

# Does propofol mode of administration influence psychomotor recovery time after sedation for colonoscopy: A prospective randomized assessor-blinded trial

## ABSTRACT

**Background:** Propofol sedation has become increasingly popular for colonoscopy. Different modes of propofol administration have been described, but their influence on psychomotor recovery time remains largely unknown. This prospective randomized assessor-blinded study tested the hypothesis that target-controlled infusion system (TCI) combined with sedation depth monitoring should be associated with a more stable sedation than intermittent bolus application with clinical monitoring of sedation depth, resulting in a faster psychomotor skills recovery. **Methods:** One hundred sixty-four patients undergoing colonoscopy were randomized to receive propofol with the former (TCI group) or the latter (bolus group) mode of administration. Psychomotor skill recovery was assessed using the Choice Reaction Time (CRT) performed before and every ten minutes after waking up from propofol sedation. Clinical recovery was also assessed using the modified Post-anesthetic Discharge Scoring System (PADS). **Results:** Induction and wake up times were longer in the TCI group, where patients received more propofol than those in the bolus group. Evolution of CRT was similar in both groups. Twenty minutes after arrival in the post-anesthesia care unit, 35 (49%) of patients in the TCI group and 43 (54%) in the bolus group achieved CRT values equal or shorter than their baseline values. Interestingly, according to the PADS score, most of the patients were considered fit for discharge at that moment. Incidence of adverse event was not different between groups. **Conclusion:** In the conditions of our study characterized by short procedure duration, target-controlled infusion of propofol does not offer any benefit in terms of psychomotor skills recovery over intermittent bolus application.

**Key words:** Colonoscopy; propofol; recovery

## Introduction


Colonoscopy is often considered as an unpleasant procedure frequently associated with abdominal pain, cramping, and bloating. In western countries, most of these endoscopic procedures are performed under some form of sedation,

which has been shown to enhance endoscopist satisfaction and to increase the compliance of the patient to undergo the procedure again.<sup>[1]</sup> Propofol sedation has become increasingly popular because of its unique pharmacokinetic properties,

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making endoscopy almost painless, with a predictable and rapid wake-up process.<sup>[1]</sup> Propofol sedation is associated with relatively good cognitive function and psychomotor skills recovery.<sup>[2,3]</sup> However, the time required for complete recovery of cognitive and psychomotor functions remains undetermined.

Adequate propofol sedation (i.e., loss of consciousness and decreased spontaneous movements) can be achieved either with the traditional intermittent bolus application, manually controlled infusion or target-controlled infusion, all of them being considered as safe.<sup>[4,5]</sup> The impact of the mode of administration of propofol on psychomotor and cognitive function recovery time remains largely unknown. On a theoretical point of view, target-controlled infusion systems (TCI) combined with sedation depth monitoring should offer a more stable plasmatic concentration than intermittent bolus application, which will result in more frequent peak plasmatic concentrations. As a result, faster cognitive and psychomotor recovery might be expected with the target-controlled infusion system. We tested this hypothesis in a prospective randomized assessor-blinded study: our primary objective was psychomotor skill recovery assessed by the "Choice Reaction Time (CRT)", which has been shown to provide sensitive assessments of progressive psychomotor performance impairment with increasing blood concentration of propofol.<sup>[6]</sup> Our secondary objectives include cognitive function recovery assessed with the Digital Symbol Substitution Test (DSST) and clinical recovery evaluated by the modified Post-anaesthetic Discharge Scoring System (PADS score).

## Methods

Our study was conducted from February 2015 to February 2020 at the outpatient surgical clinic of the Brugmann University Hospital, Brussels, Belgium. The protocol and consent document were approved by our institutional Ethic Committee (CE 2014/175) and the study was registered at [clinicaltrials.gov](http://clinicaltrials.gov) (NCT 02314559). Patients aged 18 to 80 years, with an American Society of Anaesthesiologist (ASA) physical status score between 1 and 3, undergoing elective outpatient colonoscopy were eligible. Exclusion criteria were the presence of a neuropsychic disorder, language barrier, the realization of combined procedures, the suspicion of full stomach, pregnancy and known allergy to propofol or soja.

Patients were assigned sequential study numbers and randomized using a computer-generated table in a 1:1 ratio to receive propofol either through intermittent bolus application (bolus group) or target-control infusion (TCI group). A member of the team who did not participate in the study

numbered 180 opaque envelopes and inserted the group assignments into the corresponding envelopes. He also created a document specifying the assignment to the group contained in each envelope. The envelopes and this document were kept secret from the members of the team involved in the study until the statistical analysis was carried out. As soon as a patient was enrolled, the anesthesiologist responsible for sedating the patient during the examination opened the corresponding envelope and noted only this number on the data recording document. The anesthesiologist in charge of evaluating the patient was not authorized to be present in the examination room. The patient was never informed of the sedation technique used, and the induction sequence was systematically performed outside his field of vision. Patients and anesthesiologists in charge of his evaluation were therefore blinded.

Eligible patients having signed an informed consent were admitted 60 min before the colonoscopy. At their arrival, the CRT and the DSST tests are explained to them. Then, they realized a blank CRT test (not recorded) to familiarize themselves with it. Finally, recording of data begins with the realization of a DSST and a CRT test, just before admission to the endoscopy room. There, they were taken in charge by a consultant anesthesiologist: they were equipped with routine monitoring including non-invasive blood pressure, a three-lead EKG and a pulse oximeter (SpO<sub>2</sub>; Philips MP5 station, Eindhoven, The Netherlands). Vital parameters were recorded every 5 min. A peripheral intravenous catheter was inserted, and the patients were perfused with Ringer's lactate solution. They also received oxygen 3 L/min through a nasal catheter. Patients randomized in the TCI group were also equipped with an entropy monitoring to assess the sedation depth (Acertis SA, Belgium). Then all patients were positioned in the left lateral decubitus. They were all sedated with propofol (AstraZeneca NV, Dilbeek, Belgium) only. No other analgesic or sedative was allowed, before or during the procedure.

In the bolus group, patients were sedated according to our routine protocol: they received a first bolus of 1 to 1.5 mg/kg, followed by additional intermittent boluses of 20 to 50 mg to maintain a sedation score of 5 on the Ramsay scale. No bolus was allowed after the gastroenterologist has reached the caecum with his endoscope or an eventual polyp has been resected.

In the TCI group, propofol was administered through a "PK" electric syringe pump (Alaris, Switzerland), using the pharmacokinetic model of Schnider to maintain the entropy value close to 60. At induction, the target site effect concentration was fixed at 3 mcg.mL<sup>-1</sup>. Effect-site

propofol concentration could be adapted through steps of 0.2 to 0.5 mcg.mL<sup>-1</sup>. Site-effect concentration has to be maintained between 1 and 6 mcg.mL<sup>-1</sup>. Infusion of propofol was stopped once the gastroenterologist has reached the caecum with his endoscope or an eventual polyp has been resected.

The patient was transferred to the post-anesthesia care unit (PACU) once he opened his eyes on the examination table.

Immediately after admission to the PACU, the patient realized a second CRT test. This test was repeated 4 times at 10 min intervals. The patient performed a second DSST test immediately after the last CRT test. The patient was also assessed by the nursing staff using the PADS score performed every ten minutes. This test is performed routinely in our institution to evaluate the ability of the patient to return safely at home with an attendant. The patient was considered “fit for discharge” after he obtained two PADS scores equal or above 9 (10-point scale).

Data collected pre-operatively were age, weight, gender, ASA score. Time to achieve adequate sedation level (induction time), time to eye opening after propofol administration was stopped (wake up time) time between eye-opening and first CRT in PACU (transfer time) have been registered, together with total propofol dose. Length of the procedure was estimated through the duration of propofol administration. Episodes of hypotension (defined as a decrease of more than 20% of the mean arterial pressure compared to baseline value), desaturation (SpO<sub>2</sub> <90%), and any respiratory outflow tract obstruction during the colonoscopy and in the PACU were also collected. The quality of sedation was evaluated at the end of the procedure by the gastroenterologist, who was not blinded to the propofol mode of administration, and by the patient when leaving the PACU, using a 11-point visual analog scale.

### Statistical analysis

A sample size estimation was carried out based on intermediate data: to demonstrate a 20% difference in CRT between the two groups in favor of the TCI group (90% versus 70%) twenty minutes after arrival in the PACU with a power of 0.90 and an alpha of 0.05 taking into account a 20% drop-out rate, 160 patients should have been recruited.

Parametric data were compared using a Student's *t* test and presented as mean ± standard deviation. When the residuals of the *t* test are not normally distributed, nonparametric data were compared using the Mann–Whitney *U* test and

presented as median [interquartile range]. Dichotomous variables were compared using the Chi-square test and presented as numbers (percentages).

For the primary outcome, we planned to determine if groups had comparable variances with Bartlett's test for homogeneity of variance and if the residuals of the *t*-test were normally distributed. In the case of non-normal distribution, a non-parametric approach would be used with the R package nparcomp<sup>[7]</sup> to take into account the non-parametric Behrens-Fisher problem.<sup>[8]</sup> This package tests whether the observations in one group tend to be different than those of another. If the 95% confidence interval does not contain 0.5 the two groups are significantly different.

A linear mixed model<sup>[9]</sup> was used to model the relationship of CRT through time in both groups, using a maximum likelihood approach, given a few missing data. We looked at the residuals of the model (QQ-plot), and the results indicate they were normally distributed.

Statistical analyses were performed using Minitab program (Paris, France) and software R, version 3.6.2 (R Core Team, 2019).

A *P* value < 0.05 was considered statistically significant.

## Results

Between February 2015 to February 2020, 184 patients were screened for inclusion in the study, of whom 164 were randomized. Ten patients were excluded for different reasons [Figure 1] leaving 79 patients sedated with intermittent bolus application and 75 with target control infusion.

Table 1 illustrates the demographic and clinical data of the studied population. The two groups were not different at baseline. Induction time and wake up time were significantly longer in the TCI group, while transfer time was similar in both groups. Patients in the TCI group received more propofol than those in the bolus group.

Gastroenterologists appeared more satisfied with the intermittent bolus application approach than with the target-control infusion strategy. Patients were highly and equally satisfied with the two propofol modes of administration.

Results of the study primary outcome are presented in Table 2. There was no difference in CRT between the two

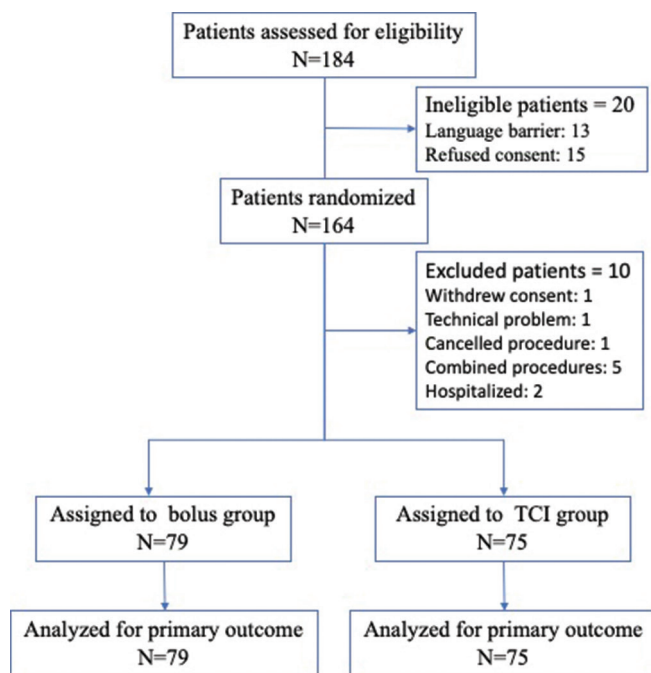


Figure 1: Consort flow diagram of the study

groups 20 min after arrival in the PACU. Absolute and relative changes from baseline values were also not different between the two groups. Figure 2 reported the evolution of the results of the CRT test in both groups at the different time points. The longitudinal data analysis did not reveal any group effect ( $P = 0.468$ ). However, it demonstrated a significant negative time effect ( $P < 0.001$ ), suggesting a decrease in CRT over the study period.

Table 3 presents the results of our secondary and safety outcomes. There was no significant difference between the two regarding DSST measured before the procedure and 40 min after arrival in the PACU. Interestingly, time to obtain to PADS equal or above 9 was 20 min in both groups. Incidence of adverse event was not different between groups.

## Discussion

In the conditions of our study, psychomotor skill recovery assessed by the “Choice Reaction Time (CRT) was influenced by the mode of administration of propofol. To our knowledge, this is the first study comparing intermittent bolus application to target-control infusion of propofol with no concomitant administration of other sedatives or analgesics.

These results might be explained by the speed of the colonoscopy. Although we did not directly measure the duration of the procedure, we could estimate it through the time of propofol administration. The fact that the procedure was quite short does not allow us to demonstrate the

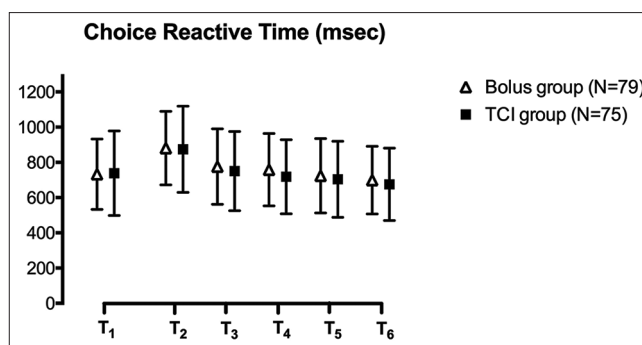


Figure 2: Choice reactive time (expressed in msec) at each measurement time point in the two groups

Table 1: Demographic and clinical data

	Bolus group (n=79)	TCI group (n=75)	P
Age (years)	58 [43-67]	59 [49-65]	0.990
Male gender (%)	32 (41)	37 (49)	0.271
BMI (kg.m <sup>2</sup> )	26±5	26±5	0.921
ASA score (%)			0.658
1	29 (36)	32 (43)	
2	45 (57)	40 (53)	
3	5 (7)	3 (4)	
Heart rate (b.min-1)			
Baseline	79 [72-86]	79 [72-85]	0.823
PACU	71 [65-77]	73 [67-79]	0.259
Mean arterial pressure (mmHg)			
Baseline	90 [82-97]	93 [85-100]	0.246
PACU	77 [74-91]	83 [73-90]	0.427
SpO <sub>2</sub> (%)			
Baseline	100 [98-100]	100 [98-100]	0.583
PACU	98 [96-100]	98 [97-100]	0.867
Induction time (sec)	75 [59 to110]	180 [125-233]	<0.001
Wake up time (sec)	246 [146-352]	318 [217-420]	0.001
Propofol administration (min)	14 [10-19]	16 [13-25]	0.004
Transfer time (min)	8 [6-10]	8 [6-10]	0.761
Propofol total dose (mg.kg <sup>-1</sup> )	3.1 [2.5-4.2]	3.7 [2.7-4.8]	0.045
Satisfaction rate*			
Gastroenterologist	9 [8-10]	8 [8-9]	<0.001
Patient	10 [9-10]	10 [9-10]	0.761

Data are presented as mean±SD, median [interquartile], or numbers (%). ASA: American Society of Anesthesiologist physical status score; PACU: Post-anesthesia Care Unit; SpO<sub>2</sub> peripheral oxygen saturation measured by pulse oximetry. \*Using a 10-points visual analog scale

advantages of a target control infusion strategy in terms of sedation stability and avoidance of drug accumulation. Although time of propofol administration appeared somewhat longer in the TCI group, this might be related to the different mode of administration rather than a longer procedure in this group. Whatsoever, a 2-minute difference between the two groups does not appear to be really clinically relevant. Our results might also be explained by the expertise of the anesthesiologists in charge of the colonoscopies. As

**Table 2: Primary outcome**

	<b>Bolus group (n=79)</b>	<b>TCI group (n=75)</b>	<b>P</b>	<b>95% CI</b>
CRT 20 min after arrival in PACU (msec)	706 [580-906]	668 [565-789]	0.193	0.346-0.531
Change from baseline (msec)	22 [-50-87]	1 [-77-66]	0.131	0.337-0.521
% change from baseline (%)	2.5 [-6.3-11.8]	-0.1 [-9.2-9.5]	0.131	0.337-0.521

Data are presented as median [interquartile]. CRT: Choice reaction time

**Table 3: Secondary and safety outcomes**

	<b>Bolus group (n=79)</b>	<b>TCI group (n=75)</b>	<b>P</b>
DSST			
T0	32 [27-41]	30 [25-42]	0.737
T6	34 [25-42]	34 [26-44]	0.664
PADS			
Fit for discharge (min)*	20 [10-20]	20 [10-20]	0.410
Intra-operative			
Upper airway obstruction (%)	5 (6.3)	4 (5.3)	0.792
Hypotension (%)	39 (49)	38 (51)	0.377
Desaturation (%)	1 (1.3)	1 (1.3)	1
Post-operative			
Hypotension (%)	17 (22)	21 (28)	0.351
Desaturation (%)	0	1 (1.3)	0.487

Data are presented as median [interquartile] or number (%). DSST: digital symbol substitution test; PADS: modified Post-Anesthesia Discharge Scoring System. \*time to achieve two consecutive PADS equal or superior to 9 (10-points scale)

the intermittent bolus administration was standard practice in our institution, they may have been more familiar with this approach than with the target-controlled infusion. However, the duration of the study was long enough for anesthesiologists to get expertise with this strategy. The target sedation level might have been different between the two groups, as the sedation depth was measured with two different techniques in the two groups. However, a good correlation has been found between the Ramsey score used in the bolus group and the entropy value used in the TCI group.<sup>[10]</sup>

Interestingly, gastroenterologists were more satisfied with the intermittent bolus approach. This might be explained by the longer induction and wake-up times observed in the TCI group.

The longer induction and wake-up time observed in our study are in line with those of Riphaut *et al.*<sup>[11]</sup> comparing the two approaches for deep sedation during long-lasting interventional endoscopy. The longer induction time observed in the TCI group can be attributed to the fact that the initial bolus dose delivered by the infusion system is administered more slowly than the one given by the anesthesiologist in the intermittent bolus application group. A higher initial target concentration could have been associated with a reduction in the induction time. The longer wake-up time reported in the TCI group could be explained by the higher

reactivity of the anesthesiologist in the bolus group. Indeed, in this group, the anesthesiologist will titrate more easily the boluses to be administered according to the evolution of the colonoscopy, to stop any administration once the gastroenterologist reached the caecum with his endoscope or an eventual polyp has been resected, than in the TCI group, where the continuous administration of propofol to target a pre-defined entropy value will be stopped only at that moment. The higher dose of propofol administered in the TCI group represents an argument in favor of this hypothesis. Again, the short duration of the procedure could have played a role as Riphaut *et al.*<sup>[11]</sup> did not report such difference in the amount of propofol administered for long-lasting endoscopy.

In our center, the patients are considered “fit for discharge” when two successive PADs equal or above 9 are reported by the nursing staff, as this has been recommended by Trevisani *et al.*<sup>[12]</sup> and Chung *et al.*<sup>[13]</sup> Interestingly, most of the patients were considered fit for discharge after a 20 min length of stay in the PACU. However, at that moment, 43 (54%) patients in the bolus group and 35 patients in the (49%) in the TCI group have CRT values equal or shorter than their baseline values. Interestingly, at the end of the study period (i.e., 40 min after admission in the PACU) 36 patients (20 in the bolus group and 16 in the TCI group) did not fully recover their baseline CRT values. In a randomized controlled study, Riphaut *et al.*<sup>[14]</sup> observed that patients undergoing endoscopic procedures of about 12 min fully recovered psychomotor (evaluated by the number connection test) and driving (evaluated by a driving simulator test) skills 2 hours after their endoscopy.

Incidence of side effects, defined as episodes of hypotension, and/or desaturation and/or upper airway tract obstruction was not different between groups. These results are in line with those reported by Riphaut *et al.*<sup>[11]</sup>, although we might have expected more side effects in the bolus group due to abrupt changes in plasma propofol concentration. Procedures of short duration and skill of anesthesiologists may also have played a role.

The main strength of this prospective randomized assessor-blinded study was to use the CRT to compare the psychomotor recovery of two different mode of administration of propofol. This test has been shown to be

one of the most sensitive and reliable methods to assess the effect of blood propofol concentration on psychomotor performance. Main limitations of this study include its monocentric design that restrains generalization of the observed results, and the absence of a similar monitoring of sedation depth in the two groups.

In conclusion, in the conditions of our study target-control infusion approach does not offer any advantage on psychomotor and clinical recovery after propofol sedation for short procedures. Future studies are required to assess the impact of different mode of propofol administration on patient's recovery after long-lasting endoscopy.

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### Conflicts of interest

There are no conflicts of interest.

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