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Effects of alfentanil or fentanyl added to propofol for sedation in colonoscopy on cognitive functions: Randomized controlled trial

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ABSTRACT

Background/Aims: To assess the effect of propofol supplemented with alfentanil or fentanyl on cognitive functions for sedation during elective colonoscopy.

Materials and Methods: Patients (n=150, 18-65 years old, American Society of Anesthesiologists risk group I-III) scheduled undergo elective colonoscopy were included. They were randomized into three groups using the closed envelope methodpropofol-alfentanil (Group A), propofol-fentanyl (Group F), and propofol only (Group P).Group A patients were given an alfentanil (10 mcg/kg)-supplemented propofol bolus infusion and 5 mcg/kg alfentanil when necessary. Group F patients were given fentanyl (1 mcg/kg)-supplemented propofol and 0.5 mcg/kg fentanyl when necessary. Group P patients were given 1 mg/kg propofol and 0.5 mg/kg propofol when necessary. Vital signs, depth of sedation, recovery parameters, and patient and endoscopist satisfaction were recorded. Trieger dot test (TDT) and Digit Symbol Substitution Test (DSST) were performed post procedure.

Results: Demographic data were similar among all patients in the groups. Bispectral index values were lower in Group P ($p<0.001$). DSST scores were higher in Group A ($p=0.004$). TDT scores and Facial Pain Scale scores were higher in Group P ($p<0.005$). Apnea incidence ($p=0.009$) and Observer's Assessment of Alertness/Sedation Scale scores ($p=0.002$) were also higher in Group P. Patient satisfaction and endoscopist satisfaction were similar among all patients.

Conclusions: Compared with propofol-alfentanil and propofol-fentanyl, propofol alone is associated with an increased incidence of apnea, drug consumption, and reported pain. Propofol-alfentanil has a less negative effect on cognitive functions than propofol alone or propofol-fentanyl.

Keywords: Sedation, colonoscopy, cognitive function, propofol

Original Article

INTRODUCTION

Sedation during diagnostic and therapeutic endoscopic procedures is becoming popular and is used for alleviating patients' anxiety, fear, and pain while providing comfort (1). Different sedation regimes (e.g., single dose, intermittent bolus, and continuous infusion) have been developed (2,3). Opioids and hypnotic agents used to provide sedation should cause minimal depression of consciousness and should not cause respiratory depression or loss of protective reflexes (3,4).

Cognition can be defined as a person's ability to gather information, solve problems, and perceive and evaluate memory and information (5). Evaluating cognition after endoscopic procedures is important for assessing early mobilization, achieving high patient turnover, and decreasing loss of work hours. Normalization of fine motor function is also important for return to daily activities.

Various anesthetic agents are known to affect the central nervous system function to varying degrees and

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durations, and some can cause acute loss of consciousness. For sedation during minor interventions, hypnotic agents and opioids with short half-lives and no cumulative effects are typically chosen. The combination of midazolam with opioids that have a half-life longer than the procedure duration results in prolonged recovery and late discharge from the hospital. Thus, the combination of a short-acting hypnotic agent with an opioid that has faster recovery and a low side-effect profile and causes reduced depression of consciousness compared with a combination of midazolam and opioid would be more suitable for sedation (6,7). We hypothesized that conscious sedation using a short-acting opioid and propofol has a reduced effect on cognitive function compared with longer acting opioids. The rationale for this was that alfentanil would provide faster recovery and earlier discharge than fentanyl and therefore be advantageous during colonoscopy procedures.

Here we aimed to compare the effect of short- and long-acting opioids added to propofol on cognitive function following procedural sedation. The primary endpoint of this study was to investigate the cognitive and motor effects of alfentanil (a short-acting opioid) and fentanyl (a long-acting opioid) added to propofol for sedation during colonoscopy. Secondary endpoints were to compare side effects and patient and endoscopist satisfaction.

MATERIALS AND METHODS

Ethics committee approval (Ethics No: 13/02, Date: 21.04.2014) (www.clinicaltrials.gov identifier: NCT02486328) and written informed consent from patients were obtained. In total, 153 patients aged 18-65 years, belonging to American Society of Anesthesiologists risk group I-III, and who were scheduled to undergo elective colonoscopy were included. The entire study was conducted in Ufuk University Dr. Rıdvan Ege hospital. Exclusion criteria were Mini-Mental Test (MMT) scores of <26, Amsterdam Preoperative Anxiety and Information Scale (APAIS) scores of >10, advanced systemic disease (e.g., chronic obstructive pulmonary disease, cirrhosis, or congestive heart failure), orientation and cooperation disorders, history of neuropsychiatric disease, chronic alcohol dependency, morbid obesity (body mass index>30 kg/m^2), history of undergoing anesthesia in the last 7 days, and known allergy to the study drugs.

After providing informed consent, the patients had to undergo the APAIS test and MMT. The patients who were enrolled underwent the Trieger dot test (TDT) and Digit Symbol Substitution Test (DSST), after which they were randomized into the following groups: propofol-alfentanil (Group A), propofol-alfentanil (Group F), and propofol only (Group P). There were 50 patients in all groups. The investigator who evaluated the cognitive function of the patients was blinded to the study groups.

All patients were administered dexketoprofen (100 mg) in 100 mL of 0.9% normal saline as an infusion 20 min before the procedure. Ondansetron (0.15 mg/kg) was intravenously administered 5 min before the procedure.

Vital signs (electrocardiography, blood pressure, and SpO_2) and bispectral index (BIS) values were monitored when patients were brought to the endoscopy room. All patients were given 2 L/min of nasal oxygen. Following positioning, Group A patients were given propofol (propofol 1%, Fresenius® Fresenius Kabi, Sweden) as an 100-mcg/kg/min intravenous infusion. Alfentanil (Rapifen 2mL®Janssen-Cilag, Italy) was given as a 10-mcg/kg loading dose. An additional 5-mcg/kg bolus was administered if the patient moved, was unable to tolerate colonoscopy, or had a Facial Pain Scale (FPS) score of >3. Group F patients were given a 100-mcg/kg/min propofol infusion. Fentanyl (Fentanyl-Janssen® 10mL Janssen-Cilag, Belgium) was given as 1-mcg/kg loading bolus. An additional 0.5-mcg/kg bolus was administered in case the patient moved, was unable to tolerate colonoscopy, or had an FPS score of >3. Group P patients were given a propofol (100 mcg/kg/min) infusion and a 1-mg/kg loading bolus. An additional 0.5-mg/kg bolus was administered in case the patient moved, was unable to tolerate colonoscopy, or had an FPS score of >3.

The MMT comprises 11 questions and is widely used to evaluate mental status. The questions measure cognitive function in orientation, registration, attention, calculation, recall, and language. A score of ≤23 from a maximum of 30 is considered as cognitive impairment (8). The APAIS measures anxiety and need for information and comprises six items that are rated between 1 and 5 by a subject. The APAIS score correlates with the State Anxiety Scale, and a score of ≥10 signifies anxiety (9). The DSST is a psychomotor test in which a subject is provided a grid consisting of numbers and matching symbols and he/she attempts to fill as many boxes as possible with symbols that match the number in 90 s (10). The TDT measures hand-eye coordination using a pencil and paper on which there are 21 dots. A subject is required to connect these dots using the pencil. TDT scoring is done by calculating the number of missed dots (11). The Observer's Assessment of Alertness/Sedation Scale (OAA/S) is a six-point scale ranging from 5 to 0 that involves eliciting a response to increasingly intense stimuli that begin with speaking in a normal voice and escalate to prodding, shaking, and finally, to a painful stimulus (trapezius squeeze) (12). The FPS is a self-report measure of pain intensity on a 0-10 metric (13).

Bispectral index values and vital signs were recorded every minute for the first 10 min after induction of sedation and then at 15, 20, 25, 30, 35, 40, and 45 min. Pain during the procedure was evaluated using the FPS (0-6), whereas pain after the procedure was evaluated using visual analogue scale (VAS) (0-10) at 5, 15, and 30 min after the procedure. Time to reach

an OAA/S score of >3 was recorded after the procedure. Patients were monitored for a further 30 min after the procedure. Desaturation (SpO_2<90%), hypotension (decrease in systolic pressure of >30% from baseline), hypertension (increase in systolic pressure of >30% from baseline), bradycardia (heart rate<50 bpm), tachycardia (heart rate>90 bpm), nausea, vomiting, and apnea (not breathing for >20 s) were recorded. The total amount of drugs given to the patients was recorded. All colonoscopies were performed by the same gastroenterologist. The patients had to take the TDT and DSST once more at 5, 15, and 30 min after the procedure. Patient satisfaction and endoscopist satisfaction were evaluated using a five-point Likert scale (1=completely dissatisfied, 5= completely satisfied).

Statistical Analysis

Statistical analysis were performed using Statistical Package for Social Sciences for Windows version 21.0 (IBM Corp.; Armonk, NY, USA). Continuous numerical variables were expressed as average±standard deviation and median (minimum-maximum), whereas qualitative variables were expressed using numbers and percentages. Conformity of continuous numerical variables to normality was evaluated using the Shapiro-Wilk test. Homogeneity of variances was evaluated using Levene's test. Differences concerning numerical variables among the groups were evaluated using unidirectional variance analysis or Welch's tests if parametric test assumptions were met. The Kruskal-Wallis test was used if parametric test assumptions were not met. Between-group differences in categorical variables were evaluated using the chi-square test.

RESULTS

In total, 153 patients were enrolled. Two Group A patients did not provide consent, and data of one of the patients were lost; therefore, effectively, only 150 patients completed the study. All colonoscopies were diagnostic. There were no statistically significant differences in demographic data among the patients in the groups (Table 1).

Bispectral index values recorded at baseline and at 1 min after induction were similar in all three groups. However, these values were significantly lower in Group P than in Group A or Group F at 2-10, 15, and 20 min after induction (p<0.001) (Figure 1). There were no between-group differences in HR, MAP, or SpO_2 values at all time points.

Trieger dot test scores were significantly higher in Group P than in Groups A and F, except for those at baseline (p<0.05). TDT scores were significantly higher in Group F than in Group A (Table 2).

While DSST scores were similar at baseline in all three groups, they were statistically higher in Group A at 5, 15, and 30 min after the procedure (p=0.004) (Table 3).

Table 1. Demographic data

	Group A (n=50)	Group F (n=50)	Group P (n=50)	p
Age (years)	57.0±10.9	53.8±12.9	56.0±12.6	0.414
Weight	72.7±11.1	74.9±12.5	76.4±18.9	0.476
Height	163.1±9.6	164.4±9.1	166.4±8.2	0.323
Sex (M/F)	24/26 (48%/52%)	22/28 (44%/56%)	23/27 (46%/54%)	0.923

Table 2. TDT Comparison

	Group A (n=50)	Group F (n=50)	Group P (n=50)	p
Baseline	28.9±7.1	30.9±5.7	32.4±7.2	0.084
5th min	35.4±9.1	39.6±8	41.2±15.3	0.036
15th min	33.4±9.1	37.1±6.6	39.3±12.2	0.020
30th min	30.7±8.7	36.9±7	40.6±8.4	<0.001

TDT: Trieger Dot Test

Table 3. DSST Comparison

	Group A (n=50)	Group F (n=50)	Group P (n=50)	p
Baseline	2.8±1.3	2.0±1.0	2.2±1.1	0.078
5th min	3.3±2.0	1.9±1.3	1.9±1.5	<0.001
15th min	3.6±2.2	2.3±1.2	2.5±1.7	0.001
30th min	3.8±2.5	2.6±1.6	2.7±1.6	0.006

DSST: Digit Symbol Substitution Test

Visual analogue scale scores were similar among the three groups after the procedure as well as at 5, 15, and 30 min after the procedure. Propofol consumption was higher in Group P than in Groups A and F (p<0.001). Time to reach an OAA/S score of >3 and FPS scores were significantly greater in Group P than in Groups A and F (Table 4).

Patient satisfaction and endoscopist satisfaction were similar across all three groups. Apnea incidence was higher in Group P than in Groups A and F (p=0.029) (Table 5).

DISCUSSION

Here we demonstrated that alfentanil-supplemented propofol for sedation during colonoscopy causes less cognitive dysfunction while providing the same side-effect profile and satisfaction level as either propofol alone or propofol-fentanyl.

As the preservation of cognitive function is as important as that of upper airway reflexes and recovery parameters (e.g., return of vital functions to presedation levels), this study aimed to investigate the effects of anesthetic agents used for sedation on cognitive functions and was performed on patients undergoing elective colonoscopy at our hospital.

Table 4. Propofol consumption, recovery data, and pain scores

	Group A (n=50)		Group F (n=50)		Group P (n=50)		
	Avrg±SD	Median	Avrg±SD	Median	Avrg±SD	Median	p
Propofol consumption (mg)	151±68	150 [50-350]	114.8±47.6	100 [10-200]	247.1±95.5	230 [120-440]	<0.001
OAAS/S>3 (min)	0.7±1.5	0 [0-8]	0.2±0.5	0 [0-2]	1.1±1.4	1 [0-5]	0.002
FPS	0.1±0.4	0 [0-3]	0.2±0.6	0 [0-2]	1.6±1.9	1 [0-5]	<0.001

FPS: Facial Pain Scale; OAA/S>3: Time necessary for the OAAS/S score to reach ≥3

Table 5. Patient and endoscopist satisfaction and apnea incidence

	Group A (n=50)	Group F (n=50)	Group P (n=50)	p
Patient satisfaction (4/5)	1/49 (2/98%)	1/49 (2/98%)	0/50 (0/100%)	0.669
Endoscopist satisfaction (4/5)	2/48 (4/96%)	0/50 (0/100%)	0/50 (0/100%)	0.164
Apnea	2 (4%)	2 (4%)	10 (22.7%)	0.029

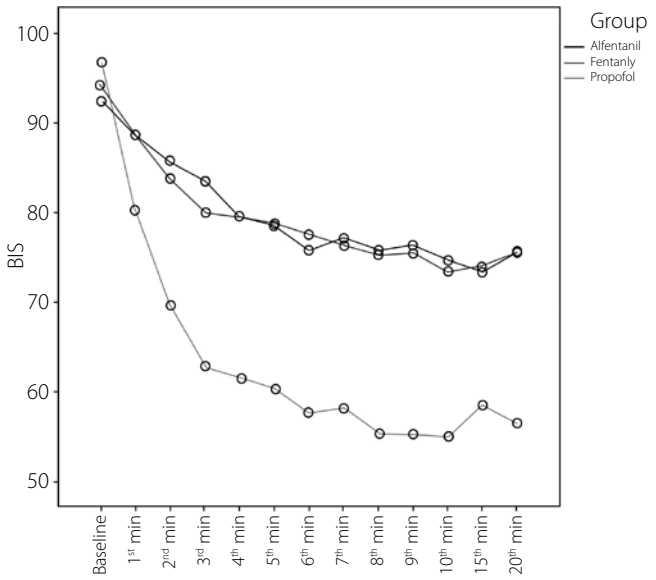

Figure 1. Bispectral index values. The graph shows the change in BIS values in time among the three groups

Anesthetic agents primarily exert their effect on the nervous system, and during the postanesthetic period, they disrupt cognitive functions (higher brain activates) to varying degrees. Fast recovery and reaching the preanesthetic levels of mental function are important targets for anesthesiologists.

There are many risk factors for postoperative mental dysfunction. These include advanced age, existing mental dysfunction, systemic diseases, alcohol abuse, electrolyte imbalance, long and complicated surgical interventions, genetic factors, hemodynamic changes, hormone levels, psychoactive medications, postoperative infection, respiratory complications, prolonged sedation, and pain (14). Sedation during endoscopic procedures facilitates the procedure and allows patients a fast and pain-free return to daily life. An ideal sedative should increase patient cooperation, shorten the recovery time, and increase endoscopist satisfaction. An agent that causes minimal cognitive dysfunction will provide a shorter recovery time.

Various sedative combinations have been used for sedation during endoscopic procedures (15). Midazolam is a commonly used agent, despite causing a longer decline in cognitive dysfunction (16). The effect of other adjuvants and opioids on cognitive functions remains unclear. Propofol is frequently selected as a hypnotic agent during colonoscopy because of its faster recovery time and low side-effect profile; although it is a good hypnotic agent, high doses are required to establish necessary conditions for the procedure, which, in turn, cause hypotension, respiratory depression, and loss of protective reflexes. The lack of analgesic activity further limits its use as a sole sedative agent (17). The necessary increase in dosage when propofol is used alone causes cognitive dysfunction as well as an increase in the incidence of apnea. Our data reveal that the addition of alfentanil, which is an agent with a short half-life, to propofol causes less cognitive dysfunction and reduces recovery time.

Sedation during endoscopic procedures should provide adequate depth of anesthesia that is appropriate to the procedure. Multiple monitoring techniques and tests have been developed to this end. BIS and spectral entropy are electroencephalography (EEG)-based parameters that are frequently used to evaluate the depth of hypnosis. BIS is a single parameter that unifies many determinants of EEG and monitors the depth of hypnosis under general anesthesia or sedation (18).

Surgical stimuli or drugs may affect BIS values. A study has shown that the electromyography (EMG) activity affects BIS values (19). Additionally, some sedative drugs can cause myoclonus and change BIS values. Although spontaneous movement has been reported with propofol (20), we did not observe myoclonus in our patients.

Multiple studies have compared BIS values and sedation scales. The Ramsey Sedation Scale, OAA/S, and Wilson Scale are the most used scales for this purpose (21). Jang et al. (22) compared OAA/S and BIS and found that BIS monitoring lowered drug consumption while increasing patient and

endoscopist satisfaction. Park et al. (23), in a series of 100 patients who were administered propofol and remifentanil, monitored BIS values and stated that additional drug consumption was lowered when sedation was correlated with BIS levels. Our data show that BIS values were lower in Group P than in Groups F and A. We believe this is caused by the increased propofol requirement due to insufficient analgesia. This resulted in more respiratory depression, and apnea was observed in 22.6% of Group P patients; although this is not a statistically significant difference, we believe that this is clinically significant.

Many studies have investigated alfentanil for sedation. In a study by Miner et al. (24), the incidence of respiratory complications was similar during emergency room sedation using either alfentanil of propofol. Nilsson et al. (25) used patient-controlled sedation with propofol and alfentanil as an adjunct to local anesthetics in 165 patients undergoing minor gynecologic operations and reported that the addition of alfentanil to propofol increased the risk of respiratory complications. Our data show that respiratory depression was less frequent in Group A than Group P.

Cognitive function after sedation can be measured using the Wechsler memory scale, tactile memory test, complex shapes test, and verbal word association test. The computerized CogState battery, which was more recently developed, can measure cognitive function in a fast and reliable manner (26). The TDT and DSST, which were used in the present study, can also be used to measure cognitive function (15). Trieger et al. (27) developed the TDT to quantitate recovery from anesthesia. A baseline value is obtained prior to anesthesia administration, and recovery can be evaluated when the test is repeated (28). Although the TDT is a reliable test, drug interactions, pain, CNS depression, postoperative drug use, anxiety, and insomnia prior to the procedure can affect its score (29).

The DSST helps evaluate neurocognitive functions using attention, visual perception, and motor sufficiency. Demographic variables such as age, gender, and level of income might affect DSST results. The DSST is easy to perform and can be used as a screening test for neurological pathologies (30). As Iohom et al. (31) have stated, the "learning curve" phenomenon, which can be observed in the TDT and DSST, can change their results in repeated applications and becomes a limiting factor.

Propofol is an often chosen agent for endoscopic sedation (32). It has been reported that the risk of complications, including aspiration pneumonia during colonoscopies, is lower under propofol sedation than under other sedation methods (33). We observed that the time necessary to achieve an OAA/S score of >3 is longer in Group P than in Groups A and F; we propose that this finding is caused by a greater propofol requirement in Group P to reach the necessary depth of sedation.

In a study by Watkins et al. (34), the cognitive effects of propofol, midazolam, and fentanyl combinations during endoscopic procedures were investigated. The authors stated that propofol, when used alone, had a less detrimental effect on cognitive function than propofol-fentanyl. Contrary to this, our data revealed less cognitive deterioration with propofol-alfentanil, which can be explained by the utilization of an opioid with a lower dose and shorter half-life. In a similar manner, Türk et al. (35) compared propofol-fentanyl and propofol-alfentanil in 80 patients undergoing sedation during colonoscopy and found that propofol-fentanyl provides better operating conditions and shortens the recovery time and is thus more advantageous. The better recovery conditions provided by propofol-alfentanil in our study can be explained by the fact that propofol was used as an infusion.

Propofol and opioid combinations have been used in different doses and methods; however, their effect on cognitive functions has not been adequately investigated. Thus, we investigated the effect of alfentanil and fentanyl boluses as adjuncts to a propofol infusion on cognitive functions and found that propofol-alfentanil had less negative effects than propofol-fentanyl and propofol alone.

Although the absence of capnography and CogState test can be seen as limiting factors, we believe that newer monitoring methods can be used as alternatives in the evaluation of cognitive functions. Using tests that provide more extensive evaluation options for the testing of more limited aspects of cognition will be more beneficial. Another limiting factor of this study was the inability to compare drug doses in the three groups as there was remarkably deeper sedation in Group P.

Ideal studies on this subject could be planned with more patients using target controlled infusion techniques focusing on new dosage and application routes.

In conclusion, we found that alfentanil added to the gold standard propofol for sedation during colonoscopy causes less postprocedural cognitive deterioration and increases patient and endoscopist satisfaction, with a lower side-effect profile, compared with propofol alone or propofol-fentanyl.

Ethics Committee Approval: Ethics committee approval was received for this study form Kırıkkale University Ethics Committee (Decision Date: 21.04.2014/Decision No:13/02).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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