

Effect of target controlled propofol infusion versus intermittent boluses during oesophagogastrroduodenoscopy: a randomized controlled trial

Catherine Ndosi, Vitalis Mung'ayi, Ednah Gisore, Samina Mir

Department of Anaesthesia, Aga Khan University, East Africa

Author details:

Catherine Ndosi Phone: + 254 203662158 Email: catherine.ndosi@aku.edu; Vitalis Mung'ayi Phone: + 254 203662175 Email: mungayi@gmail.com; Ednah Gisore Phone: + 254 203662175 Email: edna.gisore@aku.edu; Samina Mir Phone: + 254 203662158 Email: samina.mir@aku.edu

Abstract

Background: Propofol is administered as intermittent boluses to achieve deep sedation to facilitate oesophagogastrroduodenoscopy. Target controlled infusion (TCI) can be employed for this purpose.

Methods: 176 adults were randomly allocated into two groups of 88 patients. Control group: Received an initial bolus of propofol 1mg/kg, with repeat boluses of 0.25mg/kg. Intervention group: Received an initial target effect-site concentration of 4mcg/ml, followed by maintenance target effect-site concentration of 2.5mcg/ml, titrated by 0.5mcg/ml from baseline infusion rate as needed. Oxygen saturation, blood pressure and heart rate were evaluated immediately before administering the sedative and at 2.50, 5.00, 7.50 and 10.00 minutes. Oxygen desaturation below 90% in both study groups was recorded. Sedation starting time, stopping time, waking up time and overall duration of time to recovery of participants in each study arm was recorded.

Results: More hypoxic episodes were observed in the intermittent bolus group with statistically significant association between control and the incidence of hypoxia: Chi square test, $p=0.037$. There were more hypotensive episodes in the TCI group but not achieving statistical significance: Chi square test for association $X^2(1) = 0.962$, $p=0.327$. The time to recovery between the two groups was comparable, with 18.84 ± 10.76 minutes in the bolus group and 19.72 ± 9.27 minutes in the TCI group; no statistically significant difference was shown: Student's t-test, $p=0.0564$.

Conclusion: TCI of propofol was associated with fewer episodes of hypoxia compared to intermittent bolus administration. Similar hemodynamic profiles and comparable time to recovery were demonstrated by these two sedation techniques.

Keywords: Target controlled propofol infusion, intermittent boluses, oesophagogastrroduodenoscopy.

DOI: <https://dx.doi.org/10.4314/ahs.v19i4.36>

Cite as: Ndosi C, Mung'ayi V, Gisore E, Mir S. Effect of target controlled propofol infusion versus intermittent boluses during oesophagogastrroduodenoscopy: a randomized controlled trial. *Afri Health Sci.*2019;19(4):3136-3145. <https://dx.doi.org/10.4314/ahs.v19i4.36>

Introduction

In recent years, there has been a notable increase in the number of patients requiring upper and lower gastrointestinal endoscopic studies as an essential part of the diagnostic and treatment strategy for gastrointestinal pathologies¹⁻². The increased training and availability of specialists performing these procedures has contributed to the steady rise in the numbers of endoscopy proce-

dures done, as has the need for provision of procedural sedation for this invasive procedure³. Sedation has been shown to be essential for gastrointestinal endoscopy to be carried out successfully^{4,5}.

The American Society of Anesthesiologists classifies sedation as minimal, moderate and deep depending on the patient's responsiveness, ability to sustain an airway that is patent, spontaneous ventilation and a reasonably sustained cardiovascular stability⁶.

At present, propofol is the intravenous sedative agent possessing properties closest to that of an ideal sedative owing to its fast onset and ultra-short duration of action; it is no wonder then how rapidly it has gained popularity as the preferred sedative for short procedures. Moreover, its favorable pharmacokinetic and pharmacodynamic

Corresponding author:

Vitalis Mung'ayi,
Department of Anaesthesia,
Aga Khan University, East Africa
Phone: + 254 203662175
Email: mungayi@gmail.com

profile gives it the unique ability to provide varying levels of sedation⁷. As such, propofol has secured a favorable position in procedural sedation as has been elaborated in guidelines published by the American Society of Anesthesiology (ASA) for the safe conduct of sedation for various diagnostic and therapeutic procedures including gastrointestinal endoscopy⁸. However, propofol is an anaesthetic agent with a narrow therapeutic range, and without a reversal agent. The clinical implication of this is that propofol has a low threshold for inducing a deeper level of sedation than intended, compounded by an increased risk of hypoventilation, apnoea or cardiovascular depression. Hence, it is largely recommended that anaesthesiologists or nurse anaesthetists administer this sedative agent.

For the conduct of procedural sedation, propofol may be administered as intermittent boluses or via continuous infusion; the latter technique requiring the use of a drug infusion pump that requires one to either manually adjust the rate of infusion or, use a target controlled infusion system – which allows more accurate rapid titration of the dose of this agent. A target sedation state refers to a pharmacologically induced alteration in the level of consciousness that allows a subject to tolerate unpleasant procedures while aiming to maintain cardiovascular and respiratory stability⁹.

The present study set out to compare the overall proportion of hypoxia between patients undergoing upper gastrointestinal endoscopy under sedation by intermittent intravenous bolus administration of propofol – the standard practice at the Aga Khan University Hospital Nairobi – and target controlled infusion (TCI) of the same sedative agent. Target controlled infusions are computerized infusion systems based on pharmacokinetics and pharmacodynamic models specified for the individual by entering variables such as age, gender and weight¹⁰. From these, a mathematical model can be designed and applied in predicting the plasma concentration profile of a given pharmacological agent after a bolus dose is given, or following an infusion of the drug. These models are deduced from the measurement of arterial or venous plasma concentration of the drug using standardized statistical methods and models of computer software that are incorporated in the infusion pump¹¹.

Numerous algorithms for targeting blood and effect site concentration have been published and several automated systems have been developed. Examples of TCI models

available for the use of Propofol are Marsh and Schnider models¹¹.

With target-controlled infusion, a steady-state level of propofol sedation can be attained by attempting to achieve a user-preset target blood drug concentration¹², with a provision for rapid titration in response to varying degrees of procedural stimulation. It therefore confers to the user a high level of confidence regarding the predictability of depth of sedation.

In theory therefore, a more consistent level of sedation can be achieved by this technique, minimizing the highs and lows of plasma levels of propofol, which are experienced when, repeated boluses of are administered¹³. In so doing, the degree of hypotension encountered would be reduced, as would the intensity of respiratory depression, which can lead to apnoea and hypoxaemia. Additionally, TCI may also be associated with a reduce need for interventions by the person administering the sedative; thus, effectively “frees” the anesthetist’s hand and allows for better direct monitoring of the patient. Endoscopic sedation presents the unique challenge of “sharing the airway” with the gastroenterologist, rendering it persistently at risk as the airway is not protected. Foremost in the prudent anesthesiologist’s safe sedation strategy is to choose a regime that is associated with fewer incidences of respiratory depression that can lead to oxygen desaturation and hypoxia.

The aim of this study was to compare the proportion of hypoxia between targets controlled infusion and intermittent bolus administration of propofol in adult patients undergoing sedation for upper gastrointestinal endoscopy. Our study question was: is there a difference in the proportion of hypoxia between targets controlled infusion and intermittent bolus administration of propofol in adult patients undergoing sedation for upper gastrointestinal endoscopy?

We hypothesized that there is no difference in the proportion of hypoxia between target controlled infusion and intermittent bolus administration of propofol in adults undergoing sedation for upper gastrointestinal endoscopy.

Methods

The study was performed following approval from the ethical and scientific review committee at the Aga Khan University Hospital, Nairobi. This was an open-label randomized controlled trial. The study was carried out

at the Aga Khan University Hospital, Nairobi, a tertiary facility with a bed capacity of 280; a facility that is home to a host of postgraduate medical education programs. Patients seeking care from this not-for-profit facility are

drawn from diverse geographical backgrounds. The patients who took part in this study were enrolled from the preanaesthesia clinic, the inpatient wards and the endoscopy department. A participant flow diagram is shown in figure 1.

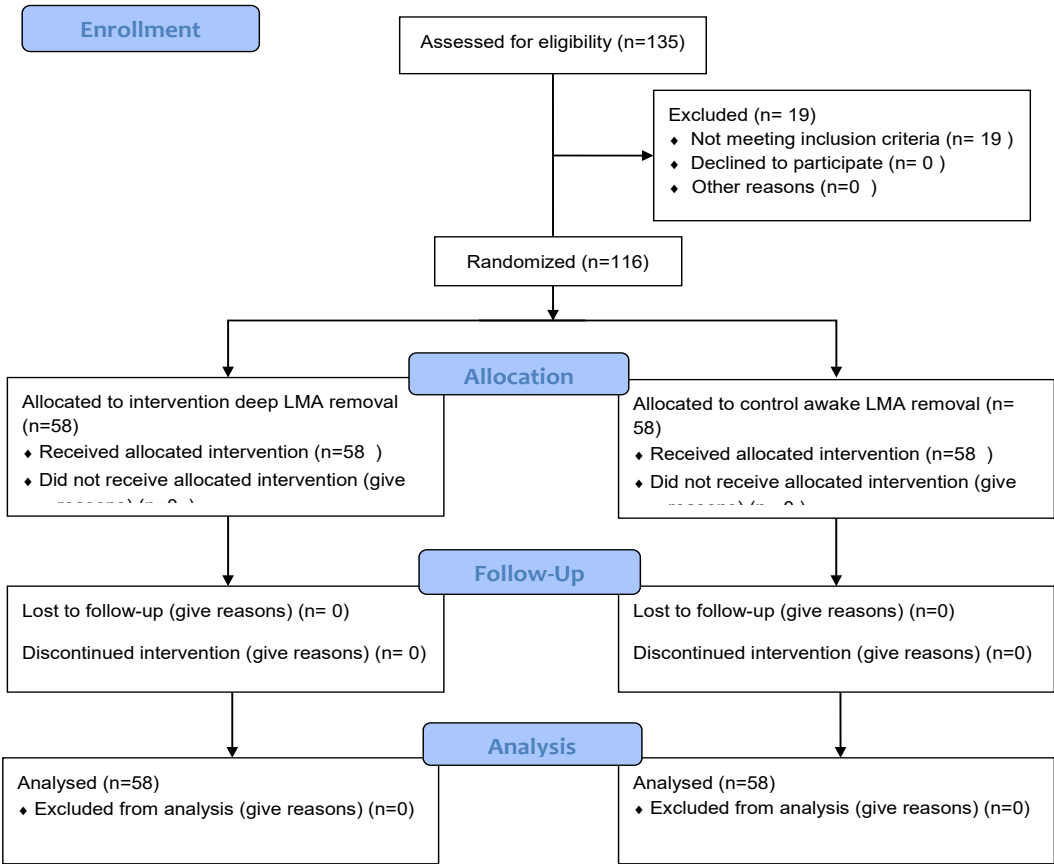


Figure 1: CONSORT Flow Diagram

The target population included all adults scheduled for non-emergent diagnostic or therapeutic upper gastrointestinal endoscopy i.e. oesophagogastroduodenoscopy (OGD) under sedation. The sample population included ASA I and II adults between the ages of 18 - 65 years who were to undergo non-emergent upper gastrointestinal endoscopy at the Aga Khan University between January 2017 and March 2017 under sedation. Reasons for exclusion from the study were:

1. Known allergy to propofol, midazolam, soybean, egg.
2. Active respiratory infection.
3. History or indicator of large airway compromise e.g. obstructive sleep apnoea, chronic obstructive pulmonary disease, presence of stridor, or known history of difficult bag-valve-mask ventilation.
4. Patients requiring additional types of sedative agents to achieve optimal sedation.

5. History of chronic exposure to sedative medication.

The present study applied a margin of 0.12; a difference of 8% was considered to be significant should there be a difference in the proportion of hypoxia observed between the two modes of administering propofol during the conduct of OGD. The sample size for the study was determined using the non-inferiority formula. This sample was sufficient for the test of non-inferiority or equivalence between target controlled infusion and intermittent bolus administration of propofol in the proportion of patients that develop hypoxia. In applying the above formula, with the assumption of a significance level of 5%, and a power of 80%, a sample size of 80 patients per arm was deemed adequate to demonstrate an 8% difference in the proportion of hypoxia between patients in these two groups. Upon accounting for up to a 10% drop-out rate,

a total sample size of 176 (88 in each arm) was arrived at. Patients scheduled for gastrointestinal endoscopy were screened and assessed for eligibility during the pre-anaesthesia assessment visit in the anaesthesia clinic, in-patient ward reviews and the endoscopy department. The use of consecutive sampling was applied, meaning: there was opportunity to recruit every subject who was found to be eligible to participate in this study. An informed consent was obtained from the patient by the primary investigator after an elaborate description of the purpose and nature of the study had been provided. Ample time was also allocated to satisfactorily address any questions that they may have had. Participants from whom informed consent had been obtained were assigned randomly to either arm. A total of 88 yellow cards and 88 blue cards were put in brown (opaque) envelopes and sealed at the start of the study. These envelopes were then mixed well together; each colored card representing one arm of the study. Yellow cards represented the intervention arm (target controlled infusion) and the blue cards represented the control arm (intermittent bolus). Once the participants provided consent to participate in the study, they were required to take any envelope and open it to display the card it contained. The revealed card was then placed in the participant's file for ease of identification of the group they had been randomized into and to guide the administration of the appropriate mode of intravenous propofol for sedation as described for the respective arms.

Upon arrival at the endoscopy suite, the anaesthetist administering sedation opened the patient's file and saw from the colour of the card contained therein which arm the patient had been randomized into. Standard monitoring was commenced: electrocardiography, automated non-invasive blood pressure measurement and pulse oximetry. Supplemental oxygen via nasal prongs at 3 liters per minute was given to all patients in both study arms at least 3 minutes before commencing sedation. Intravenous midazolam 0.05mg/kg was administered to subjects in both study arms. In the intermittent bolus group: An initial bolus propofol 1mg/kg, followed by repeat boluses of 0.25mg/kg as needed was given till the end of the procedure. In the target controlled infusion group: Effector targeted Schneider model was used via target controlled infusion pump model, Injectomat TIVA agilio™. Initial target effect-site concentration of 4mcg/ml for propofol was given until loss of consciousness was achieved. This was immediately followed by a target effect-site concentration infusion of 2.5mcg/ml, titrated by 0.5mcg/

ml upward or downward as needed till the end of the procedure. A Ramsay sedation score of <5 was used as criteria for additional dosing¹⁴. We opted to use the Ramsay Sedation Scale because it is the scoring system most commonly referred to at our facility.

Patients were monitored continuously; non-invasive blood pressure measurements were time-cycled to take automated readings at 2.5-minute intervals. The heart rate, respiratory rate and oxygen saturation was depicted by continuous respective waveforms and corresponding numerical values on the monitor screen throughout the procedure.

Upper gastrointestinal endoscopy was started by gastroenterologist only after patient entered deep sedation. Any episode of oxygen desaturation below 90% was documented; airway maneuvers such as chin-lift and jaw-thrust were applied promptly to re-establish patency of airway. If the patient became apnoeic, the endoscopy procedure was to be interrupted and mask ventilation with high-flow 100% oxygen was to be administered until there was resumption of spontaneous ventilation. The end of the endoscopy sedation procedure was marked by withdrawal of the endoscope from the mouth. The patient was then transferred to the post-sedation recovery room for continuous monitoring till point of being discharged from the endoscopy suite to go home or to the ward. The time to recovery from sedation was recorded for each patient in both study arms i.e. duration of time from the end of the endoscopy procedure signaled by withdrawal of the scope from the oral cavity and cessation of administration of the sedative, to the time to respond to a verbal command. This was assessed at 5-minute intervals. The verbal command was given by the recovery room nurse who stood by the patient's bed on the side he or she was facing, and called them by their name no more than twice at a time, in a normal/conversational tone. The patient was neither touched nor subjected to any other form of stimulation in an attempt to determine their level of wakefulness. This routine was also well described to the recovery room nurses as well as practically demonstrated to them how to correctly make this assessment. In addition, I frequently went to the recovery room to ensure this was uniformly adhered to.

Data was checked for accuracy and completeness, then entered and analyzed by use of SPSS (Version 21.0, Chicago-Illinois). Continuous data was analyzed and summa-

rized as means and standard deviation while the categorical data was analyzed and displayed by use of frequencies and proportions. The proportion of patients with hypoxia (primary outcome) between the TCI and intermittent bolus groups was compared with the use of Chi-square test. The secondary outcome (hypotension and time to recovery in minutes) was compared with the use of independent sample t-tests. Where applicable, P-values and 95% confidence intervals (CIs) were also to be calculated. A P value <0.05 was considered statistically significant, based on two-sided tests.

Results

The age, sex, weight, and height were not significantly different ($p=0.502$; $p=0.546$; $p=0.388$; $p=0.054$) in both groups as shown in table 1. The TCI group had a systolic blood pressure of 120.25 ± 18.87 , while that of the Bolus group was 123.73 ± 19.13 ; a difference of 3.48mmHg that was not statistically significant (95% CI, -2.18 to 9.13), $t(174) = 1.214$, $p = 0.226$. However the bolus group had a baseline diastolic blood pressure of 75.84 ± 14.73 , while that of the TCI group was 72.45 ± 10.63 ; a difference of 3.39mmHg which also was not statistically significant (95% CI, -0.44 to 7.21), $t(174) = 1.749$, $p = 0.082$.

Table 1: Comparison of Baseline Characteristics between Bolus and TCI Groups

	Frequency n (%)		p-value
	BOLUS	TCI	
	Mean(\pm SD)	Mean(\pm SD)	
Age	38.6(13.2)	39.0(11.3)	0.502
Sex			
Male	39 (44.3)	43 (48.9)	0.546
Female	49 (55.7)	45 (51.5)	
ASA classification			
I	53 (60.2)	66 (75.0)	0.036
II	35 (39.8)	22 (25.0)	
Mean Weight	71.3(12.3)	74.1(14.62)	0.388
Mean Height	167.4(7.1)	169.3(6.57)	0.054
Mean BMI	25.5 (3.7)	25.6 (4.29)	0.655
Mean Initial blood pressure (mmHg)	Mean \pm SD		
	Bolus	TCI	
Systolic	123.7 (19.1)	120.3 (18.9)	0.226
Diastolic	75.8 (14.7)	72.5 (10.6)	0.082
Mean HR	83.2 (13.9)	85.2 (13.4)	0.338
Mean SpO2	95.57 (1.7)	96.8 (1.8)	0.304

The bolus group had more cases of hypoxia ($n = 28$) than the TCI group ($n = 16$). This was statistically significant, $p = 0.037$ (95% CI, 1.039 to 4.243). This is shown in table 2.

The bolus and TCI groups were assessed for occurrence of hypotension. As earlier defined in this study, hypotension was described as a 20% decrease in the baseline systolic blood pressure.

Table 2: Proportion of Hypoxia between Bolus and TCI Groups

Group	Frequency n (%)		p-value
	Yes	No	
Bolus	28 (31.8)	60 (68.2)	0.037
TCI	16 (18.2)	72 (81.8)	

An independent-samples t-test applied to determine if there were differences in the initial systolic blood pressure in patients receiving Bolus and TCI for sedation.

It was found that of those in the TCI group, 30 (34.1%) had experienced hypotension compared to 24 (27.3%) of the Bolus group. This finding was not statistically significant, $p=0.327$ (95% CI, .381 to 1.380). This shown in table 3.

Table 3: Proportion of Hypotension between Bolus and TCI Groups

Group	Frequency n (%)		p-value
	Yes	No	
Bolus	24 (27.3)	64 (72.7)	0.327
TCI	30 (34.1)	58 (65.9)	

The Bolus arm had a mean heart rate of 83.17 ± 13.94 compared to the TCI arm (85.15 ± 13.35), a difference of 2.06 (95% CI, -6.04 to 2.08), $t(174) = 1.214$, $p = 0.338$. This is shown in table 4.

Table 4: Comparison of Heart Rate between Bolus and TCI Group

	Bolus	TCI	p-value
Heart rate (Mean \pm SD) - Initial	83.17 ± 13.94	85.15 ± 13.35	0.338

An independent-samples t-test carried out to determine if there were differences in the heart rate in patients receiving Bolus and TCI for sedation.

It was found that participants in the Bolus group had a comparable duration of sedation to those in the TCI group (6 ± 3 and 6 ± 1 minute, respectively). Not only was the duration of sedation not statistically different, but the difference was also clinically insignificant. (95% CI, -0:00 to 0:01), $t(174) = 1.214$, $p = 0.519$. This shown in table 5.

Table 5: Comparison of Duration of Sedation between bolus and TCI groups

	Mean \pm SD		p-value
	Bolus	TCI	
Duration of Sedation (in minutes)	6 ± 3	6 ± 1	0.519

An independent-samples t-test run to determine if there were differences in the duration of sedation in patients receiving Propofol boluses versus TCI during sedation.

The Bolus group had a shorter recovery time (18.84 ± 10.77) compared to the TCI group (19.72 ± 9.28); a difference that was not statistically significant (95% CI, -2.12 to 3.87), $t(174) = 0.578$, $p = 0.564$. This is shown in table 6. No statistically significant association between inter-

vention and duration taken to wake up was demonstrated, $\chi^2(26) = 8.592$, $p = 0.198$. This is shown in table 7. Of the patients who took longer than 30 minutes to wake up in either group, the majority of them woke up between 31 and 40 minutes. The longest time asleep in the TCI group was 42 minutes, and 48 minutes in the Bolus group.

Table 6: Comparison of Recovery Time between Bolus and TCI Groups

	Bolus	TCI	p-value
Recovery time in min (Mean \pm SD)	18.84 \pm 10.77	19.72 \pm 9.28	0.564
Range (min)	5 - 66	3 - 42	

An independent-samples t-test run to determine if there were differences in the recovery times in patients receiving Bolus and TCI for sedation.

Table 7: Distribution of Patients by Duration Taken to Wake Up

Duration (minutes)	Frequency n (%)		p-value
	Bolus	TCI	
≤ 5	2 (2.3)	5 (5.7)	0.198
6 – 10	18 (20.5)	6 (6.8)	
11 – 15	24 (27.3)	25 (28.4)	
16 – 20	13 (14.8)	14 (15.9)	
21 – 25	13 (14.8)	13 (14.8)	
26 – 30	7 (8.0)	11 (12.5)	
>30	11 (12.5)	14 (15.9)	
Total	88 (100.0)	88 (100.0)	

A C

Discussion

The conduct of gastrointestinal endoscopy has in recent years seen an appreciable rise in the numbers of diagnostic and therapeutic procedures being carried out. This is perhaps driven by an increasing awareness by the lay public of the benefits of undergoing this investigation given the apparent rise in the incidence of gastrointestinal pathologies – including cancers, alongside the increasing training opportunities and growing availability of gastroendoscopy specialists. With this comes the inevitable need to avail procedural sedation to facilitate the conduct of these invasive investigations. Manual intermittent bolus administration of propofol has been the main-stay mode of providing a Propofol-based sedation regimen. However, in the recent years, target controlled infusion of propofol for procedural sedation has steadily gained popularity.

The present study set out to investigate and compare the proportion of hypoxia between adults receiving intermittent boluses of propofol versus target controlled

infusion of propofol for sedation during upper gastrointestinal endoscopy. In addition, the study was also guided by the following secondary objectives: to compare the proportion of hypotension and bradycardia between the two study arms, as well as the time to recovery between the two groups.

The key finding was that the occurrence of hypoxia was proportionally higher in the intermittent bolus group (31%) compared to that in the TCI group (18%) - a finding that was deemed statistically significant $p = 0.037$. Yi-Ting Chang et al found a similar observation in a study involving 100 subjects, where he explored the quality and plausibility of propofol TCI as a sedation method for endoscopy¹⁵. Although it was reported that there was no statistically significant difference in the overall respiratory effects observed between the two arms, the actual number of patients who experienced oxygen desaturation requiring intervention was higher in the control group. In both instances, respiratory depression and hypoxia was observed soon after administering the induction dose of

propofol. This may be attributed to the sudden surge in the plasma and target site concentration of propofol that is characteristic of bolus administration of a relatively large dose of the drug within a short period. While this may well confer the advantage of rapid loss of consciousness and achievement of the desired depth of sedation, the respiratory-depressant effect of propofol is accentuated leading to bradypnoea, hypopnea or apnoea, and oxygen desaturation. In a study similar to the present one, Arif H M Marsaban et al compared sedation outcomes between these two sedation techniques, including the total consumption of propofol, side effects and recovery time⁴. Here too, the incidence of desaturation was found to be proportionally larger in the bolus group (12%) than in the intervention group (4%). However, the variable power of the study was very low and so the accuracy of the conclusions of this particular study could not be ascertained.

Concerning haemodynamic parameters, the proportion of hypotension was found to be proportionally higher in the intervention group, with 34% of subjects in the TCI arm recording systolic blood pressures below 20% of the baseline value, compared to 27% in the bolus group. However, a statistically significant association between intervention and hypotension was not demonstrated. In a clinical trial involving 100 participants undergoing OGD and 120 scheduled for colonoscopy Chan WH et al¹² found that, of the subjects undergoing OGD, significantly lower trough systolic blood pressures were documented in the control group (105 +/- 19mmHg) versus TCI group (113 +/- 20mmHg) $p=0.043$. However, this study did not report analysis of the variation of the systolic blood pressure from the baseline. This may have been significant. Important to note, too, is that the participants in that study had been randomly enrolled to receive TCI with propofol or intermittent boluses of a cocktail regimen containing propofol, midazolam and alfentanil. The latter two drugs (a benzodiazepine and an opioid) are pharmacological agents with cardiovascular depressant effects in their own right; the drop in blood pressure that was experienced by these patients was probably because of the combination of the peripheral vasodilatory effect of propofol and the direct cardio-depressant effects of alfentanil. Repeated bolus administration of this sedative cocktail would likely – and predictably – render a cumulative cardiovascular depressant effect, leading to higher rate of hypotension in the patients receiving boluses of the cocktail regimen than those in the TCI group who received an infusion of propofol alone. This may

have influenced the findings of the study in this regard. By not including the use of an opioid agent in only one arm of the sedation protocol, the present study obviated the confounding influence of an opioid on the overall haemodynamic profile of the patients, thereby arriving at a more accurate conclusion of the effect of either sedation techniques on the haemodynamic parameters of the patients.

It is prudent now to acknowledge that, in the current study as well as in the referenced trials, the pre-procedure fluid status of the participants was not known; we therefore cannot rule out the possibility of some of them being relatively fluid-depleted at the start of administration of the sedation regimen. As such, the association of either mode of propofol administration (TCI or intermittent boluses) to the occurrence of hypotension may have been exaggerated.

In the present study, one patient experienced a transient, self-limiting episode of bradycardia (defined by a heart rate below 50 beats per minute) whose lowest heart rate recorded was 47 beats per minute. This subject was in the bolus group; of note is that this participant had a relatively low initial heart rate of 61 beats per minute (compared to the mean baseline heart rates of 83.17 ± 13.94 and 85.15 ± 13.35 – in the control and TCI groups, respectively) that may have predisposed the patient to developing an even slower heart rate soon after receiving the induction dose of Propofol. This event was not clinically significant as it lasted less than 30 seconds, with resumption of normal heart rate without requiring any pharmacological intervention to treat it. The patient's blood pressure was not adversely affected and remained stable throughout the rest of the course of the procedure.

Upon analysis of the recovery time between the two groups, it was noted that of those who responded to a verbal command within 5 minutes of cessation of the sedation regimen, most had been recipients of a target controlled infusion of Propofol; perhaps a representation of the patients whose procedure time was relatively shorter than the rest and therefore had an overall lower consumption of Propofol, predictably leading to a faster recovery time. With the exception of the cluster of patients in the Bolus group who woke up 6 – 10 minutes that formed the majority in that time cluster, the overall time to recovery between the two propofol sedation techniques was largely found to be comparable; with no significant difference demonstrated in the bolus ($M=18.84$, $SD=10.767$) and TCI ($M=19.72$, $SD=9.276$) arms, $t(174)$

= .578, $p=.564$, suggesting that the time to recovery was not affected by the method used for sedation.

In revisiting the study protocol, specific interventions were to be administered promptly in case any serious respiratory or cardiovascular complications occurred. With the exception of one patient in the TCI group who developed moderately severe laryngospasms at the end of the procedure, no other serious complication was observed in any of the other study participants. A single or combination of factors may trigger laryngospasm in a patient undergoing an invasive diagnostic or therapeutic intervention. In an analysis of incidences reported to the Australian Incident Monitoring Study (AIMS) that involved voluntary reporting of any unintended incident that occurred in the course of care of a patient, of the first 4000 reports, 189 were cases of laryngospasm. Amongst the precipitating factors attributed are airway manipulation (44%), blood/secretions in the pharynx (12%), regurgitation/vomiting (9%), surgical stimulus (5%), moving patient (4%), irritant volatile agent (2%) and failure of anaesthetic delivery system (2%). In 22% of patients who experienced laryngospasm no clear cause could be identified¹⁶. Propofol in itself has a suppressive effect on the airway reflexes; compared to volatile anesthetic, the use of propofol sedation/anesthesia is associated with reduced airway hyperreactivity¹², and is in fact the agent of choice in the management of laryngospasm by increasing the depth of anaesthesia, with or without paralysis with succinylcholine¹⁸. It is therefore improbable that target controlled infusion of this agent was a precipitating factor of laryngospasms in that single subject in the TCI group. Instead, it more likely would have been attributed to the production of excessive airway secretions during the conduct of OGD, an observation that was peculiar to this patient, and perhaps the stimulation of the oropharynx with the endoscope in a moment of a lighter plane of sedation than was intended. This complication was expeditiously managed by oropharyngeal suctioning of secretions and administering continuous positive pressure ventilation of 100% Oxygen via a Mapleson A circuit, with resolution of the airway spasms soon after. The patient went on to recover from sedation without any further untoward events.

By demonstrating a lower proportion of hypoxia with the use of target controlled infusion compared to intermittent bolus administration of Propofol, the results of this study therefore rejects the null hypothesis: there is no difference in the proportion of hypoxia between targets controlled infusion of propofol and intermittent bolus

administration in adults undergoing sedation for upper gastrointestinal endoscopy.

Strengths

This study is the first of its kind to be conducted in a tertiary facility in this region of the globe.

Limitations

As this was a single-centre trial conducted at a tertiary facility, the results obtained in this study may not be generalizable across different clinical set-ups and patient populations. Secondly, neither the anaesthesiologist nor the endoscopist was blinded in this study, resulting in a Hawthorne effect, which may have invariably influenced the sedation outcomes under study. However, the nature of the study in itself rendered blinding of the anaesthesiologist and endoscopist impossible. Thirdly, the induction and maintenance doses of Propofol in either arm of the study were empirically determined; at best, these were closely related to the doses used in comparable studies^{12,16,17}. Even then, for both propofol sedation techniques the sedative was given by titrating it to effect, with the goal of achieving a Ramsay score of 5.

Conclusion

In conclusion, based on the findings of this study, target controlled infusion of propofol at a targeted effector site concentration of 2.5mcg/ml is associated with a lower proportion of hypoxia compared to intermittent bolus administration of Propofol at 0.25mg/kg given as required. In this regard, TCI mode of propofol sedation has been demonstrated to provide a safer alternative to the traditional manual intermittent bolus administration of the same sedative agent. The single episode of laryngospasms observed in one patient in the TCI group may have been attributed to the presence of copious airway secretions rather than the mode of propofol sedation given. Additionally, the results of this study suggest that the haemodynamic profile as well as the time to recovery is not influenced by the choice of propofol sedation technique used.

Trial registration PACTR201708002325400

Conflict of interest

None declared.

References

1. Riphaut A, Geist C, Schrader K, Matchenko K, Wehr-

- mann T. Intermittent manually controlled versus continuous infusion propofol for deep sedation during interventional endoscopy: A prospective randomized trial. *Scand J Gastroenterol*. 2012; 47:1078-85. <http://dx.doi.org/10.3109/00365521.2012.685758>
2. American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. Practice guidelines for sedation and analgesia by non-anesthesiologists. *Anesthesiology*. 2002; 96:1004-17.
3. Absalom AR1, Glen JI, Zwart GJ, Schnider TW, Struys MM. Target-Controlled Infusion: A Mature Technology. *Anesth Analg*. 2016; 122:70-8. <http://dx.doi.org/10.1213/ANE.0000000000001009>
4. Marsaban AHM, Sumaratih L, Pryambodho. Comparison between intermittent propofol bolus techniques and target controlled infusion in patients undergoing gastrointestinal endoscopy. *The Indonesian Journal of Gastroenterology, Hepatology and Digestive Endoscopy*. 2013; 14:132-138.
5. Bannert C1, Reinhart K, Dunkler D, Trauner M, Renner F, Knoflach P, Ferlitsch A, Weiss W, Ferlitsch M. Sedation in screening colonoscopy: impact on quality indicators and complications. *Am J Gastroenterol*. 2012; 107:1837-48. <http://dx.doi.org/10.1038/ajg.2012.347>
6. Hawthorne C, Sutcliffe N. Total intravenous anesthesia. *Anaesthesia and Intensive Care Medicine*. 2013; 14:129-13. <http://dx.doi.org/10.1016/j.mpaic.2013.01.006>
7. Langdon AM, Diwan R. Safe sedation of children for diagnostic and therapeutic procedures. *Anaesthesia and Intensive Care Medicine* 2016; 17: 299-302. <http://dx.doi.org/10.1016/j.mpaic.2016.03.006>
8. Epstein SB. The American Society of Anesthesiologist's Efforts in Developing Guidelines for Sedation and Analgesia for Nonanesthesiologists. *Anesthesiology* 2003; 98:1261-8.
9. National Institute for Health and Care Excellence Clinical Guideline. Sedation in under 19s: using sedation for diagnostic and therapeutic procedures. December 2010. <http://nice.org.uk/guidance/cg112>,
10. Lichtenstein DR, Jagannath S, Baron TH, Anderson MA, Banerjee S, Dominitz JA, Fanelli RD, Gan SI, Harrison ME, Ikenberry SO, Shen B, Stewart L, Khan K, Vargo JJ. Sedation and anesthesia in GI endoscopy. *Gastrointest Endosc*. 2008 ;68:205-16. <http://dx.doi.org/10.1016/j.gie.2008.06.002>
11. White M, Kenny GN. Intravenous propofol anaesthesia using a computerised infusion system. *Anaesthesia*. 1990; 45:204-9.
12. Chan WH, Chang SL, Lin CS, Chen MJ, Fan SZ. Target controlled infusion of propofol versus intermittent bolus of a sedative cocktail regimen in deep sedation for gastrointestinal endoscopy: comparison of cardiovascular and respiratory parameters. *J Dig Dis*. 2014; 15:18-26. <http://dx.doi.org/10.1111/1751-2980.12101>
13. Seeff LC1, Manninen DL, Dong FB, Chattopadhyay SK, Nadel MR, Tangka FK, Molinari NA. Is there endoscopic capacity to provide colorectal cancer screening to the unscreened population in the United States? *Gastroenterology*. 2004; 127:1661-9.
14. Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. *Br Med J* 1974; 2:656-9.
15. Chang YT, Tsai TC, Hsu H, Chen YM, Chi KP, Peng SY. Sedation for gastrointestinal endoscopy with the application of target-controlled infusion. *Turk J Gastroenterol*. 2015; 26:417-22. <http://dx.doi.org/10.5152/tjg.2015.0206>
16. Visvanathan T, Kluger MT, Webb RK, Westhorpe RN. Crisis management during anaesthesia: laryngospasm. *Qual Saf Health Care*. 2005; 14:e3.
17. Parameswara G. Anesthetic concerns in patients with hyper-reactive airways. *Karnataka Anaesth J* 2015; 1:8-16. <http://dx.doi.org/10.4103/2394-6954.149714>
18. Gavel G, Walker RWM. *Laryngospasm in Anaesthesia. Continuing Education in Anaesthesia, Critical Care and Pain*. 2014; 14:47-51. <http://dx.doi.org/10.1093/bjaceaccp/mkt031>