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# Target Controlled Infusion for non-anaesthesiologist propofol sedation during gastrointestinal endoscopy: The first double blind randomized controlled trial

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ABSTRACT

*Background:* Target Controlled Infusion is a sophisticated tool for providing optimal sedation regimen avoiding under or oversedation in gastrointestinal endoscopy.
*Aims:* To compare standard moderate sedation vs. non-anaesthesiologist-administered propofol sedation during gastrointestinal endoscopy.
*Methods:* Randomized controlled trial of 70 consecutive colonoscopies and 70 consecutive esophagogastroduodenoscopies (EGD). Standard group ($n=70$), received fentanyl (1 μg/kg) + midazolam (0.03–0.04 mg/kg) or midazolam only; propofol group ($n=70$), received fentanyl (1 μg/kg) + propofol Target Controlled Infusion (1.2–1.6 μg/ml) or propofol Target Controlled Infusion only. Discharge time, endoscopist satisfaction and patient satisfaction were recorded in all endoscopies.
*Results:* Colonoscopy: discharge time was significantly shorter in the propofol than the standard group (1.1 ± 0.3 vs. 5 ± 10.2 min, respectively; $P=0.03$). Endoscopist satisfaction was significantly higher (98.3 ± 11.4/100 vs. 87.2 ± 12/100; $P=0.001$); patient satisfaction was significantly higher (95 ± 9.3/100 vs. 85.5 ± 14.4/100; $P=0.002$) in the propofol compared to the standard group.
EGD: discharge time was not significantly different in the propofol and standard groups (1.1 ± 0.7 vs. 3.9 ± 9.2 min, respectively; $P=0.146$). Endoscopist satisfaction was significantly higher (92.7 ± 14.3/100 vs. 82.8 ± 21.2/100; $P=0.03$); patient satisfaction was significantly higher (93.8 ± 18.2/100 vs. 76.5 ± 25.2/100; $P=0.003$). In the propofol group 94.3% of patients vs. 71.4% of patients in standard group asked to receive the same sedation in the future ($P=0.021$).
*Conclusion:* Target Controlled Infusion is a promising method for non-anaesthesiologist-administered propofol sedation.


## 1. Introduction

Several anaesthesiological strategies have been devised for patients undergoing gastrointestinal endoscopy, ranging in a continuum from mild conscious sedation to general anaesthesia.

Optimal sedation should provide the highest degree of comfort together with the highest degree of safety. Although sedation is widely employed for gastrointestinal endoscopy, the appropriate level of sedation in this setting has not yet been established and a debate is ongoing on the possibility of non-anaesthesiologists providing sedation [1,2].

Moderate sedation during esophagogastroduodenoscopy (EGD) or colonoscopy is commonly provided by intravenous opioids and/or benzodiazepines boluses, but it may also be induced and maintained with a combination regimen using propofol. Propofol introduction into clinical practice radically changed physicians' and patients' attitudes towards sedation, so its popularity for use in gastrointestinal endoscopy has steadily increased worldwide.

One of the main advantages of propofol is its fast recovery time (RT). The major concern regarding propofol is its narrow therapeutic range because of the risk of apnoea. In fact propofol can easily run deeper from moderate to deep sedation. This is often

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the case when painful procedures are attempted, since propofol is devoid of analgesic properties. To counteract this occurrence, balanced propofol sedation (BPS) has been implemented. BPS combines propofol with small doses of opioids and/or benzodiazepines aiming at enhancing sedation effectiveness while minimizing the adverse effects of each drug, which can be administered in lower doses.

A further significant improvement in propofol sedation has been reached with the introduction of the Target Controlled Infusion (TCI) System, one of the most sophisticated systems for providing effective and safe propofol sedation and avoiding both under- and oversedation. This automated system applies algorithms, which take into account age, weight and the desired plasma propofol concentration to determine the optimal drug infusion rate. This avoids any serum peak concentration responsible for serious side effects [3].

In two previous prospective trials, we reported our routine clinical practice with propofol TCI, titrated to a deep level of sedation, providing effective and safe sedation in endoscopic retrograde cholangiopancreatography and upper endoscopic ultrasound [4,5]. In these works sedation was administered by anaesthesiologists.

On the other hand, the issue of non-anaesthesiologist propofol sedation (NAPS) during gastrointestinal endoscopy has recently raised much interest. Since concerns about its safety have been raised [6–9], it is conceivable that TCI would help in improving the safety and effectiveness of propofol during NAPS.

Our study aimed at comparing propofol TCI and midazolam i.v. boluses with respect to their effectiveness and safety for maintaining moderate sedation during esophagogastroduodenoscopies and colonoscopies. Both sedation regimens were administered by the endoscopist. Our primary end-points were patient's and endoscopist's satisfaction about the sedation regimen.

## 2. Methods

### 2.1. Study protocol

This randomized double-blind controlled trial involved 140 consecutive outpatients scheduled to undergo EGD or colonoscopy from February 2014 to May 2014 (ClinicalTrials.gov registration number: NCT02062177).

Approval by the local Ethics Committee was obtained before the beginning of the study and written informed consent was obtained from all patients at time of enrolment.

Exclusion criteria were: clinically significant systemic disease (American Society of Anaesthesiologists (ASA) risk class III–IV), morbid obesity (BMI $\geq$ 30), severe sleep apnoea, predictably difficult airway management, Mallampati score >2, history of allergic reactions to study drugs, chronic use of opioids, psychiatric disorders, pregnancy, age <18.

All procedures were performed by a single experienced endoscopist (LF) using a standard technique with a high definition video-endoscope (Pentax, Hamburg, Germany). The endoscopist had performed more than 100 propofol sedations during endoscopy before and was experienced in airway management and resuscitation (ACLS-certified). Patients were kept in the left lateral decubitus.

Propofol (Diprivan®, AstraZeneca, Italy) was administered by a TCI pump (Terufusion-TIVA/TCI TE372 Terumo Europe N.V., Leuven, Belgium) making use of the Marsh TCI model (Diprifusor™ AstraZeneca, Macclesfield, UK) [10].

On patient's arrival in the endoscopy suite a peripheral intravenous cannula was inserted. Throughout endoscopy electrocardiogram and pulse oximetry (SpO2) were continuously monitored, and non-invasive arterial blood pressure was monitored every 5 min.

Sedation was administered, under the endoscopist's supervision, by a gastroenterology attending fellow (GR) not directly involved in the procedure, who was the only one not blinded towards the randomized sedation regimen.

In our Unit, all medical and nursing staff members are ACLS-certified and have received non-anaesthesiologist training for sedation for gastrointestinal endoscopy, including the basic principles of sedation and practical training in NAPS. GR was trained in propofol administration and advanced cardiac life support, developed a long-standing interest in sedation during gastrointestinal endoscopy and has been collaborating in clinical and research activity on this issue for the past four years.

Sedation depth was evaluated by the gastroenterology fellow using the Observer's Assessment of Alertness/Sedation Scale (OAAS, Supplementary Figure S1), ranging from 1 (asleep/unarousable) to 5 (awake/alert) [11], registered at baseline and every 5 min during and after endoscopy until discharge. Supplemental oxygen was not routinely administered.

On arrival in the endoscopy suite patients were randomly assigned to one of two groups according to a previously computer-generated list (Fig. 1).

Group S (standard midazolam sedation): Intravenous bolus 0.04 mg/kg if aged <70, 0.03 mg/kg if aged $\geq$70, followed by 1 mg i.v. boluses up to a maximum of 5 mg.

Group P (propofol TCI sedation): Target concentration was initially set at 1.2–1.6 μg/ml (side effect concentration), according to patient's body weight and general condition, then titrated with 0.1 μg/ml increments up to a maximum of 2 μg/ml. Thereafter, if any moderate/severe pain or discomfort appeared, normal saline placebo i.v. boluses were administered to maintain blinding of patient and endoscopist.

Patients in both groups undergoing colonoscopy received also i.v. fentanyl (1 μg/kg) for pain control.

The decision to start procedure was taken by endoscopist taking into account the ongoing level of sedation (OAAS < 3), body movements and vital signs. During EGD, tongue relaxation and gagging suppression during endoscope insertion were considered signs of adequate sedation.

Because of the well-known different physical appearance of study drugs, a fabric curtain was drawn across the patient's arm, concealing the i.v. line and the TCI pump both to the patient and to the endoscopist.

During EGD, sedative administration was discontinued upon completion of the exam.

During colonoscopy, moderate sedation was maintained throughout the scope-in phase, the most painful phase of the procedure, whereas sedative administration was discontinued upon caecal intubation.

We recorded the following endoscopy timing data: time from insertion of endoscope to the reaching of caecum, time from insertion of endoscope to its withdrawal, time to obtain biopsies or to perform polypectomy. Drug administration and complications were also recorded.

In both groups the administration of sedatives was temporally stopped if one of the following "safety end points" was reached: SpO2 < 90%, mean arterial pressure (MAP) < 60 mmHg, heart rate (HR) < 50 or >110 b/min for at least 1 min and any change in heart rhythm.

After endoscopy, patients were transferred to a recovery area and evaluated every 5 min until they were ready to be discharged from Endoscopy Unit. Recovery was assessed using the Modified Aldrete Scoring System: patients were considered fit to discharge when they achieved a score of 18 or more, had stable vital signs, were able to tolerate oral fluids, had no nausea, vomiting, or itching and could walk unaided [12].