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ORIGINAL INVESTIGATION

Safety and efficacy of target-controlled infusion versus intermittent bolus administration of propofol for sedation in colonoscopy: a randomized controlled trial

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Abstract

Background: Our objective was to compare the safety and efficacy of Target-Controlled Infusion (TCI) versus intermittent bolus of propofol for colonoscopy sedation.

Methods: We conducted a randomized (1:1), single-blind, parallel-group superiority trial with fifty ASA I or II patients, both sexes, aged 18 to 65 years, Body Mass Index $\leq$ 30 kg.m^{-2}, undergoing colonoscopy, allocated to receive propofol by TCI (effect-site, 2 μg.mL^{-1} plus 0.5 μg.mL^{-1} until unconsciousness and as necessary for agitation) or intermittent bolus (1 mg.kg^{-1} plus 0.5 mg.kg^{-1} every 5 minutes or as above). The primary safety outcome was the need for airway maneuvers and the primary efficacy outcome was the need for interventions to adjust the level of sedation. Secondary outcomes included incidence of agitation, propofol dose, and time to recovery.

Results: The median (IQR) number of airway maneuvers and interventions needed to adjust sedation was 0 (0–0) vs. 0 (0–0) ($p = 0.239$) and 1 (0–1) vs. 3 (1–4) ($p < 0.001$) in the TCI and control groups, respectively. Agitation was more common in the intermittent bolus group – 2 (0–2) vs. 1 (0–1), $p < 0.001$. The mean $\pm$ SD time to recovery was 4.9 $\pm$ 1.4 minutes in the TCI group vs. 2.3 $\pm$ 1.6 minutes in the control group ($p < 0.001$). The total propofol dose was higher in the TCI group (234 $\pm$ 46 μg.kg^{-1}.min^{-1} vs. 195 $\pm$ 44 μg.kg^{-1}.min^{-1} ($p = 0.040$)).

Conclusions: During colonoscopy, TCI is as safe as intermittent bolus of propofol while reducing the incidence of agitation and the need for dose adjustments. However, intermittent bolus administration was associated with lower total propofol dose and earlier recovery.

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Introduction

Colonoscopy is indicated for diagnostic and therapeutic purposes in several colorectal disorders.[1] However, colonoscopy is considered an invasive procedure and is associated with discomfort. The patient's fear of experiencing pain can result in anxiety and uncooperativeness.[2] Therefore, the use of intravenous sedation is widely recommended. Although a combination of a benzodiazepine and an opioid may be used, propofol is usually the agent of choice, as it is associated with rapid arousal, shorter postanesthetic recovery time, and higher patient satisfaction.[3]

The conventional technique for propofol sedation in colonoscopy involves manual administration of intermittent boluses. This leads to fluctuations in plasma concentration of the anesthetic agent and may therefore be associated with undesirable effects such as agitation and respiratory depression[4] due to insufficient and excessive depths of anesthesia, respectively. Conversely, in target-controlled infusion regimens, the dose is automated to reach and maintain a pre-set concentration,[5] which can be titrated according to the patient's response, reducing the fluctuations associated with the conventional technique. Target-controlled infusion is now a well-established technique for administering total intravenous anesthesia in the operating theatre,[6] but can also be useful for outpatient procedures requiring sedation. Research has shown that the target-controlled infusion of propofol increases the safety of sedation for outpatient procedures by reducing the incidence of respiratory depression.[7] However, few studies have compared target-controlled infusion with the conventional intermittent bolus technique in colonoscopy.

The present study was thus designed to compare the safety and efficacy of target-controlled propofol infusion versus the intermittent manual bolus technique for sedation during colonoscopy. The hypothesis was that target-controlled infusion would result in less need for interventions (such as dose adjustments and airway maneuvers), reduced agitation, and no increase in respiratory depression during the procedure.

Methods

Study design

Randomized (1:1), single-blind, parallel-group superiority trial.

Inclusion criteria

Inclusion criteria were age between 18 and 65 years, ASA (American Society of Anesthesiologists) physical status I and II, Body Mass Index less than or equal to 30 $kg.m^{-2}$, scheduled for elective colonoscopy. Patients with a known allergy to any of the drugs used for sedation were excluded, as were those with a history of chronic alcohol, benzodiazepine, or opioid use. The clinical phase of the trial was carried out in a tertiary hospital in Cuiabá, Mato Grosso, Brazil, first from October 2017 to February 2018 and, subsequently, in September and October 2020.

Interventions

Ethical approval for this study (Plataforma Brasil certificate n° 58452416.0.0000.8055) was provided by the Ethical Committee of the Federal Institute of Education, Science and Technology of Mato Grosso (IFMT), Cuiabá, MT, Brazil (chairperson Marilu Lanzarin) on August 11, 2017, and registered in the Brazilian Registry of Clinical Trials with accession number RBR-2dxshp (https://ensaiosclinicos.gov.br/rg/RBR-2dxshp). The provisions of the CONSORT statement were followed throughout. After ethical approval had been obtained, 50 patients were selected and allocated randomly (1:1) by one member of the care team using the sealed opaque envelope method into two groups, depending on the sedation regimen: target-controlled infusion (experimental group) or intermittent manual bolus (control).

During the preanesthetic evaluation, patients scheduled to undergo colonoscopy were informed of the study and invited to participate; those who agreed then signed an informed consent form. In the endoscopy suite, patients were placed on multi-parameter monitoring (ECG, pulse oximetry, noninvasive blood pressure) and received oxygen via a nasal cannula (2 $L.min^{-1}$). Peripheral venous access was established with a 22G cannula. Due to the substantial differences between the two sedation techniques, blinding the anesthesiologist responsible for patient care was impossible.

Patients in the target-controlled infusion group were sedated with a single bolus of intravenous (IV) fentanyl, 1 $\mu g.kg^{-1}$, followed by target-controlled infusion of propofol with an initial target of 2 $\mu g.mL^{-1}$ and titrated in 0.5 $\mu g.mL^{-1}$ increments until loss of responsiveness to tactile stimulation, corresponding to a score of 1 on the Observer's Assessment of Alertness/Sedation (OAA/S) Scale.[8] (Table 1). Colonoscopy was begun once the target level of sedation had been achieved. If the patient developed agitation at any time during colonoscopy, additional 0.5 $\mu g.mL^{-1}$ target adjustments were performed. The target-controlled infusion was based on the Schnider et al pharmacokinetic model[9,10] which provides for effect-site targeting. In the control group, patients were sedated with fentanyl 1 $\mu g.kg^{-1}$ IV, followed by propofol 1 $mg.kg^{-1}$ IV. Additional 0.5 $mg.kg^{-1}$ boluses of propofol were administered as needed to achieve the loss of responsiveness to tactile stimuli (OAA/S = 1), and colonoscopy was begun. To maintain sedation in the control group, 0.5 $mg.kg^{-1}$ propofol boluses were repeated every 5 minutes, or in case of agitation or patient movement. In both groups, if the peripheral oxygen saturation fell below 90%, ventilatory assistance with a jaw-thrust maneuver and noninvasive ventilation with 100% oxygen via face mask was provided; in the target-controlled infusion group, the target was reduced by 0.5 $\mu g.mL^{-1}$ as well. Given obese subjects were not included in our study, we used total body weight-

Table 1 Observer's Assessment of Alertness/Sedation (OAA/S) Scale.

Responsiveness	Score
Responds readily to name spoken in normal tone	5
Lethargic response to name spoken in normal tone	4
Responds only after name called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to prodding or shaking	1
Does not respond to deep stimulus	0

based regimens for the *bolus* dose and the target-controlled infusion. Upon completion of the procedure, patients were observed until they were responsive to the sound of their names (OAA/S = 4) and then transferred to the postanesthesia care unit. All data were collected or supervised by the same investigator (first and second authors).

Outcomes

The primary outcome was designed to test the hypothesis of superiority of the target-controlled infusion method in controlling the level of sedation by reducing the need for anesthesiologist interventions during colonoscopy compared to the control group. Interventions were defined as propofol dose adjustments, whether additional boluses or target corrections (primary efficacy outcome), as well as maneuvers to ensure airway patency and assist ventilation if necessary (primary safety outcome).

Additional analyses were carried out for the incidence of agitation, defined as any movement made by the patient in reaction to endoscope manipulation; time to arousal after completion of colonoscopy; total dose of propofol administered during sedation; and the predicted effect-site Concentration (Ce) of propofol at loss and at the recovery of consciousness.

Sample size calculation

Considering an average colonoscopy duration of 20 minutes[11] and the need to repeat manual propofol boluses every 5 minutes to maintain sedation in the control group (four interventions), we estimated that a reduction of at least one intervention would occur in the target-controlled infusion group (i.e., three interventions would be required), with a standard deviation of one intervention. To detect this difference at a significance level of 5% and statistical power of 90%, a minimum sample size of 24 patients in each group was established. Considering possible losses, we approximated the sample size upward to 50 patients. A two-tailed means comparison test for two samples was used for this calculation.

Statistical analysis

Kolmogorov-Smirnov test and Levene's test of variances were used for evaluating the assumptions of normality and homoscedasticity of the studied variables, respectively. Pearson's Chi-Square test was used to compare proportions. Student's *t*-test for independent samples and the Mann-Whitney U test were used to compare means between the groups as appropriate. Pearson's correlation test was used to analyze the correlation between the Ce of propofol at loss and recovery of consciousness. Statistical significance was accepted at $p < 0.05$.

Results

Of 133 eligible subjects, we included 50. Fourteen refused to participate, and 69 did not meet the inclusion criteria. The CONSORT flow diagram of the study is shown in Figure 1.

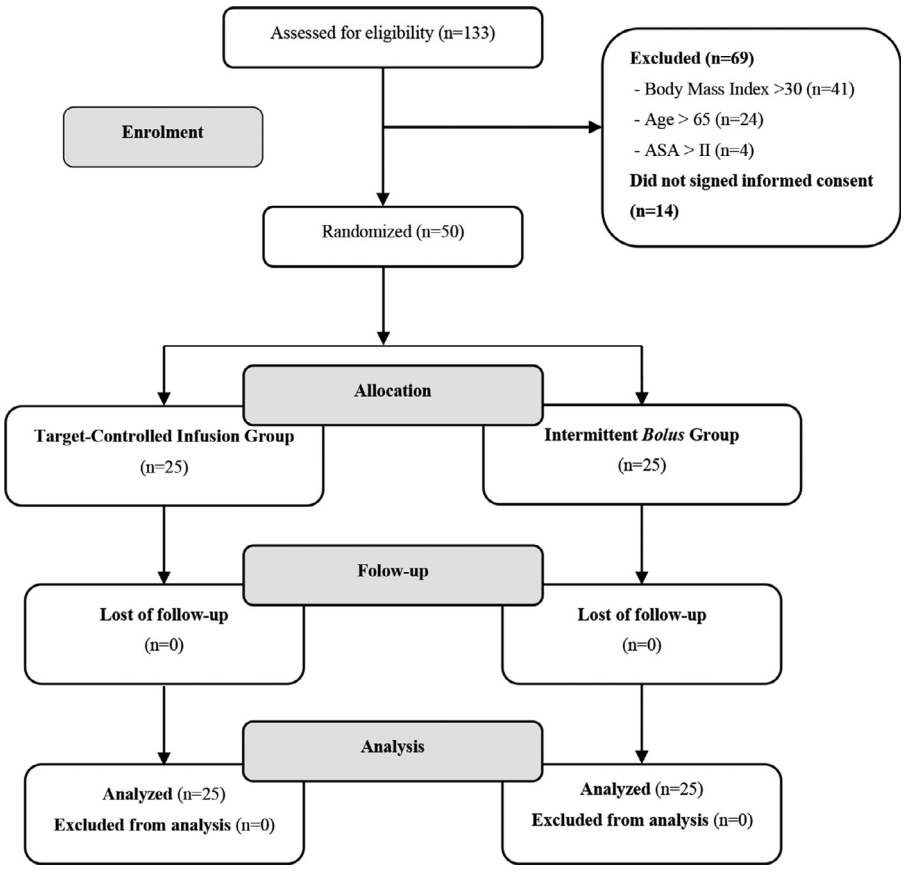

Figure 1 CONSORT flow diagram of patient inclusion.

Table 2 Demographic characteristics of patients and duration of the procedure. Values are given as numbers (percentage) or mean ± Standard Deviation.

Parameter	Group	
	Target-controlled infusion (n = 25)	Intermittent *bolus* (n = 25)
Sex		
Male	8 (32%)	12 (48%)
Female	17 (68%)	13 (52%)
Age (years)	45.4 ± 14.1	43.4 ± 11.5
Weight (kg)	68.5 ± 11.6	70.8 ± 11.6
Height (m)	1.66 ± 0.08	1.67 ± 0.09
Body mass index, $kg.m^{-2}$	24.6 ± 3.2	25.1 ± 2.8
Duration of procedure, minutes	13.1 ± 3.4	12.7 ± 4.1

Table 2 presents the demographic characteristics and duration of colonoscopy in the groups. There was no significant difference in the duration of colonoscopy.

Table 3 describes the detailed results on the variables of interest. The Target-Controlled Infusion (TCI) group required fewer dose adjustments and had a lower incidence of agitation during colonoscopy. There was no between-group difference in safety, i.e., the number of airway maneuvers performed secondary to hypoxemia. There was also no significant difference between groups in the number of patients who experienced respiratory depression during sedation. The total dose of propofol was significantly higher in the TCI group. The time required to achieve the desired level of sedation and recovery was significantly longer with TCI.

In the TCI group, the mean (standard deviation) predicted effect site concentrations for loss and recovery of consciousness were 3.6 (0.7) $\mu g.mL^{-1}$ and 1.6 (0.5) $\mu g.mL^{-1}$, respectively. Figure 2 illustrates the analysis of the observed values for these variables. Despite the significant difference, a positive correlation (49%) was observed between the predicted effect-site concentration of propofol at loss and recovery of consciousness with Schnider's pharmacokinetic model (Fig. 3).

Discussion

Our study demonstrated that target-controlled infusion of propofol for sedation during colonoscopy is safe and effective. Compared to the intermittent manual bolus technique, target-controlled infusion reduced agitation during sedation without increasing the incidence of respiratory depression, requiring less interventions by the anesthesiologist. Although propofol is the drug of choice for sedation in gastrointestinal endoscopy, its use may result in complications. High doses are often necessary to provide ideal conditions for the examination, which can result in intercurrent events such as respiratory depression. Keeping the patient still and breathing spontaneously is usually the greatest challenge during this procedure, in which adequate sedation not only provides patient comfort but can also optimize diagnostic potential.[12]

Satisfactory control of the degree of sedation depends on maintaining adequate effect-site concentration in the central nervous system of propofol in balance with plasma levels, and target-controlled infusion is considered the best method to achieve this.[13]

Campbell et al. reported on the use of patient-controlled sedation with target-controlled propofol infusion for colonoscopy.[14] They concluded that the method was well tolerated by patients; however, sedation was titrated to target plasma levels, and patients took quite a long time to reach an adequate depth of sedation (15 to 20 minutes). Plasma targeting of infusion rates has several limitations; among them, the clinical response is always delayed in relation to the predicted plasma concentration, which probably contributed to the delay in inducing sedation in the aforementioned study. Plasma targeting of infusion is the only option for the Marsh model with "slow" blood-brain equilibration rate constant k_{e0} value (0.26 min^{-1}).

In our study, sedation was titrated with effect-site targeting, and we observed an accordingly faster induction of sedation, with an average time of approximately 4 minutes to loss of consciousness and lack of responsiveness to tactile stimuli (OAA/S = 1). Effect-site targeting is more practical

Table 3 Clinical variables. Values are given as mean ± Standard Deviation, median (interquartile range) or number (percentage).

Parameters	Groups		*p*-value
	Target-controlled infusion (n = 25)	Intermittent *bolus* (n = 25)	
Total interventions[a] (number of interventions)	1 (0–1)	3 (1–4)	< 0.001
Dose adjustments (number of adjustments)	1 (0–1)	3 (1–4)	< 0.001
Airway maneuvers[b] (number of maneuvers)	0 (0–0)	0 (0–0)	0.239
Respiratory depression (number of patients)	3 (12%)	6 (24%)	0.269
Agitation (number of episodes)	1 (0–1)	2 (0–2)	< 0.001
Time to induction[c] (minutes)	3.8 ± 1	1.6 ± 1	< 0.001
Total propofol dose ($\mu g.kg^{-1}.min^{-1}$)	234 ± 46	195 ± 44	0.040
Time to recovery (minutes)	4.9 ± 1.4	2.3 ± 1.6	< 0.001

[a] Dose adjustment plus airway maneuvers.
[b] Jaw thrust and/or facemask ventilation.
[c] Time required for the patient to reach a score of 1 on the OAA/S after the start of propofol administration.

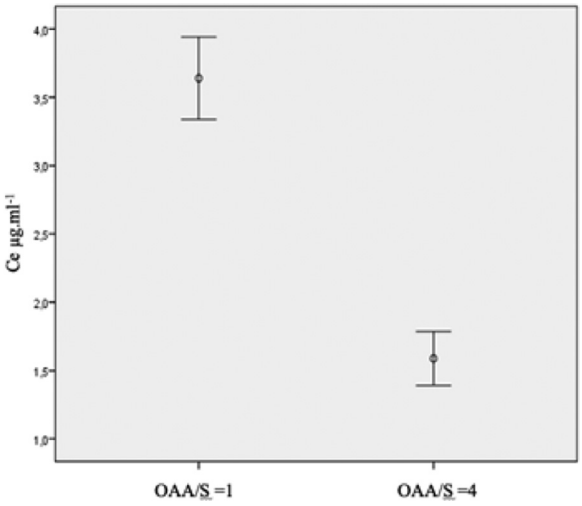

Figure 2 Predicted effect-site Concentration (Ce) of propofol for sedation (OAA/S = 1) and arousal (OAA/S = 4). Values are given as mean and standard deviation ($p < 0.001$).

and logical, considering that pharmacological action correlates better with predicted concentrations at the site of action (Ce) than in plasma (Cp).[15,16] Effect-site targeting should also allow faster achievement of a given depth of anesthesia or sedation, so that subsequent titration of the level of anesthesia could also be easier.

Stonell et al.[17] investigated patient-maintained, target-controlled sedation in colonoscopy, comparing it with the intermittent bolus method. The authors found similar results on patient satisfaction, endoscopist satisfaction, and operating conductions. Although it has been studied for decades,[18-20] patient-controlled sedation has yet to enter widespread use, and its benefits are still controversial. In our study, the target-controlled infusion was assisted by the anesthesiologist, while in the control group, the intermittent bolus method was chosen because it is the standard technique used in our digestive endoscopy service. A standardized regimen consisting of a loading dose of 1.0 $mg.kg^{-1}$ followed by intermittent boluses of 0.5 $mg.kg^{-1}$ has been recommended for sedation in colonoscopy.[21] According to our pharmacokinetic simulations in Tivatrainer® software, this protocol leads to peak concentrations at the effect site of 3 to 4 $\mu g.ml^{-1}$, which are close to the mean values observed for loss of consciousness in the experimental group of our study.

The two main pharmacokinetic models used for target-controlled infusion of propofol in clinical practice are those proposed by Marsh et al.[22] and Schnider et al. Although there is no evidence of superiority of one over the other, our choice of the Schnider model was based on several reasons. First, because it provides for effect-site targeting of the infusion, which allows a more appropriate and rapid titration. Furthermore, unlike in the Marsh model, Schnider includes additional covariables besides weight, such as age, sex, and height; this is appropriate, as the pharmacokinetics of propofol are not influenced solely by weight.[23] Finally, because its equilibrium constant (k_{e0}) and all other parameters have been derived from a single study, in our opinion, this model offers a more robust option for effect-site targeting.

Propofol sedation blunts the ventilatory response to hypoxemia,[24] and combined administration of opioids, although common in clinical practice, potentiates respiratory depression.[25] Therefore, supplemental oxygen is mandatory. In our study, low-flow oxygen (2 $L.min^{-1}$) was given via a nasal cannula to make oxygen saturation more sensitive to respiratory depression, thus allowing easier detection of any difference between the groups; high-flow oxygen via facemask was

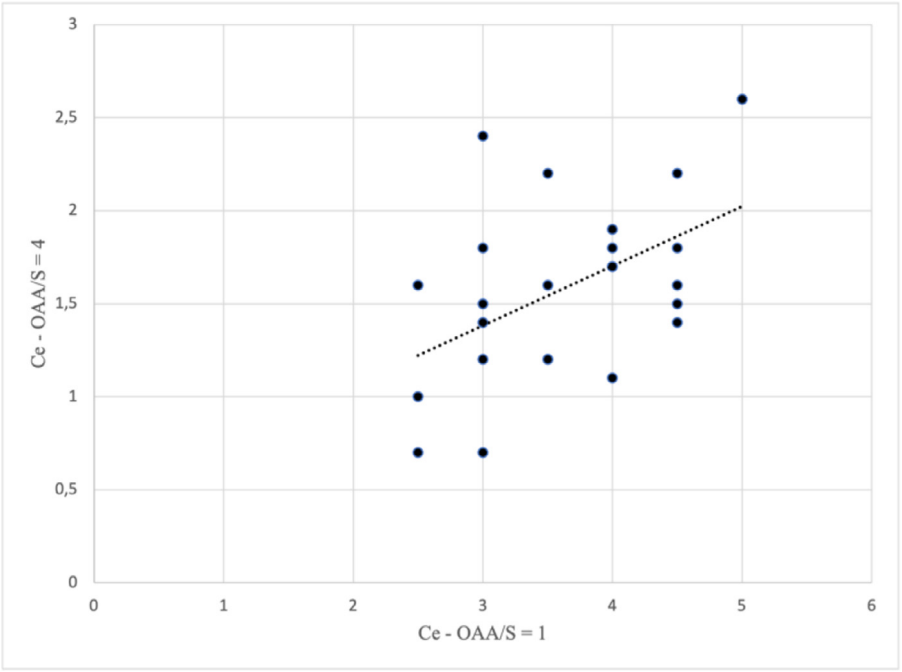

Figure 3 Statistically significant ($p = 0.013$) correlation between predicted effect-site concentration (Ce) of propofol for sedation (OAA/S = 1) and arousal (OAA/S = 4).

reserved for cases of hypoxemia. Although not statistically significant, we consider the twofold occurrence of hypoxemia in the intermittent bolus group to be clinically relevant. Perhaps a larger sample size could provide more conclusive results on safety.

We observed a higher total propofol dose and time to recovery in the target-controlled infusion group. We attribute this finding to the decision to maintain the same propofol target throughout colonoscopy as long as there was no need for correction, and to stop the infusion only at the end of the procedure. However, there is less discomfort during endoscope withdrawal, which should allow a reduction of the infusion target. Moerman et al reported faster recovery reducing the propofol infusion rate near the time of procedure completion.[26] Despite the significant between-group difference in time to arousal, we do not consider it clinically relevant. The difference was minor, of only a few minutes, and did not impair patient flow within the unit. Furthermore, there were no reports of any complications in the postanesthesia care unit with either technique.

We observed that arousal occurred at significantly lower effect-site concentrations of propofol than at the time of loss of consciousness. Despite this difference, there was a positive correlation between the two. A similar result was obtained by Simoni et al with the modified Marsh model.[27] We did not find any publications that investigated this correlation with the Schnider model.

The present study has many strengths that contribute to the literature on the role of target-controlled infusion in sedation for gastrointestinal endoscopy, but it also has some limitations that need to be discussed. First, we did not use a depth-of-anesthesia monitor. Nevertheless, propofol was titrated during sedation induction according to clinical response measured by the OAA/S scale, which correlates well with the bispectral index[28] and can be used to assess the hypnotic effect of anesthetic drugs.

Second, our study is single-blinded because there are important differences between infusion techniques. Although the intermittent bolus could have been administered by a third assistant using a syringe pump, so that the anesthesiologist who recorded the data would have been blinded, we proposed to replicate in the control group the reality of most anesthesiologists, which we believe is the administration of propofol by a manual intermittent bolus.

Third, the hemodynamic response was not evaluated as a primary safety outcome. Propofol causes dose-related cardiovascular depression and its use is associated with hypotension, but adverse respiratory effects, such as hypoxemia, may be more frequent.[29] Although hemodynamics were not formally evaluated, we did not record any significant adverse changes in the hemodynamic pattern requiring intervention or treatment in either group.

Finally, a possible limitation would be the narrow criteria for patient inclusion in the study. However, Marsh and Schnider's pharmacokinetic models have been validated for a selected population that includes young, healthy, and nonobese adults, a group in which the models show good accuracy, with the difference between measured and predicted plasma concentrations being less than 25%.[30] Thus, the inclusion of patients with other characteristics could affect the performance of the infusion system and bias the results.

We conclude that target-controlled infusion of propofol for sedation during colonoscopy is as safe as the intermittent manual bolus technique in terms of adverse respiratory effects (hypoxemia) and is superior in terms of reducing the incidence of agitation/patient movement and the need for dose adjustments by the anesthesiologist. Nevertheless, intermittent manual boluses are associated with faster recovery after completion of the procedure and a lower total propofol dose.

Conflicts of interest

The authors declare no conflicts of interest.

Links

Institutional Research Board Approval: https://plataformabrasil.saude.gov.br/visao/publico/indexPublico.jsf

CAAE: 58452416.0.0000.8055

Study Registry: https://ensaiosclinicos.gov.br/rg/RBR-2dxshp

DATA repositor: https://data.mendeley.com/datasets/m4drb6wbt6/draft?a=b732d073-66fb-4202-a186-e2d9e40e5d02

Presentation

Partial results of this study were presented at the 65th Congresso Brasileiro de Anestesiologia (Belém do Pará, 2018) and at the European Anaesthesiology Congress — Euroanaesthesia 2019 (Vienna, Austria, 2019).

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