Turk J Gastroenterol *2015; 26: 417-22*

Sedation for gastrointestinal endoscopy with the application of target-controlled infusion

LIVER

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Original Article

ABSTRACT

Background/Aims: A majority of esophagogastroduodenoscopy (EGD) and colonoscopy procedures are performed under sedation, with the intravenous administration of a hypnotic agent combined with an opioid analgesic agent. The goal of our study was to establish the quality and plausibility of target-controlled infusion (TCI) as a sedation mechanism for upper and lower gastrointestinal (GI) endoscopies.

Materials and Methods: A randomized, single-blinded, controlled clinical trial was arranged in a local community hospital. In total, 100 adult outpatients scheduled for upper and lower GI endoscopies were included and randomly allocated to a control group (n=50) and a TCI group (n=50). The sedation quality was assessed using the simplified quality of an anesthesia scoring system. Categorical parameters were compared using Pearson's chi-square test. Continuous parameters that were normally distributed were further compared using Student's t-test, and the others were compared using the Mann–Whitney test.

Results: The significantly lower anesthesia quality score in the TCI group (12.2 vs. 12.7) indicated that the anesthesia quality was better in this group.

Conclusion: This study showed that sedation using TCI for GI endoscopy provided safe and effective sedation and was associated with a better sedation quality. We believe that TCI can be used to provide routine sedation for patients receiving GI endoscopy.

Keywords: Endoscopy, sedation, propofol

INTRODUCTION

Esophagogastroduodenoscopy (EGD) and colonoscopy are interventional medical procedures that are commonly performed worldwide. In recent years, the quantity of routine endoscopic examinations has grown considerably because of an aging population and an increased subject awareness of the benefits of cancer screening (1,2). Upper and lower gastrointestinal (GI) endoscopic examinations have been recommended for first-line screening of cancer because of increasing safety. However, the recognition that these procedures are painful and uncomfortable prevents many patients from consenting to endoscopic examinations. Providing sedation techniques may make these unpleasant procedures more endurable to patients; however, malpractice of sedation can cause complications, even life-threatening ones.

A majority of GI endoscopy procedures are performed under sedation, with the intravenous administration of a hypnotic agent combined with an analgesic agent, often opioid. The most widely recognized medications utilized for sedation during endoscopic procedures are benzodiazepines such as midazolam, which can either be utilized alone or with an opioid such as pethidine (3-5). A common alternative sedative drug is propofol, which has advantages over traditional sedative agents, including a rapid onset of effect, the ability to accomplish satisfactory sedation, and an ultra-short recovery time. Propofol is currently used in 25%–33% of endoscopic examinations in the United States, with the potential for considerable growth in its use (6,7).

Cardiovascular and respiratory depressions are the most common adverse effects during sedation (4,5,8).

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Received: January 23, 2015 **Accepted:** July 15, 2015

 • Available online at www.turkjgastroenterol.org • DOI: 10.5152/tjg.2015.0206

This risk increases with propofol because of its narrow therapeutic window and its synergistic effect with opioids; therefore, it is important to avoid excessive administration, which may be associated with undesirable adverse events. A few studies have assessed the safety of physician- and nurse-administered propofol sedation (9,10). However, many practitioners never receive formal instruction in sedation methods. As a result, some researchers question whether non-anesthesiologists possess the skill to safely administer propofol and opioids (11).

Target-controlled infusion (TCI) is a novel drug delivery mode used in anesthetic administration to achieve a preset target blood drug concentration (12). TCI is easy to use and provides a high level of confidence regarding the predictability of anesthetic effects. Relatively few studies have evaluated the use of TCI for sedation during GI endoscopy (13,14). In our study, we used TCI to administer propofol and alfentanil during endoscopic procedures. Furthermore, a grading scale was used to compare the sedation quality of TCI to manual administration. The aim of our study was to establish the quality and feasibility of TCI as a sedation mechanism for upper and lower GI endoscopies.

MATERIALS AND METHODS

This is a randomized, single-blinded, controlled clinical trial that was performed in a local community hospital. After receiving ethics committee approval from the Institutional Review Board, written informed consent was obtained from all patients. In total, 100 adult outpatients scheduled for upper and lower GI endoscopies were included in this study. All subjects had an American Society of Anesthesiologists (ASA) Physical Status classification of I, II, or III. The exclusion criteria included the following factors: an allergic reaction history to any of the study drugs, eggs, or soybeans; chronic exposure to opioid analgesics or sedative medication; inpatient status; a history of obstructive sleep apnea; seizure disorders; and gross obesity [a body mass index (BMI) greater than 42 in males or 35 in females).

Patients were randomly allocated to a control group (n=50) and a TCI group (n=50) using computer-generated randomization blocks. The participants were given a colon-cleansing preparation the evening before the examination, and all participants fasted during the 4 h prior to the study procedure. After routine evaluation, standard monitoring instruments were set up, including a non-invasive automatic blood pressure cuff, an electrocardiogram, a pulse oximeter, and a capnograph. A 22G intravenous cannula was inserted and connected to an infusion of 0.9% saline. Oxygen was administered at a flow rate of 5 L/min using a nasal cannula. The same physician performed the endoscopy procedures, and sedation was provided by the same nurse anesthetist. In the control group, patients were administered a dose of 0.27 mg of alfentanil and a dose of 2–2.5 mg midazolam based on their age and body weight. After 3 min, propofol was administered and titrated to the desired sedation effect with a dose of 20–30 mg. After the patient was unconscious, EGD and colonoscopy were performed in turn. If necessary, the nurse anesthetist empirically administered additional doses of alfentanil and propofol based on the patient's response during the procedures. In the TCI group, the patients were also given a dose of 2–2.5 mg of midazolam. Subsequently, we administrated propofol and alfentanil through an intravenous cannula utilizing a TCI system. The TCI system included two unit infusion pumps (Orchestra® Base Primea; Fresenius Kabi, Germany) controlled by a microprocessor system. The pharmacokinetic data distribution and elimination of propofol and alfentanil were programmed in the TCI system. We used the pharmacokinetic model proposed by Schnider et al. (15) for propofol and the model proposed by Scott et al. (16) for alfentanil. The patients received an initial target effect-site concentration of 4 µg/mL for propofol until loss of consciousness (loss of verbal contact) was achieved. This was immediately followed by a target effect-site concentration of 2.5 µg/mL. During the endoscopy procedures, the maintenance concentration was adjusted to 0.5 µg/mL higher or lower when needed. The target effect-site concentration was set at a constant dose of 35 ng/mL for alfentanil. Both infusions were terminated when the colonoscope reached the ileocecal valve. In both the TCI and control groups, small doses of 5–10 mg of ephedrine were administered intravenously to treat severe hypotension if needed. A face mask was used for assisted ventilation if the pulse oximetry value dropped below 90%. The face mask was discontinued upon the return of spontaneous respiration. After the endoscopy procedures were completed, the patients were sent to a recovery room for observation.

The patient data were recorded, including sex, age, height, weight, BMI, ASA classification, and propofol and alfentanil consumption. The endoscopy duration was calculated from the time the esophagogastroduodenoscope was inserted to the time the colonoscopy was completed. Adverse effects were also recorded, including movement in response to procedure stimulation during maintenance, awareness, hiccups, cough, cardiovascular side effects, inadequate respiration, nausea or vomiting, amnesia, and dizziness. Any interventions to restore normal physiology or respiration were noted. Immediate recovery was assessed by evaluating the patient's response recovery time. The time intervals at which the patients opened their eyes by verbal command, were able to follow a request to squeeze a nurse's hand, and were able to provide their date of birth were recorded. The sedation quality was assessed using the simplified quality of an anesthesia scoring system (Table 1) proposed by Ding et al. (17).

All statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) statistical software (IBM Corp. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Categorical parameters were compared using Pearson's chi-square test. We used the Kolmogorov–Smirnov test (K–S test) to confirm whether the continuous parameters fit a normal distribution. If the continuous parameters fit a normal distribution, we compared them further using Student's t-test,

Table 1. Quality of the anesthesia scoring system

Movement in response to procedure stimulation during maintenance	
None	0
Mild (procedure not interrupted), 1–2 times	5
Mild (procedure not interrupted), >2 times	10
Marked (procedure interrupted), 1–2 times	15
Marked (procedure interrupted), >2 times	20
Hemodynamic stability	
MAP* change <10% from baseline	0
MAP change 10%–20%	2
MAP change 20%–30% or HR >100 bpm	4
MAP change >30% or HR >120 bpm	6
Respiratory stability	
Mean $EtCO_2$† 30–40 mmHg	0
Mean $EtCO_2$ 40–50 mmHg or <30 mmHg	2
Mean $EtCO_2$ 50–60 mmHg	4
Mean $EtCO_2$ >60 mmHg or assisted ventilation (SpO_2 <95%)	6
Recovery time from end of procedure to eye opening on command	
<5 min	0
5–10 min	5
10–20 min	10
20–30 min	15
>30 min	20

*MAP: mean arterial pressure
†$EtCO_2$: end-tidal CO_2

Table 2. Demographic data*

	TCI† (n=50)	Control (n=50)	p value
Sex			0.69
Male	23 (46%)	25 (50%)	
Female	27 (54%)	25 (50%)	
Age (years)	50.0±13.5	51.4±14.2	0.60
Height (cm)	163.6±9.0	163.8±8.5	0.88
Weight (kg)	66.0±15.7	65.9±14.7	0.98
BMI‡	24.5±4.2	24.4±4.1	0.90
ASA§			0.72
1	30 (60%)	26 (52%)	
2	19 (38%)	23 (46%)	
3	1 (2%)	1 (2%)	

*Data are presented as means±standard deviations or numbers (%)
†TCI: target-controlled infusion
‡BMI: body mass index
§ASA: American Society of Anesthesiologists Physical Status classification

and other parameters were compared using the Mann–Whitney test (non-parametric, independent, two-group comparisons). All tests were two-tailed.

RESULTS

A total of 100 patients underwent both EGD and colonoscopy procedures. The demographic characteristics of the study participants are shown in Table 2. There were no significant differences between the TCI group and the control group with respect to sex (female: 54% vs. 50%), median age (50.0 vs. 51.4), body height (163.6 vs. 163.8), body weight (66.0 vs. 65.9), BMI (24.5 vs. 24.4), and overall distribution of ASA risk classifications. The Kolmogorov–Smirnov test was used to assess continuous variables, including age, body height, body weight, BMI, procedure time, total propofol dose, total alfentanil dose, and anesthesia quality score. The following continuous variables were not normally distributed: total propofol dose, total alfentanil dose, and anesthesia quality score. Therefore, we used the Mann–Whitney U test to compare these variables between the two groups.

The clinical characteristics of both study groups are shown in Table 3. No significant differences were noted between the TCI group and the control group with respect to procedure time (19.2 min vs. 21.3 min) and the incidences of cough (0% vs. 2%) and hiccups (0% vs. 2%). In the evaluation of respiratory stability, the incidence of severe respiratory depression [mean end-tidal CO_2 ($EtCO_2$) >60 mmHg or assisted ventilation] was higher in the control group (TCI group: 14% vs. control group: 24%); however, there were no statistically significant differences in the overall respiratory stability parameters between the study groups. In addition, none of the patients developed prolonged apnea (defined as cessation of breathing for 20 s or longer). The incidence of movement in response to procedure stimulation was significantly higher in the control group. No procedure-related colonoscopic perforations or other complications occurred in this study. TCI had a greater hemodynamic influence on the patients. Obvious declines in blood pressure were noted in the TCI group [mean arterial pressure (MAP) change >30% or heart rate (HR) >120 bpm: TCI group 54% vs. control group 28%). Two patients in the TCI group were treated with low doses of ephedrine because of severe hypotension. Awareness during the endoscopic procedure occurred in five patients in the control group. The recovery time was longer in the TCI group; however, all patients recovered within 20 min. No prolonged sedation was noted in either group. There were no significant differences between these groups with respect to nausea/vomiting, amnesia, and dizziness.

The TCI group had a higher propofol consumption (144.9 mg vs. 118.3 mg); however, the alfentanil consumption was lower (493.5 μg vs. 619.1 μg). There were no complications related to the anesthetic procedures in either group. The significantly lower anesthesia quality score in the TCI group (12.2 vs. 12.7) indicated that the anesthesia quality was better in this group.

DISCUSSION

Endoscopy is considered to be a useful diagnostic and therapeutic procedure for GI tract diseases; however, it can be an unpleasant as well as painful experience unless adequate sedation and analgesia are provided. Among the widely used sedative agents, propofol has remarkable advantages in comparison to benzodiazepines because of its rapid onset of action and faster recovery time. However, it is difficult to determine the optimal individual propofol dose for each patient. In addition, undesirable cardiovascular or respiratory side effects may occur when propofol is used with opioids. Although previous studies have revealed that propofol is safe when given by registered nurses without any involvement by anesthesia specialists, several patients may require a brief period of mask ventilation for the management of prolonged apnea (10,18-20). This side effect occurs because of the narrow therapeutic range and the lack of an antidote in cases of over-sedation and subsequent apnea. In addition, it is generally difficult to maneuver patients during EGD or colonoscopy when they have been sedated with propofol.

In our study, we have assessed the use of a TCI system for propofol and alfentanil administration during EGD and colonoscopy. We chose alfentanil as the analgesic agent because it is the only opioid for which a TCI model has been established. The results demonstrated that the TCI group had a significantly better sedation quality during the endoscopy procedures. Although significant hemodynamic changes in MAP were documented in the TCI group, the actual clinical significance of these changes is debatable. In two cases, the patients were treated for hypotension to prevent stroke because they had a history of poorly controlled hypertension. There were no cardiovascular complications in either group. To fasten induction, we empirically set a higher initial target effect-site concentration of 4 µg/mL for propofol. A reduction in MAP occurred immediately prior to or at the start of the endoscopy procedures. This reduction may have occurred because the mean total propofol dose was higher in the TCI group than in the control group, and propofol is known to have obvious dose-dependent cardio-depressant and vasodilatory effects. In addition, the patients may have been mildly because of the colonic preparation, which could exaggerate these blood pressure effects.

The incidence of movement in response to procedure stimulation was significantly higher in the control group. The procedures were more likely to be successful, and the patients required less repositioning in the TCI group. Awareness occurred in five control patients during the endoscopy procedures; however, none of the patients remembered the period of awareness when they awakened. This result indicates that TCI provided superior analgesia and sedation. There were no significant differences in the overall respiratory effects between the two groups; however, the incidence of treatment for desaturation caused by hypoventilation was higher in the control group. This finding may be due to the dose-dependent respiratory depression of alfentanil and the fact that the total alfentanil dose was higher in the control group. As expected, the patients in the TCI group had a longer recovery time be-

Table 3. Clinical data*

	TCI† (n=50)	Control (n=50)	p value
Procedure time (min)	19.2±4.3	21.3±7.9	0.10
Movement in response to procedure stimulation during maintenance			<0.05
None	39 (78%)	18 (36%)	
Mild (procedure not interrupted), 1–2 times	9 (18%)	28 (56%)	
Mild (procedure not interrupted), >2 times	1 (2%)	2 (4%)	
Marked (procedure interrupted), 1–2 times	1 (2%)	2 (4%)	
Marked (procedure interrupted), >2 times	0 (0%)	0 (%)	
Hemodynamic stability			<0.05
MAP‡ change <10% from baseline	2 (4%)	5 (10%)	
MAP change 10%–20%	5 (10%)	11 (22%)	
MAP change 20%–30% or HR >100 bpm	6 (32%) 1	20 (40%)	
MAP change >30% or HR >120 bpm	27 (54%)	14 (28%)	
Respiratory stability			0.44
Mean $EtCO_2$§ 30–40 mmHg	5 (10%)	4 (8%)	
Mean $EtCO_2$ 40–50 mmHg or <30 mmHg	38 (76%)	34 (68%)	
Mean $EtCO_2$ 50–60 mmHg	0 (0%)	0 (0%)	
Mean $EtCO_2$ >60 mmHg or assisted ventilation (SpO_2 <95%)	7 (14%)	12 (24%)	
Recovery time from end of procedure to eye opening on command			<0.05
<5 min	15 (30%)	40 (80%)	
5–10 min	25 (50%)	8 (16%)	
10–20 min	10 (20%)	2 (4%)	
20–30 min	0 (0%)	0 (0%)	
>30 min	0 (0%)	0 (0%)	
Cough	0 (0%)	1 (2%)	0.32
Hiccup	0 (0%)	1 (2%)	0.32
Awareness	0 (0%)	5 (10%)	<0.05
Alfentanil consumption (µg)	493.5±53.6	619.1±226.8	<0.05
Propofol consumption (mg)	144.9±27.1	118.3±38.7	<0.05
Anesthesia quality score	12.2±1.5	12.7±1.8	<0.05

*Data are presented as means±standard deviations or numbers (%)
†TCI: target-controlled infusion
‡MAP: mean arterial pressure
§$EtCO_2$: end-tidal CO_2

cause they received higher propofol doses; however, the difference in recovery time was small, and it should not affect the patient turnover time. Clinically, the significantly lower anesthesia quality score in the TCI group indicated that TCI provided more optimal sedation depth and more ideal analgesia.

A training guideline for the use of propofol in endoscopic examination has been published by the American Society for Gastrointestinal Endoscopy (21). The guideline proposes instructional and practical training in the pharmacology of propofol and airway management provided by anesthesiologists as a part of a formal educational module. However, the majority of sedation administrators never attend formal courses. In addition, although there are some firm foundations in a number of high-quality audit products, the current guidelines are consensus documents based on a combination of expert opinion and first principle analysis. Therefore, it is difficult to differentiate between "good" and "bad" practice, and the nature of the evidence is not sufficiently solid to overcome the various difficulties that impede valid changes in practice. In our study, we used the anesthesia quality score to evaluate the quality of different sedation regimens. Although the plasma concentration of the drugs may not have been predicted accurately, the TCI system can make proportional changes in the concentration, which permits rapid titration of the drug concentration to good effect. This feature helped the practitioners to provide high-quality sedation and analgesia with propofol and alfentanil in patients with different ages. In addition, this method resulted in fewer undesired side effects. Our study showed that in comparison to sedation by manual administration, the TCI system provided a better sedation quality during the endoscopy procedure.

There are some limitations to our study. First, neither the nurse anesthetists nor the endoscopists were blinded. This limitation may have resulted in the Hawthorne effect, which can influence the quality of sedation. However, it is difficult to blind the nurse anesthetists and endoscopists. Second, the target effect-site concentrations of propofol and alfentanil were determined empirically and may not be optimal for endoscopy procedures. In fact, it was difficult to determine the optimal concentrations because the different skills of the endoscopists may influence the required sedation and analgesia intensity. A fixed target effect-site concentration would not be appropriate for different endoscopists. Third, this study was performed in a tertiary hospital; however, there is no reason to believe that the results cannot be applied to most hospitals and most endoscopists.

In summary, our study showed that sedation using TCI for GI endoscopy provided effective and safe sedation and was associated with better sedation quality. The depth of sedation appeared to be appropriate and allowed the patients to be easily maneuvered during the procedures. We believe that TCI can be used to provide routine sedation for patients undergoing GI endoscopy. However, additional studies are needed to evaluate the performance of TCI sedation administered by non-anesthesiologists and nurses.

Ethics Committee Approval: Ethics committee approval was received for this study.

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

Peer-review: Externally peer-review.

Author contributions: Concept - S.Y.P., T.C.T., Y.T.C.; Design - H.H., S.Y.P., Y.T.C.; Supervision - Y.M.C., K.P.C.; Resource - Y.M.C., K.P.C.; Materials - T.C.T.; Data Collection &/or Processing - T.C.T., Y.T.C., H.H.; Analysis &/or Interpretation - Y.T.C., H.H., S.Y.P.; Literature Search - Y.T.C., H.H., S.Y.P.; Writing - Y.T.C., T.C.T., H.H.; Critical Reviews - S.Y.P., K.P.C., Y.M.C.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that the study had no financial support.

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