Original Paper

The Role of Analgesia in the Identification and Treatment of Digestive Tract Lesions: A Randomized, Prospective, Double-Blind Study

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ABSTRACT: The association of sedation with analgesia in endoscopic procedures represents the ideal combination of anesthetic drugs, which allows these exploratory procedures to be carried out safely, in an outpatient setting. The aim of this study is to compare the results of the use of simple Propofol or Propofol associated with Fentanyl in order to ensure optimal sedation necessary for the detection of benign or malignant lesions of the digestive tract. In this study, 80 patients aged between 18 and 80 years were included, 40 in Group 1 who were administered Propofol alone and 40 in Group 2 in which Propofol was administered associated with Fentanyl. The onset of anesthetic sleep was 19.3±5.1 seconds in Lot 2 versus 29.6±9.1 seconds in Lot 1. The average dose of Propofol used was 203.6±82.8 mg in Lot 1 and in Lot 2 it was lower, 166.3±8.3mg. Cardio respiratory changes were more frequent in Lot 2. The wake-up time was 3.2±1.2 minutes in Lot 1 as a result of the administration of Propofol alone and 7±1.4 minutes in Lot 2. The discharge time was equal for patients in both groups. The degree of postanesthesia safisfaction was 10 for all patients from Lot 2, due to the analgesia provided by the administration of Fentanyl. The use of Propofol associated with Fentanyl in gastrointestinal endoscopic procedures is associated with a rapid recovery of cognitive function at the time of discharge and minimal adverse events, ensuring optimal conditions of analgesia and stability of vital functions.

KEYWORDS: *Sedation, vital functions, digestive tract injuries.*

Introduction

Sedation and analgesia are key elements for the endoscopic examination of outpatients with gastrointestinal pathology [1-5].

Conscious or moderate analgesia is normally used in digestive endoscopic procedures to reduce the patient's anxiety, pain and discomfort, but also to maintain the stability of respiratory and cardiac function.

The pain during the colonoscopy occurs as a result of the air distension of the colon and the traction manoeuvres of the mesocolon, which is why most patients request the examination of the digestive tube under sedation and analgesia [5,6].

The ideal method of analgesia is the one that offers the rapid onset of sleep, maintaining hemodynamic and respiratory balance during the procedure, as well as rapid post-procedural recovery [4,7].

A deeper level of sedation is associated with a higher rate of complications such as hypotension and respiratory depression [5,8,9].

The association of anaesthesia during colonoscopy increased from 3.1% in 1989 to 34.4% in 2011, with certain states reaching even 80% [10].

Propofol is a sedative-hypnotic agent, which induces sleep immediately, with a short duration of action, and patients' recovery after stopping its administration is fast, but with the lack of analgesic effect, which is why it was associated with an opioid-type analgesic, endoscopic procedures are much easier to tolerate by the patient [8,11-14].

Fentanyl is a synthetic opioid discovered in 1960 and first used in 1963, which acts on μ-type receptors, with simple synthesis and low production costs.

It has thus become the most important opioid used in pain management due to its increased availability for intravenous, transdermal and transmucosal administration [9,15-17].

Fentanyl is the most widely used opioid administered intravenously to ensure analgesia, with a fast onset time and short duration of action, with the absence of histamine release in the circulation and vasodilatation, the anesthetic induction being faster than after the administration of morphine [9,15,18].

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The aim of the study was to compare the effect of combining Propofol with Fentanyl, with the administration of Propofol alone during endoscopic procedures.

Questionnaires were drawn up to evaluate the degree of satisfaction of postanesthesia patients.

Materials and Methods

We performed a prospective analysis of upper and lower digestive endoscopies performed between September 1, 2022, and December 30, 2022, at the Centre for Research in Gastroenterology and Hepatology, UMF Craiova.

We excluded from the analysis the following groups of patients:

- patients who had more than one colonoscopy during the course of the study
- patients who requested colonoscopies without sedation
- uncooperative patients
- patients with liver or kidney failure.

Inclusion criteria:

- patients scheduled for elective gastrointestinal endoscopy
- patients with ASA I, II, III
- patients aged between 18-80 years.

Sedation was provided by a nurse who administered Fentanyl and Propofol under the careful supervision of the anaesthesiologist, using a dose calculated according to the patient's body weight.

The study included 80 patients from the specialized outpatient clinic who underwent colonoscopy and gastroscopy, after obtaining the patient's written informed consent.

We formed 2 study lots, Lot 1 and Lot 2, each including 40 patients, men and women, older than 18 years.

Personal pathological history (drug and alcohol consumption, surgical interventions, hypertension, diabetes) was recorded for each patient, using a standard registration form.

In Lot 1, 2mg/kg of Propofol Fresenius Kabi 10mg/ml, 20ml vials, (Fresenius Kabi Deutschland GMBH) were used for anesthetic induction, followed by the injection of an additional dose of 10-20mg Propofol at an interval of 5-6 minutes, on request.

For those in Lot 2, Fentanyl Kalceks 50 micrograms/ml, vials of 10ml each, (Akcju Sabiedriba Kalceks, Latvia) 0.01 micrograms/kg was used 5 minutes before the start of the actual procedure, adding the same dose of Propofol.

The endoscopic procedure started approximately 3 minutes after the end of the administration of the anesthetic drug.

To determine the quality of the colon preparation, in the research study we used the score based on the Boston bowel preparation scale.

Each colon segment, right (cecum, ascending colon and hepatic flexure), transverse and left recto colon (splenic flexure, descending colon, sigmoid colon, rectum), is numbered from 0-3, after washing the colon wall during the procedure.

The final score is calculated by adding the score from all 3 segments, 9 being the highest score, representing an excellent preparation of the colon mucosa.

A segment score of less than 2 was associated with unobserved lesions [19].

Sedation procedure

All patients included in the study were evaluated by the anaesthesiologist one hour before the endoscopic procedure.

Standard monitoring of vital parameters such as BP (blood pressure), HR (heart rate), SpO_2 (peripheral oxygen saturation) was performed using the General Electric B125 VSP 2.0 monitor of the Research Centre of UMF Craiova.

Venous access was ensured using a 20G flexure mounted on the hand or forearm.

A dose of 50-100 micrograms of Fentanyl was administered 3-5 minutes before starting the procedure to all patients in Lot 2.

During the entire length of the procedures, humidified oxygen 4-6L/min was administered to all patients via the nasal cannula to prevent hypoxemic episodes associated with hyperextension of the mandible and maintaining it in this position to ensure an efficient respiratory flow.

Before starting the upper digestive endoscopy, all patients were given topical anaesthesia with Lidocaine spray 4.6mg/dose (Egis Pharmaceuticals PLC. Hungary).

Blood pressure was recorded every 5 minutes, heart rate and SpO_2 were recorded continuously.

The endoscopic procedure was performed using the standard equipment (Olympus X1 CV 1500 CF-EZ1500DL 3.7 type) by a gastroenterologist, accompanied by the resuscitation kit and the Datex-Ohmeda Aespire anaesthesia machine of the Research Centre in Gastroenterology and Hepatology, UMF Craiova.

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The depth of sedation was evaluated using the Ramsay sedation scale (Table 1), in which a value of 5 or higher indicates a deep level of sedation and if the score was lower than 5 or the patient presented sudden movements of the extremities, it was administered Propofol 20mg.

Table 1. Ramsay sedation scale-RSS [11].

Score	Response
1	Anxious and agitated or restless or both
2	Cooperative, oriented and tranquil
3	Responds to commands only
4	Brisk response to light glabellar (forehead) tap or auditory stimulus
5	Sluggish response to light glabellar (forehead) tap or loud auditory stimulus
6	No response

After the procedure, the patients were monitored in the recovery room for 30 minutes.

For discharge, the Aldrete scale was used, the total score of which was 10.

Data collection

The patients' data were recorded before the start of the procedure: age, sex, ASA, comorbidities.

Ventricular rhythm, blood pressure, peripheral oxygen saturation were recorded throughout the procedure, from the administration of anesthetic drugs until the patient woke up.

The duration of the procedure, the awakening time, the total doses of Propofol and Fentanyl were also recorded.

During the procedure, the following adverse events were recorded: hypotension, bradycardia, hypoxia.

Hypotension is defined as mean arterial pressure lower than 60mmHg or 20% lower than the baseline value.

Bradycardia is defined by a heart rate <50bpm or a 20% decrease from the initial value.

Respiratory depression is defined as a respiratory rate less than 8 breaths/minutes or an oxygen saturation below 90% [20].

Discharge criteria

The patient must be awake, alert and hemodynamically stable.

Patient satisfaction was assessed using a 10 point visual analog pain scale (1=least satisfied and 10=most satisfied) and a satisfaction questionnaire.

This research was approved by the local Ethics Committee of the University of Medicine and Pharmacy of Craiova and were in line with the Helsinki Declaration.

All patients gave their written consent to participate in this study.

Statistical Analysis

The statistical analysis of the obtained data was carried out using an Excel (Microsoft, USA).

Student's t-test and Fisher's exact test were used for cantitative factors with normal distribution. Categorical data were assessed using the chi-square (X^2 test) statistics.

P value less than .05 were considered statistically significant.

Result

A total of 80 patients undergoing endoscopic procedures performed under sedation and analgesia at the Centre for Research in Gastroenterology and Hepatology, UMF Craiova, were included in the study.

42 patients were female and 38 male, according to the graph below (Figure 1) and the average age in Lot 1 was 55±13 years and 55±16 years in Lot 2.

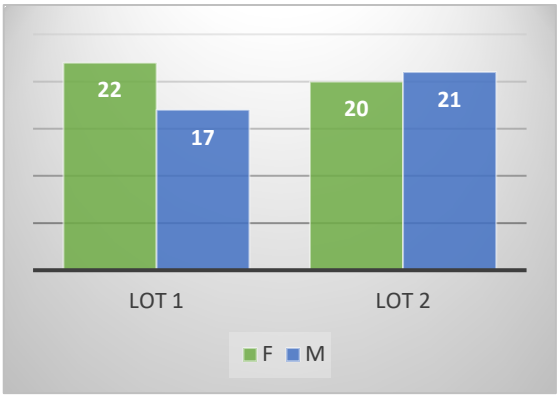

Figure 1. Gender distribution: The chi-square statistic is 0.4666. The p-value is 494564. The result is not significant at p<.05.

The patients included in the study were divided into 3 ASA risk groups according to the Table 2.

Table 2. Demographic data (n=40 per lot).

Parameter	Lot 1 (n=40)	Lot 2 (n=40)	*P value*
Male/Female	17/21	21/20	The chi-square statistic is 0.332. The *p-value* is .564485. The result is not significant at *p*<.05.
Average age (standard deviation)	55±13	55±16	*p*>00.5
ASA I, II, III	10 ASA I 14 ASA II 16 ASA III	11 ASA I 19 ASA II 10 ASA III	The chi-square statistic is 2.1898. The *p-value* is .334571. The result is not significant at *p*<.05.
Comorbidities	29	18	The chi-square statistic is 6.9064. The *p-value* is .008589. The result is significant at *p*<.05.
Hypertension	30	16	The chi-square statistic is 11.7476. The *p-value* is .000609. The result is significant at *p*.05.
Diabetes	5	8	The chi-square statistic is 0.6576. The *p-value* is .417393. The result is *not* significant at *p*<.05.

Both lots included patients with hypertension as a comorbidity, thus there were 30 in Lot 1 and 16 in Lot 2 (Figure 2) and diabetes (Figure 3).

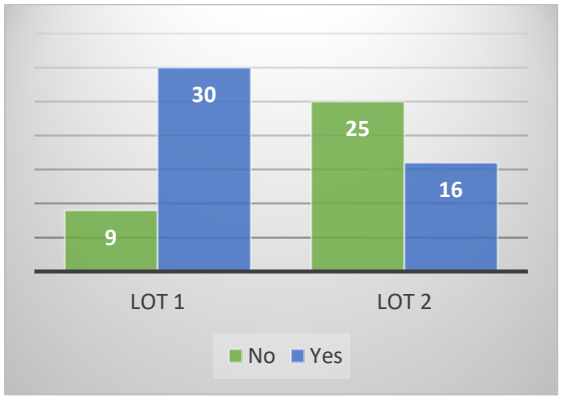

Figure 2. The prevalence of hypertension: The chi-square statistic is 11.7476. The p-value is 000609. The result is significant at p<.05.

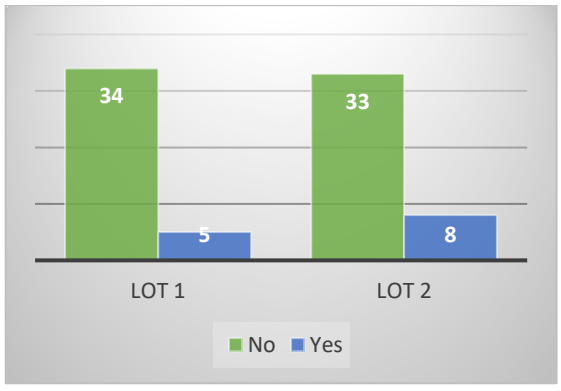

Figure 3. The prevalence of diabetes: The chi-square statistic is 0.6576. The p-value is 417393. The result is not significant at p <.05.

The digestive tract lesions identified in the 80 patients investigated endoscopically were:

In Lot 1:

- ✓ pedunculated polyps-6
- ✓ reflux esophagitis-2
- ✓ erosive gastritis-2
- ✓ colon neoplasm-1

In Lot 2:

- ✓ pedunculated polyps-11
- ✓ gastritis erosive-3
- ✓ hiatus hernia-1
- ✓ achalasia-1
- ✓ colon neoplasm-2

Adverse events

In Lot 2, 15 cases of hypotension and 12 cases of bradycardia were recorded, but the recorded values did not require correction by administering positive inotropic substances such as Atropine or Ephedrine (Figure 4).

In Lot 1, the number of patients who suffered episodes of hypotension was lower, only 6 patients, compared to patients from Lot 2.

Bradycardia was encountered at 7 patients.

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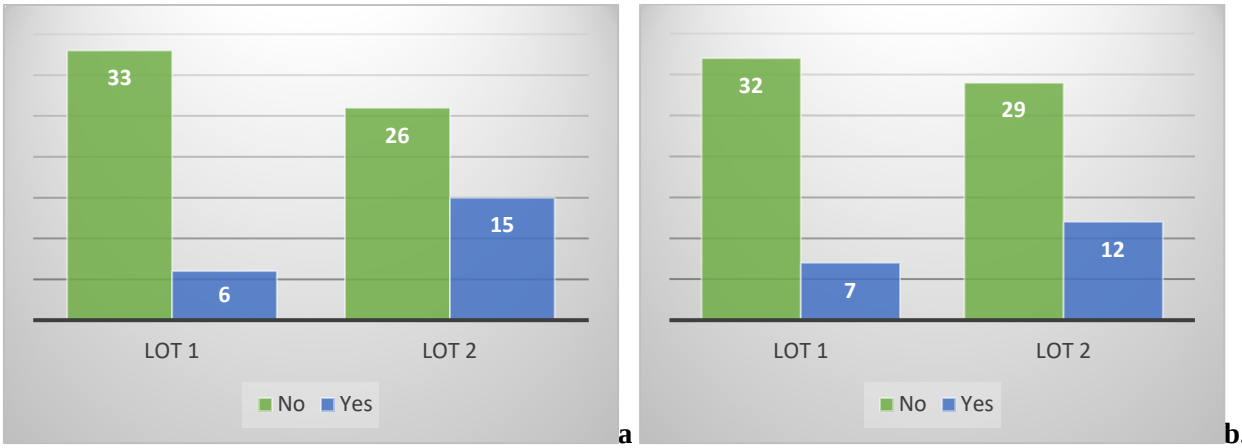

Figure 4. Cardio respiratory changes: a. Hypotension-The chi-square statistic is 4.6406. The p-value is 031225. The result is significant at p<.05. b. Bradycardia-The chi-square statistic is 1.4142. The p-value is 234358. The result is not significant at p<.05.

The association of the two substances led to a decrease in the need for Propofol, not requiring the administration of an additional dose during the investigation, due to the addition of the sedative component of morphine (Fentanyl).

Exceptions were also found, in the sense that 50-100 micrograms of Fentanyl and 20-40mg of Propofol were administered to patients in whom the investigation and procedure required a longer period of time(polypectomies).

The score given by the Boston Bowel Preparation Scale (BBPS, from 0 to 9) was applied to all patients who were going to undergo a lower digestive endoscopy, after a prior preparation (24 hours) with Fortrans solution (polyethylene glycol) 4 sachets dissolved in 4 liters of water.

In 4 of the 80 patients, the score determined by the BBPS could not be used, because they were investigated only at the level of the upper digestive tract.

Of the 76 patients who underwent lower digestive endoscopy, 6 had a BBPS of 8 and the remaining 70 had a BBPS of 9, which reveals an ideal preparation of the colonic mucosa, resulting in the identification, in all examined cases, of digestive tract injuries

Table 3. Procedure data (n=40 per lot).

Parameter	Lot 1	Lot 2	*P value*
Length of procedure (minutes)	17.9±5.0 minutes	14.7±2.6 minutes	*P*<0.0001
Anesthetic induction (seconds)	29.6±9.1 seconds	19.3±5.1 seconds	*P*<0.0001
Wake-up time (minutes)	3.2±1.2 minutes	7±1.4 minutes	*P*<0.0001
Average dose of Propofol use (mg)	203.6±82.8 mg	166.3±8.3 mg	*P*<0.0001

The length of procedure in Lot 2 was on average 15 minutes and in Lot 1 it was 18 minutes.

The installation of anesthetic sleep was faster in Lot 2, by 10 seconds, due to the administration of Fentanyl 3-5 minutes before the injection of Propofol and the start of endoscopic investigations, in Lot 1 it was 29 seconds.

The awaking time was shorter in Lot 1 compared to Lot 2, due to the lack administration of the opioid component.

The average dose of Propofol used was higher in the lot in which only Propofol was administered, and in Lot 2, the dose of Propofol used in combination with Fentanyl, was smaller, due to the cumulative effect of the 2 substances.

To determine the level of sedation of the patients, following the administration of anesthetic drugs, we used the RSS (Figure 5).

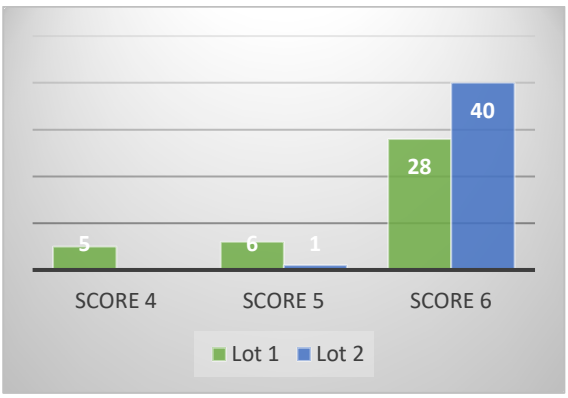

Figure 5. Ramsay sedation score.

In Lot 1, 31 patients had an ideal level of sedation with a score of 6, 5 patients had a score of 5, and 3 patients a score of 4.

On the other hand, in Lot 2, due to the administration of Propofol in combination with Fentanyl, the sedation score was 6 in all patients (Table 4).

Table 4. Ramsay sedation score.

Ramsay score	Lot 1 (n=40)	Lot 2 (n=40)	*P value*
Score 4	5	0	Fisher's Exact probability: 0.00184948
Score 5	6	1	
Score 6	28	40	

The level of patient satisfaction, according to the questionnaires completed after waking up from anaesthesia, showed a level of 10 for all patients in Lot 2 (Figure 6).

In Lot 1, due to the lack of analgesic component determined by the administration of Fentanyl, the level of satisfaction was 10 for 35 patients and in the rest of the patients 9.

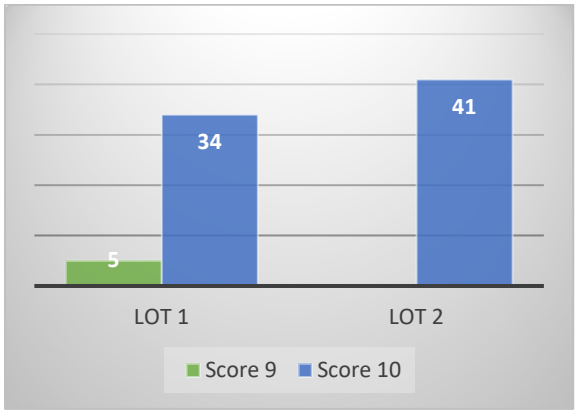

Figure 6. The level of satisfaction of the patients included in the study.

Discussions

Patients who undergo endoscopic procedures could benefit from adequate sedation [20].

An ideal anaesthesia, according to specialist guidelines, requires hemodynamic stability, adequate sedation, minimal adverse effects, rapid recovery and discharge [21,9].

Gastrointestinal endoscopy was known as an traumatic invasive procedure, used for the prevention, diagnosis and treatment of some diseases of the digestive tract [5,13].

Although the procedure itself does not require a long period of time (10 minutes to 30 minutes in the case of therapeutic interventions, such as polypectomies), the patient may feel a high degree of pain and discomfort during the examination [9].

The dose and depth of sedation is individualized according to the needs of each patient.

An optimal sedation during procedures reduces anxiety and stress related to the procedure, reduces the prevalence of complications, increases the success rate of the endoscopic procedure and last but not least, improves the comfort of the patient and the gastroenterologist [20].

The drugs used for anesthetic induction can be classified into 2 groups:

1. sedatives such as Propofol, Midazolam;
2. opioid-type analgesics such as Fentanyl, Morphine [23].

Endoscopic procedures are minimally invasive procedures that can cause pain and discomfort, so sedation with quick awakening, as well as recovery of cognitive function, is an important objective in choosing the most effective anesthetic.

A group of specialists who researched the role of sedation and analgesia in endoscopic procedures, of short duration, performed in outpatients, defined two great benefits of sedation and analgesia:

✓ sedation and analgesia allow patients to tolerate unpleasant procedures by decreasing anxiety, discomfort and pain;

✓ in children and uncooperative adults, sedation and analgesia allow the performance of procedures that, although not uncomfortable, require the patient to remain motionless [24].

Propofol used alone offered a high degree of patient satisfaction and a quick recovery, being recommended as a safe anaesthesia technique for patients requiring endoscopic investigations in the ambulatory [11].

This is the most commonly used intravenous anesthetic drug.

The onset of sleep is fast (10-20 seconds) after a dose of 10-20mg/kg and awakening after stopping the administration is immediate.

The most common cardiovascular complication of Propofol is the lowering of blood pressure [30].

The interaction of Propofol with muscarinic cholinergic receptors is dependent on the administered dose and can induce bradycardia [5].

Many studies have demonstrated the effect of Propofol on cerebral blood pressure and oxygen consumption.

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Cerebral blood flow decreased by up to 50% in patients given Propofol, with a decrease in oxygen consumption of up to 36% [24].

Once administered, Propofol is rapidly distributed from the central blood compartment to the central nervous system, due to its lipophilic properties.

From the CNS it is redistributed back into the blood and simultaneously into less perfused tissues, such as lipid tissue.

The level of Propofol in the patient's serum should be greater than 1 microgram/ml to produce narcosis.

At lower levels, awakening from anaesthesia occurs [24].

Reducing the consumption of Propofol is an important aspect, to be taken into account by every doctor, because it has no antidote or antagonist [5,28].

If Propofol and Fentanyl are used simultaneously, adverse effects may be exacerbated, and the risk of apnoea and hemodynamic changes is greater [25].

Fentanyl, a semi-synthetic lipophilic opioid is 80 to 100 times stronger than morphine.

It has a fast onset of action (3-5 minutes) and short duration (25-30 minutes), without amnesiac effect [11,25,29].

It is the preferred opioid by anaesthesiologists in patients with hemodynamic instability.

Fentanyl metabolites can accumulate, but are inactive and non-toxic [24].

The half-life of Fentanyl is significantly shorter than that of other opioids and that of Propofol, offering an advantage in terms of recovery time [26].

Through its action on the μ receptors of the central nervous system,

Fentanyl produces fatigue, sedation, nausea, vomiting, dizziness, respiratory depression, going up to apnoea in high doses, bradycardia, due to the central vagal action and anaesthesia in the case of the use of high doses, regardless of the mode of administration.

It is mostly absorbed at the gastrointestinal level and completely binds to the proteins in the bloodstream [9].

Short-acting substances, such as Fentanyl and Propofol, provide rapid, short-acting sedation, which allows patients to immediately recover cognitive functions and be discharged quickly [24].

The most important complication of Fentanyl is hypotension, which is exacerbated by the simultaneous administration of a sedative, followed by a decrease in ventricular output [25].

The occurrence of hypotensive episodes was higher in Lot 2, where the combination of two anesthetic drugs, Propofol and Fentanyl (n=15), was used, compared to Lot 1, where the number of patients who experienced a drop in blood pressure was lower (n=6).

Bradycardia were more frequent in patients in Lot 2, due to the cumulative effect of the 2 substances (n=12), compared to patients in Lot 1, who received simple Propofol (n=7).

The risk factors favouring the occurrence of these adverse cardiovascular effects are: advanced age, associated co morbidities (anaemia, respiratory diseases, dementia, neoplasias), as well as the background medication, hypotensive or beta-blocking, of the patients.

We had some limitations of the study:

I. The bispectral index (BIS) or Narcotrend index (NTI) for monitoring the depth of sedation during endoscopic procedures were missing from the Gastroenterology and Hepatology Research Centre. Instead, we used the Ramsay sedation scale and assessed reflexes to estimate the level of sedation.

II. After the patient's discharge, we no longer had information regarding his health status and any complications that occurred 12-24 hours post-anaesthesia.

Hypoxia is a complication encountered during patient sedation and is often due to an overdose of sedative agent or lack of proper ventilation [20,27].

In the study, we observed a decrease in the respiratory excursions of the ribcage, which were materialized on the monitor by the decrease of SpO_2, reaching a value of 95-96% in the patients of Lot 2 (n=15), the administration of humidified oxygen via a nasopharynx tube was enough to counteract these phenomena during the procedure.

To emphasize the degree of preparation of the colon for lower digestive endoscopies, we used the score determined by the BBPS, 70 of the 80 patients included in the study having an ideal preparation of the digestive tract mucosa, totalling a score of 9.

For the depth of the patients' sedation level, we used RSS, we had significant differences in the 2 lots, so that in Lot 2 the level of sedation was 6 in all patients (n=40), and in Lot 1, the level of sedation was from 6 to 31 patients out of 40 patients.

Overall, sedation was well maintained during the procedure.

Propofol associated with Fentanyl can obtain an ideal sedative effect, ensuring the patient an ideal state of awakening, cardiac and respiratory stability, with the safety of the gastrointestinal procedure [9].

The evaluation of the data obtained following the endoscopic investigations by the gastroenterologist showed no changes between the two groups, demonstrating the fact that anaesthesia, regardless of the drug combinations used, facilitates the visualization of the mucosa of the digestive tract and its possible lesions, through the absence of active movements of the patient.

The satisfaction questionnaires completed by the patients in the recovery room showed a level of 10 on the visual analogue scale of pain in all patients in Lot 2. In Lot 1, due to the lack of analgesia provided by the opioid derivative Fentanyl, the level of satisfaction was from 10 to 35 of the patients, and for the rest of the patients it was 9.

Regarding the cost of the drugs used, it was higher in Lot 2 due to the use of two anesthetic drugs (Propofol 1 vial 7 lei, Fentanyl 1 vial 12.5 lei), on the other hand, in Lot 1 the cost was 2 times lower, administering only Propofol.

The possibility of discharge from the outpatient clinic as quickly as possible is an important aspect in choosing the optimal sedation.

In our study, regardless of the anesthetic technique used, all 80 patients were discharged with a modified Aldrete-Kroulik index of 10, 30 minutes after the end of the endoscopic procedures [5].

Conclusion

Propofol associated with Fentanyl provided an effective analgesia, sufficient for performing advanced endoscopic procedures under optimal conditions, with a stable hemodynamic and respiratory status, with a low incidence of bradycardia, hypotension and hypoxia.

Conflict of interests

The authors declared that they had no conflict of interest regarding the content of the article.

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