ORIGINAL ARTICLE

A comparison of different doses of fentanyl for patients undergoing elective colonoscopy: a randomized double-blind clinical trial

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ABSTRACT

Aim To investigate analgesic and side effects of different doses of fentanyl in combination with propofol for colonoscopy.

Methods This prospective randomized double-blind study conducted between 2019 and 2020 included 64 patients. Patients were randomized: Group 1 (fentanyl 0.5 μg/kg) and Group 2 (fentanyl 1.0 μg/kg) both in combination with propofol. Ramsay sedation score (RSS) was obtained at 5 with an additional dose of propofol. The primary outcome was the patient's postprocedural pain and adverse events during and after the procedure.

Results The RSS means were statistically lower for Group 2 at the beginning and every 5 minutes of the procedure. Mean arterial pressure (MAP) for Group 2 (first, 5, 25 and 30 min) was significantly lower (p=0.000, and heart rate (HR) was significantly higher for Group 1 (during the entire procedure) (p=0.000) than in another group; peripheral oxygen saturation (SpO_2) was significantly lower for measurements within both groups (Group 1, 5, 10, 15 min; Group 2, 5, 10,15 min) (p=0.000 and p=0.000, respectively). Anxiety (p=0.010), weakness (p=0.000) and confusion (p=0.023) proved to be significantly higher for Group 1, and hypotension (p=0.001) for Group 2 than in another group. No statistical significance of Visual Analogue Pain Scale (VAS) (p=0.501) and Aldrete recovery score (ARS) (p=0.845) was found.

Conclusion There was no significance in postprocedural abdominal pain between the group of patients administered fentanyl at a dose of 0.5 μg/kg and the group of patients administered fentanyl at a dose of 1.0 μg/kg; however, prevalence of complications was more significant in the group with a fentanyl at a dose of 0.5 μg/kg.

Key words: abdominal pain, incidence, opioid

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INTRODUCTION

Colonoscopy is widely used primarily as a diagnostic tool for malignant and inflammatory conditions of colon in all age structures, increasingly in younger ones. It is associated with abdominal pain or some other abdominal discomfort (1). Patients may be deterred from the colonoscopy procedure, so therefore patient comfort is an important outcome measure in colonoscopy assessment (2). As a painful and unpleasant procedure, colonoscopy is one of the main barriers to patients' participation in colorectal cancer screening (3). Causes of pain are various, and they are mainly the result of stretching of the mesenterium and distension of the intestinal lumen by air (4). Postprocedural pain can be present for varying lengths of time; according to some studies up to 30 days after colonoscopy (5). Factors related to pain have already been established during colonoscopy in deep sedation (6).

Although propofol sedation is the first of choice in most countries (7), the analgesic agents' properties are still not sufficient for patient satisfaction when it comes to pain. Several studies have examined pharmacological and nonpharmacological pain interventions during endoscopy (8,9). Of the pharmacological ones, opioids are most commonly used (10). Opioid agents provide good analgesia with rapid onset and cessation of action, making it an ideal choice for administration (11).

Fentanyl as a powerful opioid is most commonly used in combination with other sedatives (12). Due to its pronounced lipophilicity, it is associated with a greater sedative effect and greater synergy with other drugs (13). Despite its positive properties, fentanyl is related with numerous side effects, such as respiratory depression, hypotension, nausea, pruritus and somnolence (14,15).

The effect of analgesia on patient tolerance in colonoscopy has been evaluated in several studies (16,17). Several trials have been conducted on different opiates, the optimal safe and well tolerated dose has not been found yet (18,19). However, to our knowledge, a randomized double-blind study to assess the dose of the currently most commonly used opioid-fentanyl for the colonoscopy procedure has not yet been conducted. The optimal dose of fentanyl that would be sufficient for analgesia is not known yet, and at the same time the dose that would cause minimal side effects, especially respiratory depression.

The aim of this study was to evaluate the efficacy and safety of two different doses of fentanyl as the most commonly used opioid.

PATIENTS AND METHODS

Patients and study design

A prospective, randomized double-blind study was conducted at the Department of Anaesthesiology and Intensive Care Unit, Cantonal Hospital Zenica, during the period between 2019 and 2020. The study included 64 outpatients older than 18 years, with physical status according to the American Society of Anesthesiologists classification system (ASA) 1-2 (20), referred for elective colonoscopy. All patients had fasted for the previous 8 hours and were prepared for the colonoscopy procedure. Pregnant women, patients with previous abdominal surgery, malignant and respiratory diseases, gastrointestinal obstruction, patients using antihypertensive and antiarrhythmic drugs, psychiatric patients, patients with other pain syndromes, ASA status 3 and higher, and patients who refused to participate in the research were excluded from the study.

A randomized computer division of the patients was done dividing them into two groups: patients to whom fentanyl was administered at a dose of 0.5 μg/kg (Group 1), and patients to whom fentanyl was administered at a dose of 1.0 μg/kg (Group 2). Syringes containing fentanyl were coded before the procedure by a nurse who was not involved in the analgosedation process, and all were prepared in a similar manner (size, shape, color). Anaesthesiologists and colonoscopists were blinded to the mode of drug administration. After admission of the patient to the endoscopic room, an intravenous fluid administration (saline) was started. Patients were placed on non-invasive monitoring of vital parameters (blood pressure, electrocardiogram - ECG, peripheral oxygen saturation – SpO2), in an appropriate position with oxygen support via a face mask and a flow of 5 L/min.

All patients have signed an informed consent.

An approval of the Ethics Committee of the Cantonal Hospital Zenica was obtained (No: 00-03-35-1277-9/20).

Methods

Premedication of patients was performed with midazolam at a dose of 0.05 mg/kg, 5 minutes before the procedure. Group 1 patients were administered fentanyl at a dose of 0.5 μg/kg and propofol at a dose of 1 mg/kg and fentanyl 1 μg/kg and propofol 1 mg/kg for Group 2. Ramsay Sedation Scale (RSS) score was maintained at the value of 5 with an additional 0.5 mg/kg bolus dose of propofol when required.

In the endoscopic room, the values of mean arterial pressure (MAP), heart rate (HR) and SpO_2 were recorded immediately and every 5 minutes during the procedure. In the follow-ups, hypertension, hypotension, bradycardia, tachycardia and desaturation were recorded. Hypertension is marked as an increase of MAP by more than 30% in relative to the initial value, and hypotension as a decrease by more than 30%. A drop of the HR below 50 beats/min was considered as bradycardia, while an increase over 100 beats/min was considered as tachycardia. Desaturation is marked as a decrease in SpO2 below 95%.

After the process of colonoscopy had started the degree of sedation was assessed by RSS, immediately after the administration of fentanyl and propofol and following every 5 minutes of the procedure. Bolus propofol doses of 0.5 mg/kg were applied to both groups, without adding fentanyl and keeping the RSS of 5. Additional bolus doses of propofol were recorded.

The subjective sensation of the patient's postprocedural abdominal pain was determined by a Visual Analogue Scale (VAS) (0-100 mm). The patient marked the experienced pain on a scale, which was assigned a numerical value according to the VAS score. Abdominal pain was assessed 15 minutes after the procedure.

The quality of patient's recovery was assessed with Aldrete recovery score (ARS) 15 minutes after the end of the procedure. The assessment with ARS is based on five criteria: motor activity, respiration, blood pressure, consciousness, and skin colour. Each of these criteria was graded separately from 0 to 2. Scores of 8 were considered satisfactory for discharge.

Complications that were monitored included unpleasant dreams, anxiety, weakness, vomiting, nausea, hallucinations and confusion. The patients were marked with YES or NO if they had any of these complications.

Statistical analysis

Normally distributed variables were analysed using the t-test, while the Mann-Whitney test was used for other variables. In addition to descriptive statistical analysis (mean, standard deviation), analysis of variance (ANOVA) with multiple repeated measurements was used for comparison within each group. Qualitative data were analysed by χ^2 test and Fisher exact test. Statistical significance was set at $p<0.05$.

RESULTS

There were no significant differences between the mean age (p=0.625) and body weight (p=0.862), as well as gender (p=0.770), distribution of the ASA score (p=0.424) and additional dose of propofol (0.501) between both groups (Table 1).

Table 1. Characteristics of two groups of patients according to a dose of fentanyl

Parameter	Patient group		p
	Group 1 (n=32)	Group 2 (n=32)	
	mean±SD		
Age (years)	55.53±12.23	57.47±12.1	0.625
Weight (kg)	76.72±12.13	76.03±12.17	0.862
Gender	No (%) of patients		0.770
Males	8 (12.5)	24(37.5)	
Females	9(14.1)	23(35.9)	
ASA score	No (%) of patients		0.424
1	9 (14.1)	23 (35.9)	
2	12 (18.8)	20 (31.3)	
No of doses of propofol	No (%) of patients		0.501
Without	5 (7.8)	2 (3.1)	
One	11 (17.2)	5 (7.8)	
Two	7 (10.9)	6 (9.4)	
Three	3 (4.7)	7 (10.9)	
4-6	4 (6.3)	7 (10.9)	
7-10	2 (3.1)	3 (4.7)	
>10	0	2 (3)	

Group 1, patients who received 0.5 μg/kg of fentanyl; Group 2, patients who received 1.0 μg/kg of fentanyl; ASA score, physical status classification system according to the American Society of Anesthesiologists

The MAP, HR and SpO2 values showed no statistical significance between the groups, while RSS values were statistically lower for Group 2 at the beginning and every 5 minutes of the procedure comparing to Group 1 (Table 2).

Repeated measurements for each group showed statistically significant lower MAP values for Group 2, in the first, 5, 25 and 30 min (p=0.000). Statistically significant higher mean values were

Table 2. Mean arterial pressure (MAP), heart rate (HR), peripheral oxygen saturation (SpO2) and Ramsay Sedation Score (RSS) according to two groups

Variable	Group	Time (minutes) mean±SD							
		Initial	1	5	10	15	20	25	30
MAP (mmHg)	Group 1	93.78±14.37	78.44±17.51	71.63±13.20	72.88±14.98 74.093 0.485	75.23±13.70	73.71±11.48	76.54±10.89	75.00±11.08
	Group 2	89.63±13.00	73.75±13.04	65.09±11.72	70.84±19.10	68.31±13.37	69.00±10.00	70.40±13.67	70.50±10.19
	p	0.230	0.229	0.055	0.638	0.060	0.133	0.104	0.180
HR (beats/min)	Group 1	91.56±15.75	84.75±18.04	79.19±16.37	76.28±14.18	72.42±14.47	73.58±15.15	75.16±13.63	74.18±13.35
	Group 2	87.22±13.00	84.28±12.78	74.50±12.72	74.09±10.43	72.77±9.97	73.68±11.89	71.50±8.91	72.20±8.07
	p	0.265	0.905	0.206	0.485	0.915	0.612	0.324	0.476
SpO2 (%)	Group 1	98.06±1.41	96.19±3.88	93.53±4.48	92.97±4.54	94.16±4.16	94.87±15.15	95.08±3.35	95.18±2.50
	Group 2	98.63±1.18	95.84±5.04	93.22±5.83	84.09±5.67	95.23±3.14	73.68±4.22	95.70±2.99	96.30±2.61
	p	0.093	0.761	0.811	0.385	0.286	0.648	0.527	0.165
RSS	Group 1	-	5.69±0.69	5.34±0.90	5.31±1.03	5.23±1.02	5.48±0.67	5.25±1.11	5.68±0.65
	Group 2	-	4.88±0.71	4.78±0.55	4.78±0.55	4.77±0.43	4.55±0.86	4.70±0.57	4.60±0.50
	p	-	0.000	0.004	0.013	0.029	0.000	0.042	0.000

Group 1, patients who received 0.5 μg/kg of fentanyl; Group 2, patients who received 1.0 μg/kg of fentanyl; MAP, mean arterial pressure; HR, heart rate; SpO2, peripheral oxygen saturation; RSS, Ramsay Sedation Score

Table 3. Mean arterial pressure (MAP), heart rate (HR), peripheral oxygen saturation (SpO2) and Ramsay Sedation Score (RSS) repeated measures according to two groups

Variable	Group	Time (minutes) mean±SD							
		Initial	1	5	10	15	20	25	30
MAP (mmHg)	Group 1	95.90±14.64	80.43±19.01	70.57±13.43	72.86±13.29 0.485	74.95±15.31	73.71±12.67	78.38±9.91	75.43±11.16
	Group 2	90.50±13.37	78.55±12.44	67.45±13.61	73.30±20.84	70.65±13.19	68.85±10.24	70.40±13.67	70.50±10.19
	p*				0.000				
	p†				0.000				
HR (beats/min)	Group 1	94.09±15.79	88.50±18.60	82.91±15.57	78.41±13.85	75.23±13.76	73.73±14.56	75.00±13.53	74.18±13.35
	Group 2	82.15±14.87	82.15±14.19	71.45±13.02	70.30±9.85	70.50±9.39	73.30±12.19	71.15±8.91	72.20±8.07
	p*				0.000				
	p†				0.000				
SpO2 (%)	Group 1	98.18±1.26	96.50±3.26	93.82±3.81	92.68±4.04	93.86±3.89	94.50±4.40	95.09±3.50	95.18±2.50
	Group 2	98.70±1.26	96.95±4.31	92.30±6.61	93.45±6.74	94.90±3.34	95.20±3.32	95.70±2.99	96.30±2.62
	p*				0.000				
	p†				0.000				
RSS	Group 1	-	5.77±0.68	5.50±0.80	5.50±0.80	5.41±0.85	5.64±0.58	5.36±0.90	5.68±0.64
	Group 2	-	4.75±0.72	4.70±0.57	4.65±0.67	4.70±0.47	4.50±0.89	4.70±0.57	4.60±0.50
	p*				0.449				
	p†				0.371				

*p <0.05 was considered statistically significant for Group 1 according to repeated measurements in the same group; †p<0.05 was considered statistically significant for Group 2 according to repeated measurements in the same group; Group 1, patients who received 0.5 μg/kg of fentanyl; Group 2, patients who received 1.0 μg/kg of fentanyl; MAP, mean arterial pressure; HR, heart rate; SpO2, peripheral oxygen saturation; RSS, Ramsay Sedation Score

found for HR in Group 1 at the beginning and during the whole procedure, and for Group 2 at 15, 20, 25 and 30 min (p=0.000 and p=0.000, respectively). The mean SpO2 value was statistically significantly lower at 5, 10, 15 and 20 minutes for Group 1, and at 5, 10, and 15 minutes for Group 2 (p=0.000 and p=0.000, respectively). The RSS has not shown statistical significance between the groups (Table 3).

A statistically significantly higher prevalence was observed only for hypotension as a complication during the procedure for Group 2 (p=0.001) comparing to Group 1 (Table 4).

Unpleasant dreams and hallucinations as complications after the procedure proved to be statistically constant, while nausea (p=0.151) and vomiting (p=0.151) were not significant. Anxiety (p=0.010), weakness (p=0.000) and confusion (p=0.023) were found to be significant for Group 1. VAS (p=0.501) and ARS (p=0.845) did not show statistical significance for repeated measurements in both groups (Table 5).

Table 4. Complications during the procedure in two groups of patients

Variable	No of episodes	No (%) of patients in the group		p
		Group 1 (n=32)	Group 2 (n=32)	
Hypertension	0	29 (45.3)	30 (46.9)	0.601
	1	1 (1.6)	0	
	2	2 (3.1)	2 (3.1)	
	3	0	0	
	>3	0	0	
Hypotension	0	15 (23.4)	3 (4.7)	0.001
	1	2 (3.1)	12 (18.8)	
	2	9 (14.1)	5 (7.8)	
	3	4 (6.3)	8 (12.5)	
	>3	2 (3.1)	4 (6.3)	
Tachycardia	0	28 (43.8)	31 (48.4)	0.533
	1	1 (1.6)	1 (1.6)	
	2	1 (1.6)	0	
	3	1 (1.6)	0	
	>3	1 (1.6)	0	
Bradycardia	0	25 (39.1)	28 (43.8)	0.530
	1	3 (4.7)	3 (4.7)	
	2	1 (1.6)	0	
	3	2 (3.1)	0	
	>3	1 (1.6)	1 (1.6)	
Desaturation	0	11 (17.2)	11(17.2)	0.635
	1	11 (17.2)	7 (10.9)	
	2	7 (10.9)	7 (10.9)	
	3	1 (1.6)	3 (4.7)	
	>3	2 (3.1)	4 (6.3)	

Group 1, patients who received 0.5 μg/kg of fentanyl; Group 2, patients who received 1.0 μg/kg of fentanyl

Table 5. Complications after the procedure in two groups of patients

Variable		No (%) of NO/YES answers in the patient groups		p
		Group 1 (n=32)	Group 2 (n=32)	
Unpleasant dreams		32/0 (50/0)	32/0 (50/0)	A
Anxiety		26/6 (40.6/9.4)	32/0 (50/0)	0.010
Weakness		11/21 (17.2/32.8)	26/6 (40.6/9.4)	0.000
Nausea		30/2 (46.9/3.1)	32/0 (50/0)	0.151
Vomiting		30/2 (46.9/3.1)	32/0 (50/0)	0.151
Hallucinations		32/0 (50/0)	32/2 (50/0)	A
Confusion		25/7 (39.1/10.9)	31/1 (48.4/1.6)	0.023
VAS	No pain	18 (28.1.0)	16 (25.0)	0.501
	Mild	11 (17.2.0)	12 (18.8)	
	Moderate	3 (4.7)	2 (3.1)	
	Severe	0	2 (3.1)	
	Extreme	0	0	
ARS	0-5	0	0	0.845
	6	1 (1.6)	1 (1.6)	
	7	4 (6.3)	2 (3.1)	
	8	16 (25.0)	20 (31.3)	
	9	8 (12.5)	6 (9.4)	
	10	3 (4.7)	3 (4.7)	

Group 1, patients who received 0.5 μg/kg of fentanyl; Group 2, patients who received 1.0 μg/kg of fentanyl; A, statistical constant; VAS, visual analogue pain scale; ARS, Aldrete recovery score

DISCUSSION

In this prospective randomized study, analgesic effect of two different doses of fentanyl for elective colonoscopy was compared. Demographic parameters, additional doses of propofol, parameters of respiratory and hemodynamic stability were monitored with the assessment of pain and quality of recovery 15 minutes after the procedure. The results showed greater variations in SpO_2 in both groups, while variations in HR and MAP were significant only for Group 1 (with fentanyl dose of 0.5 μg/kg). Anxiety, weakness and confusion were significant for Group 1 after the procedure, and hypotension as a complication during the procedure for Group 2. Pain and quality of recovery were equal in both groups.

There is no study that described an effect of dose of fentanyl on pain for colonoscopy, but there are numerous studies that have compared different opioids for the same procedure. Singh et al. (21) demonstrated a lower additional dose of propofol if a colonoscopy procedure was performed in combination with fentanyl. Our results showed equal requirements for an additional dose of propofol in both groups. Consistent with our results is Sultan SS. study including 80 patients and comparing alfentanil and remifentanil, that showed greater hemodynamic variations in the remifentanil group, but no differences in RSS (22).

Blood pressure, heart rate and oxygen levels saturation were similar during the endoscopic procedure in patients receiving tramadol or placebo (23). In colonoscopies using fentanyl and meperidine, the recovery time was shorter in patients receiving fentanyl than in those receiving meperidine, while there was no difference in pain perception (24). Compared to morphine, fentanyl has similar effects in outpatients and a low rate of side effects (25). A dose of 100 μg fentanyl intravenously for routine outpatient endoscopy is considered significantly improved procedural sedation according to Khan et al.; this study showed that fentanyl shortens the procedure time and allows less application of midazolam. The dose of fentanyl as a predictor of apnoea was the total dose of 1.02–1.6 or 50 μg, typically after 5 minutes of medication administration (26). Our results showed that even a higher dose of fentanyl is safe regarding the prevalence of desaturation.

Although it was expected that RSS should be better in the group of the patients with a higher dose of fentanyl, our results proved to be the opposite. This can be explained by the side effects that fentanyl causes at higher doses. In our study

hypotension was significant for Group 2 (with fentanyl dose of 1 μg/kg). Hypotension is also the most common adverse event of deep sedation in endoscopic retrograde cholangiopancreatography with fentanyl doses of 0.5–1 μg/kg (27). This is probably due to an indirect reduction in central sympathetic outflow and reduction in systemic vascular resistance (28). Significant decrease in the heart rate was found with the dose of fentanyl of 1 μg/kg, during and after colonoscopy. In the same group nausea, vomiting and hypoxia were common in fentanyl at the dose of 1 μg/kg (29). Neves et al. recorded hypotension in patients receiving fentanyl at the same dose (30), which corresponds to our results when it comes to hypotension. Usually as a cause of vasovagal episode or the use of sedatives and anaesthetics that suppress sympathetic outflow, especially in combination with midazolam and propofol (31). Side effects during and after sedation for colonoscopy are not common, and are mainly vasovagal reactions and hypoventilation as previously stated (32). The only study that examined the dose of fentanyl was based on the mean concentration of propofol with different doses of fentanyl did not show severe adverse events, except for prolonged waking (33). Predictors of side effects of fentanyl on cognitive functions according to Thompson et al. were a dose of fentanyl >50 μg or midazolam >3 mg in combination with propofol (34). Our study showed that fentanyl at a higher dose alleviates anxiety, weakness and confusion side effects. Evaluation of pain in our study showed that there was no difference when it comes to the dose of fentanyl. Similar results are seen when it comes to assessing patient recovery. It should be noted that the data from our study represent selected group of patients without significant comorbid conditions. The right choice of patients for analgesia-based sedation is very important for daily practice and most likely reduces the rate of adverse events. The use of pulse oximetry for monitoring of desaturation is useful, however, the assessment of alveolar ventilation with pulse oximetry alone is not sufficient (35), especially in patients with higher ASA status.

The main limitation of this study is a small number of low-risk patients. High-risk patients are unlikely to have the same tolerance to this type of sedation and are more prone to a complication. Our study also demonstrates safety of fentanyl use with few side effects of clinical significance.

The addition of fentanyl results in significantly better patient satisfaction during and after the procedure. Increasing the dose of fentanyl from 0.5 to 1 μg/kg has no significant effect on postprocedural pain and recovery time, and did not show major side effects, especially in the group of patients with a higher dose of fentanyl. Further studies should focus on an analysis of higher doses of fentanyl, and be based on high-risk patients.

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REFERENCES

1. Holme Ø, Bretthauer M. Pain and sedation during colonoscopy - a never ending story. Endosc Int Open 2016; 4:538–9.
2. Chan BPH, Hussey A, Rubinger N, Hookey LC. Patient comfort scores do not affect endoscopist behavior during colonoscopy, while trainee involvement has negative effects on patient comfort. Endosc Int Open 2017; 5:1259–67.
3. Bugajski M, Wieszczy P, Hoff G, Rupinski M, Regula J, Kaminski MF. Modifiable factors associated with patient-reported pain during and after screening colonoscopy. Gut 2018; 67:1958–64.
4. Allen P, Shaw E, Jong A, Behrens H, Skinner I. Severity and duration of pain after colonoscopy and gastroscopy: a cohort study. J Clin Nurs 2015; 24:1895-903.
5. Baudet JS, Diaz-Bethencourt D, Avile´s J, Aguirre-Jaime A. Minor adverse events of colonoscopy on ambulatory patients: the impact of moderate sedation. Eur J Gastroenterol Hepatol 2009; 21:6.
6. Elphick DA, Donnelly MT, Smith KS, Riley SA. Factors associated with abdominal discomfort during colonoscopy: a prospective analysis. Eur J Gastroenterol Hepatol 2009; 21:1076–82.
7. Trevisani L, Zelante A, Sartori S. Colonoscopy, pain and fears: Is it an indissoluble trinomial? World J Gastrointest Endosc 2014; 6:227-33.
8. Leung FW. Methods of Reducing Discomfort During Colonoscopy. Dig Dis Sci 2008; 53:1462–7.
9. Sue-Chue-Lam C, Castelo M, Tinmouth J, Llovet D, Kishibe T, Baxter NN. Non-pharmacological interventions to improve the patient experience of colonoscopy under moderate or no sedation: a systematic review protocol. BMJ Open 2020; 10:e038621.

10. Grilo-Bensusan I, Herrera-Martín P, Jiménez-Mesa R, Aguado-Álvarez V. Prospective study of the factors associated with poor tolerance to ambulatory colonoscopy under conscious sedation. Rev Esp Enferm Dig 2018; 110:223-30.
11. Lazaraki G, Kountouras J, Metallidis S, Dokas S, Bakaloudis T, Chatzopoulos D, Gavalas E, Zavos C. Single use of fentanyl in colonoscopy is safe and effective and significantly shortens recovery time. Surg Endosc 2007; 21:1631–6.
12. Hirsh I, Vaissler A, Chernin J, Segol O, Pizov R. Fentanyl or tramadol, with midazolam, for outpatient colonoscopy: analgesia, sedation, and safety. Dig Dis Sci 2006; 51:1946–51.
13. Perez-Maña C, Papaseit Fontanet E, Fonseca F, Farré A, Torrens M, Farre M. Drug interactions with new synthetic opioids. Front Pharmacol 2018; 9:1145.
14. Friesgaard KD, Nikolajsen L, Giebner M, Rasmussen CH, Riddervold IS, Kirkegaard H, Christensen EF. Efficacy and safety of intravenous fentanyl administered by ambulance personnel. Acta Anaesthesiol Scand 2016; 60:537–43.
15. Schug SA, Ting S. Fentanyl formulations in the management of pain: an update. Drugs 2017; 77:747–63.
16. Shingina A, Ou G, Takach O, Svarta S, Kwok R, Tong J, Donaldson K, Lam E, Enns R. Identification of factors associated with sedation tolerance in 5000 patients undergoing outpatient colonoscopy: Canadian tertiary center experience. World J Gastrointest Endosc 2016; 8:770–6.
17. Soral M, Altun GT, Dinçer PC, Arslantaş MK, Aykaç Z. Effectiveness of the analgesia nociception index monitoring in patients who undergo colonoscopy with sedo-analgesia. Turk J Anaesthesiol Reanim 2020; 48:50-7.
18. Wadelek J. Medications commonly used for analogizations during a colonoscopy. Br J Gastroenterol 2020; 2:168-73.
19. Lin OS. Sedation for routine gastrointestinal endoscopic procedures: a review on efficacy, safety, efficiency, cost and satisfaction**.** Intest Res 2017; 15:456-66.
20. Doyle DJ, Goyal A, Garmon EH. American Society of Anesthesiologists Classification. StatPearls. Treasure Island (FL): StatPearls Publishing; 2022.
21. Singh SA, Prakash K, Sharma S, Dhakate G, Bhatia V. Comparison of propofol alone and in combination with ketamine or fentanyl for sedation in endoscopic ultrasonography. Korean J Anesthesiol 2018; 71:43-7.
22. Sherif S. Sultan. Patient-controlled sedation with propofol/remifentanil versus propofol/alfentanil for patients undergoing outpatient colonoscopy, a randomized, controlled double-blind study. Saudi J Anaesth 2014; 8:36-40.
23. Grossi L, Cappello G, Marzio L. Premedication with tramadol in patients undergoing colonoscopy: a double-blind randomized placebo-controlled study. Dig Dis Sci 2004; 49:1641–45.
24. Hayee B, Dunn J, Loganayagam A, Wong M, Saxena V, Rowbotham D, McNair A. Midazolam with meperidine or fentanyl for colonoscopy: results of a randomized trial. Gastrointest Endosc 2009; 69:681-7.
25. Fleischman RJ, Frazer DG, Daya M, Jui J, Newgard CD. Effectiveness and safety of fentanyl compared with morphine for out-of-hospital analgesia. Prehosp Emerg Care 2010; 14:167–75.
26. Khan KJ, Fergani H, Ganguli SC, Jalali SC, Spaziani R, Tsoi K, Morgan DG. The benefit of fentanyl in effective sedation and quality of upper endoscopy: a double-blinded randomized trial of fentanyl added to midazolam versus midazolam alone for sedation. J Can Assoc Gastroenterol 2019; 2:86–90.
27. Amornyotin S, Srikureja W, Chalayonnavin W, Kongphlay S. Dose requirement and complications of diluted and undiluted propofol for deep sedation in endoscopic retrograde cholangiopancreatography. Hepatobiliary Pancreat Dis Int 2011; 10:313-18.
28. Mahiswar AP, Dubey PK, Ranjan A**.** Comparison between dexmedetomidine and fentanyl bolus in attenuating the stress response to laryngoscopy and tracheal intubation: a randomized double-blind trial. Braz J Anesthesiol 2022; 72:103-9.
29. Seleem WM, El Hossieny KM, Abd-Elsalam S. Evaluation of different sedatives for colonoscopy. Curr Drug Saf 2019; 14.
30. Das Neves JFNP, das Neves AMMP, Paiva Araújoa F, Ferreiraa CM, Neves Duartea FB, Pacea FH, Ornellas LC, Baronc TH, Castro Ferreira LEVV. Colonoscopy sedation: clinical trial comparing propofol and fentanyl with or without midazolam. Rev Bras Anestesiol 2016; 66:231-6.
31. Amornyotin S. Sedation-related complications in gastrointestinal endoscopy. World J Gastrointest Endosc 2013; 5:527-33.
32. Manta R, Tremolaterra F, Arezzo A, Verra M, Galloro G, Dioscoridi L, Pugliese F, Zullo A, Mutignani M, Bassotti G. Complications during colonoscopy: prevention, diagnosis, and management. Tech Coloproctol 2015; 19:505-13.
33. Li S, Yu F, Zhu H, Yang Y, Yang L, Lian J. The median effective concentration (EC50) of propofol with different doses of fentanyl during colonoscopy in elderly patients. BMC Anesthesiology 2016; 16:24.
34. Thompson R, Seck V, Riordan S, Wong S. Comparison of the effects of midazolam/fentanyl, midazolam/propofol, and midazolam/fentanyl/propofol on cognitive function after gastrointestinal endoscopy. Surg Laparosc Endosc Percutan Tech 2019; 29:441–6.
35. Arakawa H, Kaise M, Sumiyama K, Saito S, Suzuki T, Tajiri H. Does pulse oximetry accurately monitor a patient's ventilation during sedated endoscopy under oxygen supplementation? Singapore Med J 2013; 54: 212-15.