collaboration, and also provides the endoscopist with better conditions for the procedure. The most commonly used sedatives, i.e., midazolam and fentanyl, can result in inadequate sedation or slow recovery when used alone, while propofol is a swift fast-acting sedative.*

Objectives: *To compare, through a systematic review, the use of sedation with midazolam, propofol and fentanyl in adult patients who underwent gastrointestinal endoscopy, according to safety; recovery time of cognitive functions and motor coordination; discomfort during and after the procedure; and patient satisfaction.*

Methods: *Studies originally published in English using the descriptors "midazolam", "propofol", "fentanyl" and "gastrointestinal endoscopy" were analyzed, considering the use of these medications and their combinations, delimiting the filters for adult humans, and published articles over the past ten years.*

Results: *103 studies were found with 11 items in a different Medline search base. According to the inclusion and exclusion criteria, five articles were selected providing sufficient data for the purpose of this research.*

Conclusion: *Sedation with propofol is associated with improved cognition to the detriment of midazolam and fentanyl alone. Deep sedation was the most comfortable for patients. The target controlled infusion with propofol combined with midazolam/fentanyl produced sedation with fewer hypotension episodes, and shorter recovery and discharge times. Concomitant administration of midazolam, fentanyl and propofol does not cause desaturation and may lead to changes in blood pressure 1 minute after the start of the endoscopy.*

Keywords: *endoscopy, fentanyl, gastrointestinal tract, midazolam, propofol, sedation*

Introduction

Gastrointestinal endoscopy plays an important role in gastroenterology, helping in the diagnosis and treatment of multiple diseases of the digestive tract. Sedation in this type of examination reduces the risks of physical damage to the patient, increases patient comfort and collaboration, and also provides the endoscopist with better conditions for the procedure. The most commonly used sedatives, i.e., midazolam and fentanyl, can result in inadequate sedation or slow recovery when used alone, while propofol is a swift fast-acting sedative [1].

Midazolam, a water-soluble benzodiazepine, but fat-soluble at a pH > 4, is one of the most frequently used

drugs for sedation. It is preferred for its fast onset of action and for its short effect, and for being highly lipophilic. For this reason, it quickly crosses the blood-brain barrier and is distributed across the central nervous system (CNS). Respiratory depression is the most feared adverse event that occurs by a decrease in carbon dioxide sensitivity of the respiratory center in the brain, in addition to the relaxation of the muscles involved in breathing [2]. Cardiovascular involvement may be observed in cases of deep sedation, with decreased cardiac output and peripheral vascular resistance, and hypotension [1,2].

Fentanyl is a highly used opioid for sedation because of its rapid onset of action and short effect. Its action occurs when it binds to specific receptors distributed in the CNS and peripheral tissues, inhibiting the ascending pathways of pain, increasing its threshold, and changing its perception. It is highly lipophilic, crossing the blood-brain barrier quickly [3]. Its effect starts 20 seconds after its administration. Its peak action is reached in approximately 5-6 minutes and persists for 20-30 minutes. The most frequent adverse effect is dose-dependent respiratory depression. In general, fentanyl is safe because it does not cause any significant cardiovascular changes [4].

Propofol is an ultra-short-acting hypnotic agent with sedative, amnestic and antiemetic properties, but with no analgesic action [5,6]. Frequently used for smaller procedures and sedation of patients admitted to the Intensive Care Unit (ICU), it potentiates the effect of benzodiazepines, barbiturates and opioids [7]. Approximately 98% of the drug binds to plasma proteins. In addition, it is highly lipophilic and rapidly crosses the blood-brain barrier, which explains its rapid onset of action, which occurs in 30-60 seconds. Propofol may cause a decrease in cardiac output, systemic vascular resistance (SVR), and blood pressure (BP). Its pharmacological profile, with fast onset of action and a short half-life, makes it suitable for endoscopic procedures [8]. In studies comparing it to benzodiazepines and opioids, it demonstrated its superiority when assessing induction and recovery times and endoscopist satisfaction [9,10].

Therefore, the purpose of this systematic review study is to compare the use of sedation with midazolam, propofol and fentanyl in adult patients submitted to a gastrointestinal endoscopy procedure, according to safety, recovery time for cognitive function and motor coordination, discomfort during and after the procedure, and patient satisfaction.

Methods

A search was performed on the PubMed platform and in the *National Library of Medicine* (Medline) database for studies which had been originally published in English using the descriptors “midazolam”, “propofol”, “fentanyl” and “gastrointestinal endoscopy”, considering the use of these medications and their combinations, delimiting filters for “randomized controlled trial”, studies with adult humans and articles published in the last ten years. The search was conducted in the first half of 2019 through February 2020. Table 1 shows the inclusion and exclusion criteria of articles for the present study.

Table1. *Inclusion and exclusion criteria*

Inclusion Criteria	
Outline	• Randomized Controlled Trial
Patients	• Adults
Intervention	• Sedation for gastrointestinal endoscopy
Language	• English language
Exclusion Criteria	
Outline	• Unclear or poorly described studies and/or method
Intervention	• Articles involving colonoscopy procedures
Form of publication	• Published more than 10 years ago • Different from research scope

Results

A total of 103 articles were found using the term descriptors in the selected databases. Of these, eleven articles found in a search base other than Medline were excluded. According to the "randomized controlled trial" criterion, thirty-six more articles were elected for the study. Then, fourteen clinical trials that had been published more than ten years before were excluded, as well as other 12 studies not involving adults. Among the ten studies found, four were associated with colonoscopy and one was a cohort study; therefore, they were not included in the investigation. Only five studies provided enough data for the purpose of this research. Figure 1 shows the flowchart of the article selection process for this review.

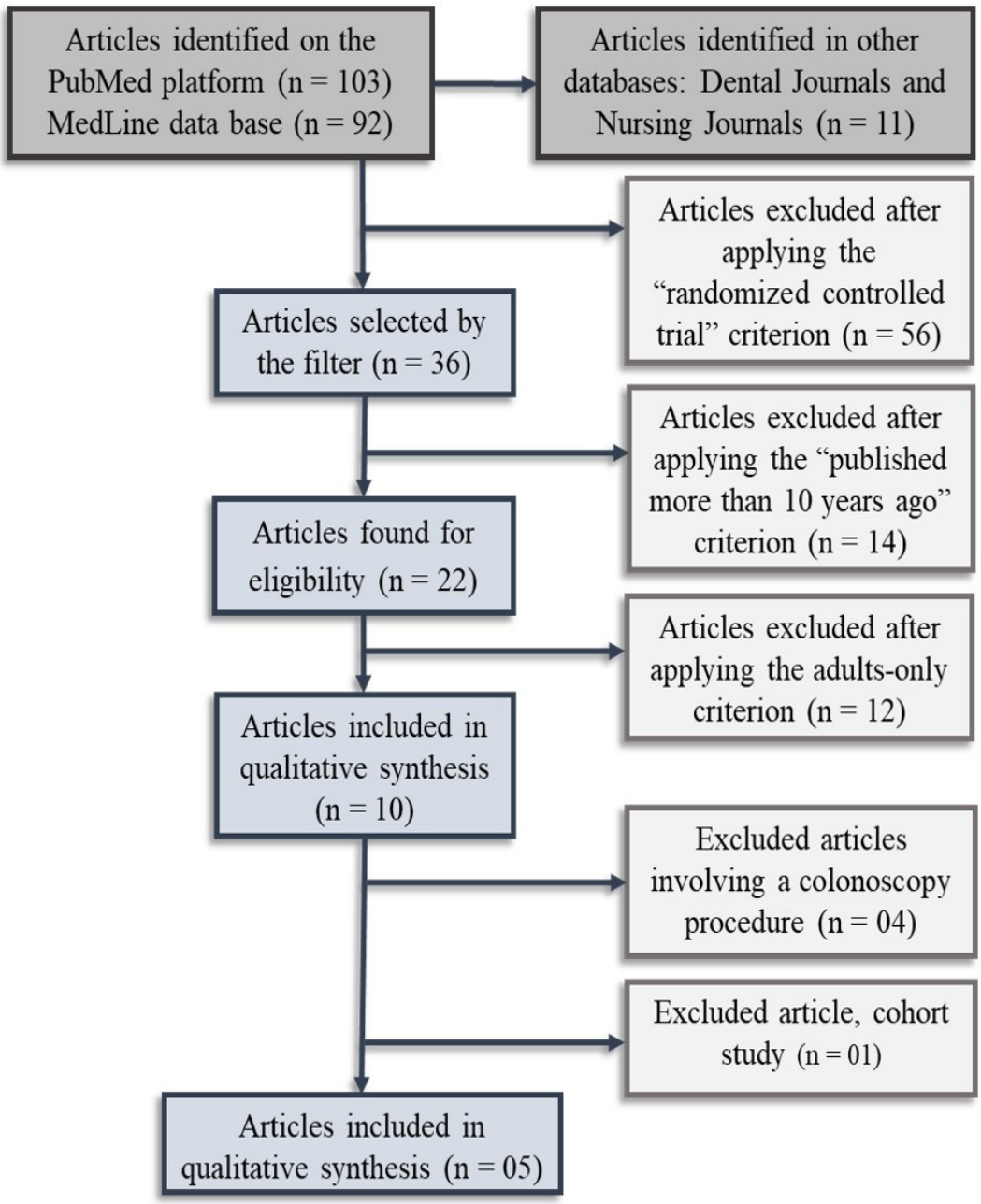

Figure1. *Flowchart of the article selection process for review*

An overview of the main studies is described in Table 2, showing a summary of the selected and reviewed studies for this research.

Table2. *Synthesis of studies and their main results for midazolam, propofol, fentanyl and combinations in Upper Gastrointestinal Endoscopy (UGE)*

Authors	Sample	Method	Results
Fanti et al. [15]	70 patients	Standard group: received F (1 μg/kg) + M (0.03-0.04 mg/kg) or only M; Group P: received F (1 μg/kg) + TCI of P (1.2-1.6 μg/mL) or only TCI of P.	Patient satisfaction was significantly higher (93.8 ± 18.2/100), Group P, 94.3% of patients vs. 71.4% of patients in the standard group asked to receive the same sedation in the future.
Hsu et al. [16]	100 patients	Randomly assigned patients in Group P (TCI P) or Group C (TCI combination P + M/F). Post-procedure records: recovery time, adverse events in the postoperative period (nausea, vomiting, dizziness, memory and pain) and satisfaction.	Recovery and Discharge Time < Group C. The post-procedural adverse events were similar in both groups. TCI of P combined with M/F achieved sedation with fewer hypotension episodes and shorter recovery and discharge time.
Lera dos Santos et al. [17]	200 patients	One group received P/F; another group received M/F (n = 100/group). BP, heart rate, respiratory rate, SpO_2 and sedation level (OAA/S scale) were monitored through electrodes on the patient's forehead connected to the wires of a BIS monitor. Records: patient and physician satisfaction, recovery time and complication rates.	Patients showed satisfaction with both combinations of drugs. However, doctors preferred the P/F combination, which showed faster recovery.
Xu et al. [18]	168 patients	Patients were randomly assigned P/M sedation (COPD with stepwise sedation (group Cs) and non-COPD with stepwise sedation (group Ns); or continuous P/M sedation (COPD with continuous sedation (group Cc) and non-COPD with continuous sedation (group Nc) Records: SpO_2, BP and pulse rate were monitored as well as patient discomfort, adverse events, medication dosage, and recovery time.	Hypoxemia occurred in the Cs, Cc, Ns and Nc groups: 4 (9.3%), 12 (27.9%), 3 (7.3%) and 5 (12.2%), in the Cs group it was lower than in the Cc group. The mean decreases in the value of SpO_2, systolic and diastolic BP in the Cs group < Cc group. P dosage and the overall rate of adverse events in the Cs group < Cc group. Recovery time in the Cs group < Cc group; and in group N < group Nc.
Talaie et al. [19]	90 patients	1st group patients: sedated w/M 0.1 mg/kg; P 1 mg/kg and F 1 μg/kg IV, patients 2nd group: saline solution as placebo. Measurements: BP, heart rate and SpO_2 before and 1 minute after endoscopy and compared.	No significant differences were found in SpO_2 and heart rate between the two groups. Systolic and diastolic BP > non-sedated group.

Midazolam (M); propofol (P); fentanyl (F); microgram per kilogram (μg/kg); milligram per kilogram (mg/kg); Target Controlled Infusion (TCI); microgram per milliliter (μg/mL); blood pressure (BP); peripheral oxygen saturation (SpO_2); Observer's Assessment of Alertness/Sedation Scale (OAA/S); Chronic Obstructive Pulmonary Disease (COPD); Intravenous (IV); standard-deviation (±); percentage (%); less than (<).

Discussion

Considering that the medication used for sedation/analgesia during the gastrointestinal endoscopy, which included midazolam, fentanyl and propofol, results in a short-term reversible decline in cognitive function [11,12], and assuming also that sedation allows patients to tolerate unpleasant endoscopic procedures, relieving anxiety, discomfort or pain, in addition to reducing the risk of physical injury during these procedures, while providing the endoscopist with an appropriate setting for a detailed study [13], and further considering that the use of propofol for endoscopic procedures has increased in recent decades [12-14], the conclusions and meanings of this investigation are as follows.

Although it was not selected as the basis for this study, since it was a cohort study, a more recently published study was found in which the main objective was to identify the sedative/analgesic scheme associated with lower cognition involvement at discharge. In that study, the patients were submitted to digestive endoscopy. The study was carried out in two hospitals in Sydney. Patients were given midazolam/fentanyl at Prince of Wales Hospital, while patients at Prince of Wales Private Hospital received midazolam/fentanyl/propofol or midazolam/propofol. For the study, the predictors for worse neurocognitive function were midazolam at a dose > 3 mg and fentanyl > 50 μg. However, the use of propofol in digestive endoscopy provided lower exposure to midazolam and fentanyl and is associated with better cognition at discharge [11].

In the first analysis series, the purpose of which was to compare the sedation levels in TCI, this was considered a sophisticated tool to provide an ideal sedation scheme, avoiding UGI endoscopy over- or undermeasurement [15]. Therefore, one standard group received fentanyl (1 μg/kg) + midazolam (0.03-0.04 mg/kg) or midazolam only; the propofol group received fentanyl (1 μg/kg) + propofol TCI (1.2-1.6 μg/mL) or propofol TCI only. Discharge time, endoscopist satisfaction and patient satisfaction were recorded in all endoscopies. Among these criteria, discharge time was not significantly different in the propofol and standard groups (1.1 ± 0.7 vs. 3.9 ± 9.2 min, respectively). Endoscopist satisfaction was significantly higher (92.7 ± 14.3/100 vs. 82.8 ± 21.2/100); patient satisfaction was significantly higher in the propofol group (93.8 ± 18.2/100 vs. 76.5± 25.2/100). In the propofol group, 94.3% of the patients vs. 71.4% of the patients in the standard group asked to receive the same sedation in the future. Therefore, TCI was seen as a promising method for a non-anesthesiologist endoscopist in administering propofol for sedation in UGI endoscopy [15].

In the second clinical trial, the objective of the study was to compare propofol alone and the combination of propofol and midazolam/fentanyl in moderate sedation for UGI endoscopy. One hundred patients were included in this study. All patients received TCI to maintain sedation during the procedure. Patients were randomly allocated in Group P (propofol TCI) or Group C (propofol TCI + midazolam/fentanyl) [16]. Demographic data, anesthetic parameters (sedation scheme, blood pressure, heart rate, and oxygen saturation), procedural parameters (procedure time, propofol consumption) and adverse events (hypoxia, hypotension, and bradycardia) were recorded. Based on post-procedure records, the mean propofol intake was 251 ± 83 mg in Group P and 159 ± 73 mg in Group C. Transient hypotension was higher in Group P. Recovery time and discharge time were lower in Group C. In general, post-procedure adverse events were similar in both groups. Post-anesthetic satisfaction was comparable in both groups. Propofol TCI combined with midazolam/fentanyl achieved sedation with fewer hypotension episodes and shorter recovery and discharge times than propofol TCI in UGE endoscopy [16].

In the following series, deep sedation with the propofol/fentanyl and midazolam/fentanyl combinations was compared in 200 randomized patients during UGE (n = 100/group). Continuous monitoring during the procedure included noninvasive blood pressure, heart rate, respiratory rate, and oxygen saturation. The sedation level was evaluated by applying the OAA/S scale and using electrodes on the patient's forehead, connected to the wires of a BIS monitor. Patient and physician satisfaction, recovery time and complication rates were evaluated. The times for sedation induction, recovery and discharge were shorter in the propofol/fentanyl group than in the midazolam/fentanyl group [17]. From the results and considerations of this study, no statistically significant differences were found between the two groups in terms of patient-reported sedation quality or procedure-related pain/discomfort. None of the patients had any adverse

reactions within the first 24 hours after discharge. Propofol/fentanyl group patients reported having resumed their domestic activities 60 minutes after discharge, compared to 80 minutes after discharge in the midazolam/fentanyl group. Although patients were equally satisfied with both drug combinations, physicians were more satisfied with the propofol/fentanyl combination. This study demonstrated that induction, recovery and discharge times were significantly lower in the propofol/fentanyl group. These results reproduce those obtained by other authors who demonstrated that propofol allows patients to resume their work activities earlier, thus increasing overall productivity. Severe complications were not seen in the groups, but hypoxemia was seen in 42% of the patients in the propofol/fentanyl group and 26% in the midazolam/fentanyl group [17].

Following the clinical trials included in the scope of this review, the peculiarity of the study below lies in investigating stepwise sedation in elderly patients with Chronic Obstructive Pulmonary Disease (COPD) during the UGI endoscopy [18]. All endoscopies were successfully completed. There were 4 (9.3%), 12 (27.9%), 3 (7.3%) and 5 (12.2%) cases of hypoxemia in groups Cs, Cc, Ns and Nc, respectively. Hypoxemia in the Cs group was significantly lower than in the Cc group. The mean decrease in SpO_2 and systolic and diastolic BP in the Cs group was significantly lower than in the Cc group. In addition, the propofol dose and the general rate of adverse events in group Cs were lower than in group Cc. Finally, recovery time in group Cs was significantly shorter than in group Cc, and recovery time in group Ns was significantly shorter than in group Nc. These results allow us to conclude that the stepwise sedation method is effective and safer than the continuous sedation method in patients with mild/moderate COPD during the UGE [18].

In the last reviewed trial, the study was developed to check the effect of sedation on endoscopy-induced arterial oxygen desaturation and determination of sedative safety during the UGI endoscopy [19]. Ninety consecutive patients scheduled for a diagnostic UGE were then categorized into two groups (n = 45). The first group was sedated with intravenous midazolam 0.1 mg/kg, propofol 1 mg/kg and fentanyl 1 μg/kg, while the second group patients received saline as placebo. In both groups, BP, heart rate and arterial oxygen saturation (SpO_2) were measured before and 1 minute after endoscopy and compared. In this study, no significant differences were found in SpO_2 and heart rate between the two groups 1 minute after endoscopy. Systolic and diastolic BPs were higher in the non-sedated group. The concomitant administration of midazolam, propofol and fentanyl did not cause arterial desaturation; however, this combination may lead to BP changes 1 minute after the start of the endoscopy [19].

Conclusion

Sedation with propofol was associated to better cognition at discharge. Patients were satisfied with both combinations, propofol/fentanyl and midazolam/fentanyl, but for physicians, the propofol/fentanyl combination provided a faster recovery.

Propofol TCI combined with midazolam and fentanyl achieved sedation with fewer hypotension episodes and shorter recovery and discharge times.

The concomitant administration of midazolam, propofol and fentanyl does not cause desaturation; however, it led to blood pressure changes 1 minute after the start of the endoscopy.

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