



Evaluation of a closed-loop intravenous total anesthesia delivery system with BIS monitoring compared to an open-loop target-controlled infusion (TCI) system: randomized controlled clinical trial

Evaluación de un sistema de administración de Anestesia Total Intravenosa en lazo cerrado con neuromonitoría, comparado con un sistema de lazo abierto de infusión controlada por objetivo (TCI): Ensayo clínico controlado

Fabián David Casas-Arroyave^{a,b}, Juan Manuel Fernández^{a,b},
John Jairo Zuleta-Tobón^b

^a Hospital Universitario San Vicente Fundación, Medellín, Colombia

^b Faculty of Medicine, Universidad de Antioquia, Medellín, Colombia.

Keywords: Anesthetics, Intravenous, Consciousness Monitors, Systems Analysis, Feedback, Propofol

Palabras clave: Anestésicos Intravenosos, Monitores de Conciencia, Análisis de Sistemas, Retroalimentación, Propofol

Abstract

Introduction: Intravenous general anesthesia is an anesthetic technique that can be administered with TCI (target-controlled infusion) or closed-loop systems. The authors designed an automatic delivery system using clinical variables such as bispectral index (BIS), heart rate, and blood pressure.

Objective: To evaluate the clinical and technical performance of this controller by comparing it to a TCI system.

Methods: This was a single-blind, randomized, controlled clinical trial in which 150 patients were recruited: 75 for the TCI group and 75 for the closed loop with BIS. Clinical performance was determined according to the mean percentage of time spent in the

BIS range of 40 to 60 during anesthetic maintenance. In addition, adequate intraoperative analgesia, technical performance, intraoperative awakening, and intraoperative recall were evaluated.

Results: The primary outcome showed a mean BIS time between 40 and 60 for the closed loop of 75.24% (± 15.78) versus 59.5% (± 20.3) for the TCI system, with an absolute difference of 15.8%, 95% confidence interval (CI): 9.9 to 21.65, $P < 0.0001$. The mean time in intraoperative analgesia was 82.4% (25.1) in closed loop and 70.77% (± 32.8) in TCI, with a difference of 4.76 (95% CI: 2.23–21.06), $P = 0.016$. There was no difference in intraoperative recall.

Conclusion: The closed-loop system was better at maintaining a BIS in the range of 40 to 60 during a general anesthetic than the open system or TCI.

How to cite this article: Casas-Arroyave FD, Fernández JM, Zuleta-Tobón JJ. Evaluation of a closed-loop intravenous total anesthesia delivery system with BIS monitoring compared to an open-loop target-controlled infusion (TCI) system: randomized controlled clinical trial. Colombian Journal of Anesthesiology. 2019;47:84–91.

Read the Spanish version of this article at: <http://links.lww.com/RCA/A863>.

Copyright © 2019 Sociedad Colombiana de Anestesiología y Reanimación (S.C.A.R.E.). Published by Wolters Kluwer. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Correspondence: Hospital San Vicente Fundación, Calle 64 No. 51D-154, Medellín, Colombia. E-mail: fabian.casas@udea.edu.co

Colombian Journal of Anesthesiology (2019) 47:2

<http://dx.doi.org/10.1097/CJ9.0000000000000110>

Resumen

Introducción: La anestesia total endovenosa es una técnica anestésica que puede administrarse con sistemas de TCI (*Target Controlled Infusion*) o de lazo cerrado. Los autores diseñaron un sistema de administración automática empleando variables clínicas como índice biespectral (BIS), frecuencia cardíaca y presión arterial.

Objetivo: Evaluar el desempeño clínico y técnico de este controlador, comparándolo con un sistema de TCI.

Métodos: Este fue un ensayo clínico controlado, aleatorizado y de ciego único, en el cual se reclutaron 150 pacientes: 75 en el grupo de TCI y 75 en lazo cerrado con BIS. El desempeño clínico fue determinado de acuerdo al porcentaje promedio de tiempo de permanencia en el rango de BIS entre 40–60 durante el mantenimiento anestésico. Adicionalmente se evaluó analgesia intraoperatoria adecuada, desempeño técnico, despertar intraoperatorio y recuerdo intraoperatorio.

Resultados: Para el desenlace primario se encontró un tiempo promedio de BIS entre 40–60 para el lazo cerrado de un 75.24% (+/- 15.78) vs. 59.5% (+/- 20.3) para el sistema TCI, con una diferencia del 15.8%, IC del 95%: 9.9 a 21.65, $p < 0.0001$. El promedio de tiempo en analgesia intraoperatoria adecuada fue del 82.4% (25.1) en lazo cerrado y 70.77% (+/- 32.8) en TCI, con una diferencia de 4.76 (IC del 95%: 2.23 a 21.06), $p = 0.016$. No hubo diferencias en recuerdo intraoperatorio.

Conclusión: El sistema de lazo cerrado fue mejor para mantener un BIS en rango de 40–60 durante un acto anestésico que el sistema abierto o TCI.

Introduction

Total intravenous anesthesia (TIVA) is a general anesthesia technique in which only a combination of medications, usually propofol and remifentanyl,¹ are administered intravenously.

TIVA is currently administered according to a specific concentration and a desired clinical effect, applying pharmacokinetic models that help predict the desired concentration of the drug. This technique is called *open loop* or TCI (target-controlled infusion).^{2,3}

Maintaining adequate anesthetic depth is directly related to optimal anesthetic dosage, which translates into administering the amount of anesthetic needed to maintain a surgical procedure. In the case of open-loop TIVA (TCI), its limitation has been demonstrated in certain populations due to the risk of over and/or underdosing.⁴⁻⁶

In response to this scenario, the authors designed a TIVA delivery system where the control of drug perfusion is automatically determined by hemodynamic clinical variables and by the bispectral index (BIS) value.⁷ The system controller automatically calculates the optimal perfusion velocity based on the current value and the desired value of the control variables, generating stable and fast anesthetic perfusion modifications more accurately. This type of anesthetic control is called a *closed loop*.⁷

Although the closed-loop systems in TIVA are not new, very few clinical studies have attempted to compare the performance of both systems, specifically small case series or trials whose outcome is purely technical, but not clinical.⁸⁻¹⁴

The objective of this study was to evaluate the therapeutic effectiveness of a new closed-loop intravenous anesthesia delivery system to maintain anesthetic depth, compared to an open-loop infusion system controlled by TCI targeting.

Methods

This was a 1:1 randomized, single-blind, 2-parallel groups, controlled superiority clinical trial. The study protocol was submitted for review and approval by the Ethics Committee of the Hospital Universitario San Vicente Fundación (Act 03-2015 of March 13, 2015; registered in clinicaltrials.gov before initiation: NCT02492282).

Participants

Adults over 18 years of age were selected for elective non-cardiac surgery requiring general anesthesia. Pregnant women, surgeries requiring peripheral nerve block before surgery and patients who did not consent to participate were excluded.

Procedure

Before the procedure, the patient was monitored: basic American Society of Anesthesiology (ASA) and electroencephalographic monitoring with BIS Vista monitor (Medical Systems, Boston, MA). Two Graseby 3400 perfusion pumps (Graseby Medical, Hertfordshire, UK) were connected to a venous access. Subsequently, both pumps were connected to the processing and control unit, made up of a personal computer with the application developed by the research team (Fig. 1). This program contained the pharmacokinetic models needed to perform both TCI and closed-loop anesthesia. If the patient was assigned to the intervention group, the controller assumed the anesthetic perfusion according to the BIS, heart rate, and blood pressure, modifying the anesthetic perfusion rate every 5 seconds according to diffuse logic, and using a BIS of 45 as reference values and a heart rate and individualized blood pressure according to the patient. If the patient was assigned to the control group, the anesthesiologist programmed the TCI pumps according to the pharmacokinetic models of Schnider (propofol) and Minto (remifentanyl), and the modifications were made manually according to the patient.

Outcomes

- Primary: Therapeutic efficacy determined by the percentage of time spent in an adequate anesthetic depth state (BIS between 40 and 60).^{15,16}

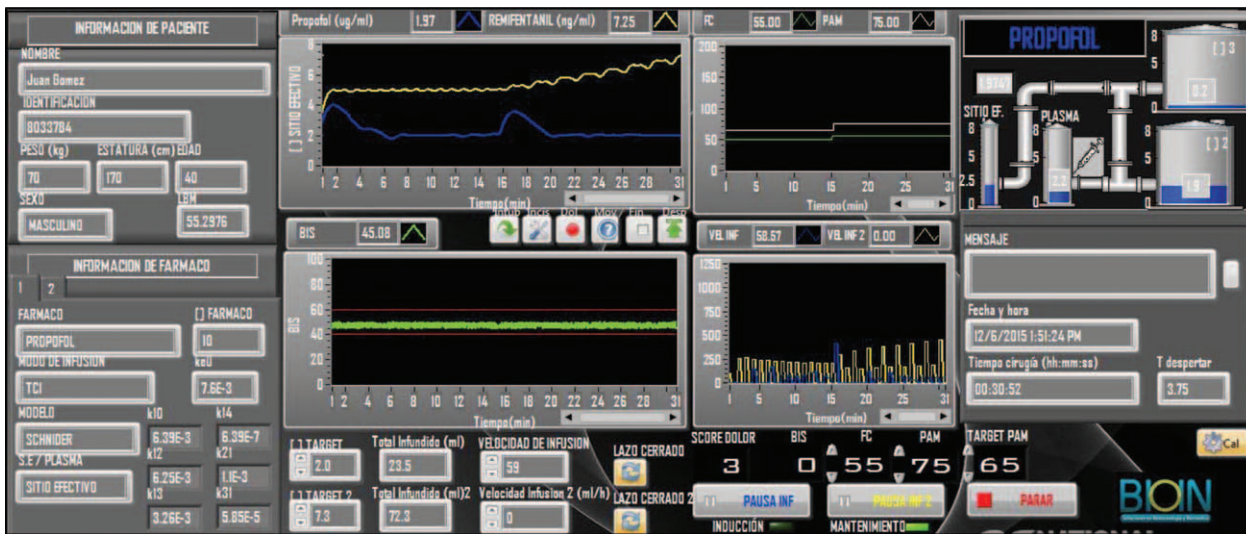


Figure 1. LabView 2010 platform, program for the administration of endovenous anesthesia in closed loop with BIS. BIS=bispectral index. Source: Authors.

- Secondary: Proportion of patients with more than 80% of the time with BIS between 40 and 60; technical performance of the controller; adequate perioperative analgesia with *analgo*score –3 to +3. *Analgo*score is a scale based on hemodynamic parameters, designed and validated to measure the state of analgesia.^{12,17} Other outcomes assessed were: manual changes in anesthetic perfusion; change from anesthetic technique to halogenated; hemodynamic instability; intraoperative recall; intraoperative patient movement.

Sample size

A sample size was calculated for a mean difference in the percentage time of the general anesthetic in adequate depth of 10%, a value determined by Hemmerling et al¹² in their clinical trial as a reference value to consider a clinically significant mean time difference between 2 intravenous anesthetic delivery systems. With a 2-tailed alpha error of 0.05 and a power of 90%, a sample of 73 per intervention group was obtained. STATA 12.0 was used (Statacorp, College Station, TX).

Randomization

Random Number Generator Software; Johns Hopkins Oncology Center, Baltimore, MD. The intervention was concealed by sequentially numbered opaque sealed envelopes and revealed before anesthetic induction.

Blinding

The study did not allow blinding of the treating anesthesiologist; however, the patients and researchers who analyzed the data were blinded. The main data were taken automatically in both groups by the controller system.

Statistical analysis

Sociodemographic and baseline clinical characteristics were described by frequencies and percentages for qualitative variables, and with measures of central tendency and dispersion for quantitative variables. For outcomes of a quantitative nature, a mean difference was made with the use of the Student t test, assuming normality in the data provided by the central limit theorem.¹⁸ For qualitative variables, relative risks were reported, and Chi-square tests were used to evaluate statistical significance. For each result their respective 95% confidence interval and their 2-tailed P value were reported, with a P of less than 0.05 being considered statistically significant.

The formulas described by Varvel et al¹⁹ were used to evaluate the technical performance of the controller:

$$PE = \frac{BIS_{medido} - BIS_{objetivo}}{BIS_{objetivo}} \times 100$$

$$MDPE_i = \text{mediana}[PE_{ij}, \quad j = 1 \dots N_i]$$

$$MDPE_i = \text{mediana}[|PE_{ij}|, \quad j = 1 \dots N_i]$$

$$\text{Wobble}_i = \text{mediana}[|PE_{ij} - MDPE_i|, \quad j = 1 \dots N_i]$$

In this formula, i is the patient number, j is the jth measure of an observation period, and N is the total number of measurements during the observation period. Performance error (PE) is defined as the difference between the actual values and the target value. The median percentage error (MDPE) is a measure of bias and the median absolute percentage error (MDAPE) measures controller inaccuracy. In this context, the Wobble is taken as a measure of intraindividual variability for PE.¹⁹

Statistical analyses were performed using STATA 12.0 and SPSS 21.0 (IBM Corporation, Armonk, NY).

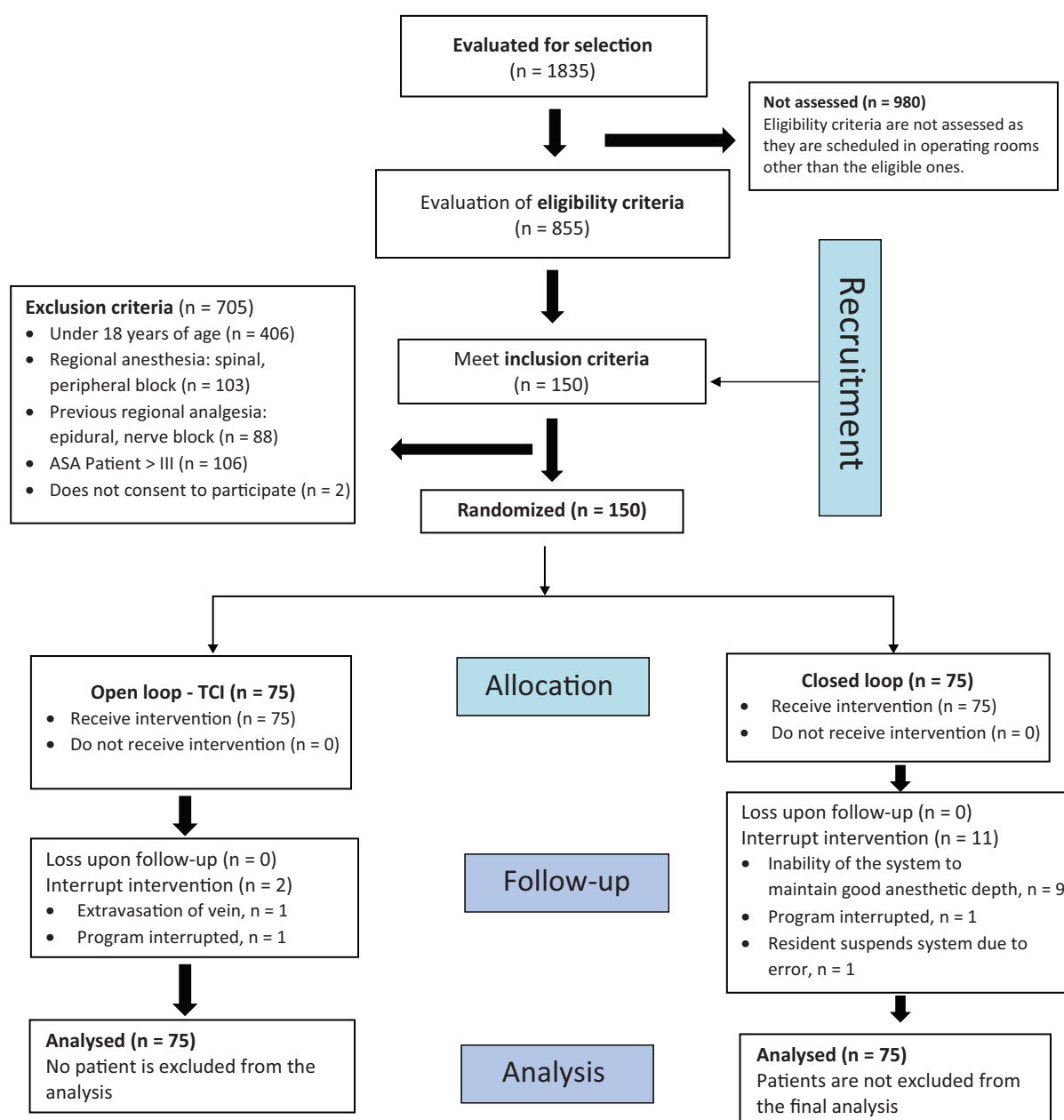


Figure 2. Patient flowchart. Source: Authors.

Results

The study was conducted between May 2015 and May 2016 (Fig. 2).

No loss during follow-up occurred; however, several interruptions of the assigned intervention were generated in each group (Fig. 2).

The basal clinical and demographic characteristics of the patients are presented in Table 1.

A difference of 15.8%, 95% confidence interval (CI) 9.9 to 21.65, was found between the 2 groups for the mean time spent in an adequate range of anesthetic depth. In addition, relative risk (RR) 2.78 (95% CI: 1.60–4.78) was

found in favor of the closed loop for a surgical time greater than 80% in adequate anesthetic depth (Fig. 3). For analgesia and other outcomes, see Tables 2 and 3.

The change in anesthetic technique within each group was less in closed-loop versus open-loop patients with RR 0.24 (95% CI 0.13–0.47).

For the safety outcomes, it was found that the incidence of hemodynamic instability in TCI was 8% compared to 2.6% in closed loop, whose difference was not statistically significant ($P=0.146$). Regarding intraoperative movement, an incidence of 12% was found in the TCI group compared to 10.7% in closed loop ($P=0.79$), and none of the groups reported episodes of intraoperative recall.

Table 1. Baseline characteristics of the patients included in the study.

Basal characteristics	Open loop—TCI (n = 75)	Closed loop (n = 75)
Age (years): mean (SD)	38.9 (14.6)	38.9 (14.5)
Gender: no./total no. (%)		
Female	39/75 (52%)	28/75 (37.3%)
Male	36/75 (48%)	47/75 (62.7%)
Weight (kg): mean (SD)	66.4 (13.6)	70.4 (12)
Size (cm): mean (SD)	163.9 (9.08)	166.4 (8.27)
Patient status: no./total no. (%)		
Ambulatory	60/75 (80%)	57/75 (76%)
Hospitalized	15/75 (20%)	18/75 (20%)
ASA classification: no./total no. (%)		
ASA I	48/75 (64%)	51/75 (68%)
ASA II	27/75 (36%)	24/75 (32%)
Type of surgical intervention: no./total no. (%)		
Orthopedics	42/75 (56%)	44/75 (58.7%)
General surgery	3/75 (4%)	4/75 (5.3%)
Gynecology—urology	13/75 (17.3%)	10/75 (13.3%)
Otorhinolaryngology	0/75 (0%)	2/75 (2.7%)
Plastic surgery	9/75 (12%)	7/75 (9.3%)
Ophthalmology	0/75 (0%)	2/75 (2.7%)
Chest surgery	4/75 (5.3%)	2/75 (2.7%)
Maxillofacial surgery	3/75 (4%)	4/75 (5.3%)
Neurosurgery	1/75 (1.3%)	0/75 (0%)
Duration of anaesthesia (min): mean (SD)	107.3 (62.6)	126.4 (53.6)
Duration of surgery (min): mean (SD)	78 (53.4)	93.2 (45.6)
Analgesic technique: no./total no. (%)		
Opioids	6/75 (8%)	3/75 (4%)
Opioids + NSAID	29/75 (38.7%)	28/75 (37.3%)
BP + NSAID	7/75 (9.3%)	9/75 (12%)
BP + opioids	2/75 (2.7%)	4/75 (5.3%)
BP + opioids + NSAID	24/75 (32%)	23/75 (30.7%)
NSAID + ketamine + opioids	7/75 (9.3%)	8/75 (10.7%)
Reverse neuromuscular relaxation: no./total no. (%)		
Yes	6/75 (8%)	0/75 (0%)
No	69/75 (92%)	75/75 (100%)

ASA = American Society of Anesthesiology, BP = peripheral nerve block, NSAIDs = nonsteroidal anti-inflammatory drugs, SD = standard deviation, TCI = target-controlled infusion.

Source Authors.

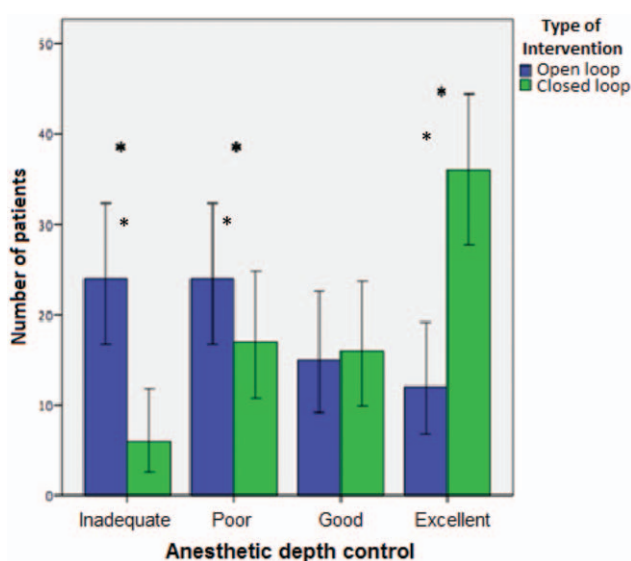


Figure 3. Anesthetic depth control categorized according to group. Excellent anesthetic control, with a percentage of anesthesia time with BIS 40 to 60 >80%; good, between 70 and 80%; poor, 50 and 70%; inadequate, <50% of the time. The data are presented in number of patients and their 95% CI. *P<0.05. BIS=bispectral index, CI=confidence interval. Source: Authors.

Discussion

The study demonstrated that the automatic anesthetic delivery system controlled by clinical variables for propofol and remifentanyl was able to maintain up to almost 3 times an adequate state of anesthetic depth based on the measurement of the bispectral index compared to the TCI systems. When evaluating the state of anesthetic depth by categories (Fig. 3), it can be observed that the closed-loop system presents a good to excellent anesthetic control in almost 80% of the patients analyzed, while the TCI system locates almost 60% of the patients in ranges of poor or inadequate anesthetic depth.

Regarding the technical performance of the system, both systems show acceptable performance, with internationally acceptable parameters for these type of devices: 10 to 20% MDPE (bias) and 20 to 40% MDAPE (precision),^{20,21} and that there is a clear statistically significant difference in favor of the closed-loop system. However, when evaluating the wobble index, which should be the closest to zero,^{20,21} neither system achieves the objective, which may be highly related to the inability of both to predict the normal course of a surgical intervention, something that supports the constant need for

Table 2. Clinical and technical performance of the controller.

	TCI open loop (n=75)	Closed loop (n=75)	Estimator	95% CI	P
BIS time between 40 and 60*	59.46 (20.3)	75.24 (15.78)	MD -15.78	-21.65 to -9.91	<0.0001
BIS 40-60 >80% anesthetic maintenance	13/75 (17.3%)	36/75 (48%)	RR 2.78	1.60-4.78	0.0001
Technical performance*					
MDPE	-11.05 (9.43)	-3.33 (5.47)	MD -7.72	-10.21 to -5.23	<0.0001
MDAPE	15.57 (6.40)	11.47 (5.29)	4.09	2.20-5.99	<0.0001
Wobble	10.22 (4.07)	9.96 (5.32)	0.26	-1.27-1.79	0.739
% Time with adequate analgesia*†	70.77 (32.8)	82.41 (25.1)	MD -4.76	-21.06 to -2.23	0.016
Good intraoperative pain control	43/75 (57.3%)	53/75 (70.7%)	RR 1.23	0.97-1.57	0.089
Surgical complications: no./total no.	0/75 (0%)	1/75 (1.3%)	DP 1.3	-1.26-3.86	0.74
Anesthetic complications: no./total no.	2/75 (2.7%)	2/75 (2.7%)	RR 1.00	0.14-6.91	1.00

BIS=bispectral index, CI=confidence interval, DP=difference of proportions, MD=mean difference, MDAPE=mean absolute performance error, MDPE=mean performance error, RR=relative risk, TCI=target-controlled infusion.

Source: Authors.

*Mean values (SD) are reported.

†An analgesia value of analgescore between -3 and +3 is considered adequate.

Source: Authors.

Table 3. Changes and modifications in endovenous techniques; quantity of medicines consumed and awakening times.

	Open loop—TCI (n=75)	Closed loop (n=75)	Estimator	95% CI	P
Change in intravenous anesthetic technique	37/75 (49.3%)	9/75 (12%)	RR 0.24	0.13–0.47	0.0001
Need to switch to halogenates	1/75 (1.33%)	2/75 (2.67%)	RR 2.00	0.18–21.58	1.00
Amount of propofol 1% (ml)*	103.43 (94.03)	102.59 (46.14)	MD 0.837	–23.13–24.8	0.95
Amount of remifentanyl 8 µg/mL (mL)*	182.79 (129.67)	209.98 (161.14)	MD –27.19	–37.4–20.2	0.26
Time to wake up (min)*	9.96 (7.35)	7.95 (4.12)	MD 2.00	0.08–3.93	0.041

CI=confidence interval, MD=mean difference, RR=relative risk, TCI=target-controlled infusion.

*Se report mean values with standard deviation (SD).

Source: Authors.

the presence and performance of the anesthesiologist in a surgical act. These findings are consistent with those reported by other authors.^{12,14}

Another result of the study was the high incidence of changes in the TCI technique (49.3%) versus the need for manual intervention in closed-loop systems (12%), mostly secondary to episodes of intraoperative movement in both groups (12% in TCI vs 10.7% in closed loop). These findings partially question the ability of the BIS to determine the state of anesthetic depth, which may eventually limit the technical and clinical capacity of this type of device (processed indices). In fact, the systematic use of BIS as the only anesthetic depth monitoring method^{21,22} is increasingly being questioned, and in this study, this situation was evident, given that the main cause of change or modification of the anesthetic technique in both groups (30.7%) was erroneous BIS information about the depth state, which led to erroneous decision-making by the anesthesiologist or the control system.

The biggest limitation was the unblinding of the anesthesiologist who performed the intervention, which could lead to a possible Hawthorne effect. Although this can bear issues of internal validity, having a clinically and statistically significant outcome with more than optimal control strengthens it.

In addition, this study was only able to determine the system's ability to follow certain electroencephalographic parameters, so it is not possible to infer from this an impact on strong clinical results.

The greatest strength of the study lies in the fact that it is the first clinical trial that simultaneously evaluates both the clinical and technical performance of a closed-loop system, using a TCI system as a comparison group.

In conclusion, the closed-loop automatic anesthetic delivery system with the BIS presents a better clinical performance in patients who will undergo intravenous general anesthesia, which does not replace the work of the

anesthesiologist, but complements it. However, more research is needed on how best to monitor the anesthetic depth status of the surgical patient.

Ethical responsibilities

Protection of people and animals. The authors declare that for this research experiments have been carried out on human beings, with the prior approval of the Institutional Ethics Committee of the Hospital Universitario San Vicente Fundación, through Act No. 03-2015 of March 13, 2015, and complying with the standards of the Declaration of Helsinki and Resolution 8430 of 1993 regulating clinical and experimental research on patients in Colombia. No animal experiments were performed.

Data confidentiality. The authors state that they have followed their workplace protocols on the publication of patient data.

Right to privacy and informed consent. Authors have obtained informed consent from patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

Assistance for the study

Dr Ángela María Tejada and Dr Ameth Javier Assia, who participated in the collection of patients.

Funding

The cost was assumed by the research group and the Hospital Universitario San Vicente Fundación.

Conflicts of interest

The intellectual property of the device studied belongs to the authors of this work.

Presentations

This paper was presented at the World Congress of Anesthesiology, WCA 2016, Hong Kong.

References

- Campbell L, Engbers F, Kenny G. Total intravenous anesthesia. *Anesthesia* 2001;33:109-119.
- Kruger-Thiemer E. Continuous intravenous infusion and multi-compartment accumulation. *Eur J Pharmacol* 1968;43:317-324.
- Struys MMRF, De Smet T, Evers A, Maze M, Kharasch E. Target-controlled infusion and closed-loop administration. *Anesthetic pharmacology basic principles and clinical practice* 2nd ed. Cambridge, UK: Cambridge University Press; 2011;103-120.
- Absalom A, Struys MMRF, Absalom A, Struys MMRF. Target-controlled infusions. An overview of TCI and TIVA 2nd ed. Ghent, Belgium: Academia Press; 2007;9-40.
- Hu C, Horstman DJ, Shafer SL. Variability of target-controlled infusion is less than the variability after bolus injection. *Anesthesiology* 2005;1023:639-645.
- Mortier E, Struys M, De Smet T, et al. Closed-loop controlled administration of propofol using bispectral analysis. *Anaesthesia* 1998;538:749-754.
- Gomez F, Casas F, Fernández J, et al. Total intravenous anesthesia in a closed loop system: Report of the first case in Colombia. *Colombian Journal of Anesthesiology* 2013;41:306-310.
- Morley A, Derrick J, Mainland P, et al. Closed loop control of anaesthesia: an assessment of the bispectral index as the target of control. *Anaesthesia* 2000;5510:953-959.
- Moerman AT, Herregods LL, De Vos MM, et al. Manual versus target-controlled infusion remifentanyl administration in spontaneously breathing patients. *Anesth Analg* 2009;1083:828-834.
- Reboso JA, Mendez JA, Reboso HJ, et al. Design and implementation of a closed-loop control system for infusion of propofol guided by bispectral index (BIS). *Acta Anaesthesiol Scand* 2012;568:1032-1041.
- De Smet T, Struys MMRF, Neckebroek MM, et al. The accuracy and clinical feasibility of a new Bayesian-based closed-loop control system for propofol administration using the bispectral index as a controlled variable. *Anesth Analg* 2008;1074:1200-1210.
- Hemmerling TM, Arbeid E, Wehbe M, et al. Evaluation of a novel closed-loop total intravenous anaesthesia drug delivery system: a randomized controlled trial. *Br J Anaesth* 2013;1106:1031-1039.
- Puri GD, Kumar B, Aveek J. Closed-loop anaesthesia delivery system (CLADS) using bispectral index: a performance assessment study. *Anaesth Intensive Care* 2007;353:357-362.
- Hemmerling TM, Charabati S, Zaouter C, et al. A randomized controlled trial demonstrates that a novel closed-loop propofol system performs better hypnosis control than manual administration. *Can J Anaesth* 2010;578:725-735.
- Johansen JW, Sebel PS. Development and clinical application of electroencephalographic bispectrum monitoring. *Anesthesiology* 2000;935:1336-1344.
- American Society of Anesthesiologists Task Force on Intraoperative Awareness. Practice advisory for intraoperative awareness and brain function monitoring: a report by the American Society of Anesthesiologists Task Force on Intraoperative Awareness. *Anesthesiology* 2006;1044:847-864.
- Hemmerling TM, Charabati S, Salhab E, et al. The Analgoscore TM: a novel score to monitor intraoperative nociception and its use for closed-loop application of remifentanyl. *J Computers* 2009;4:311-318.
- Grinstead CM, Snell JL. Grinstead CM, Snell JL. Central limit theorem. *Introduction to probability* 2nd ed. Providence, RI: American Mathematical Society Press; 1997;325-355.
- Varvel JR, Donoho DL, Shafer SL. Measuring the predictive performance of computer-controlled infusion pumps. *J Pharmacokinetic Biopharm* 1992;20:63-94.
- Schuttler J, Kloos S, Schwilden H, et al. Total intravenous anaesthesia with propofol and alfentanil by computer-assisted infusion. *Anaesthesia* 1988;43 (suppl):2-7.
- Glass P, Jacob J, Reves J. Glass P, Jacob J, Reves J. Total controlled infusion. *Intravenous drug delivery anesthesia* New York: Springer; 1990;367-386.
- Zhang C, Xu L, Ma Y-Q, et al. Bispectral index monitoring prevent awareness during total intravenous anesthesia: a prospective, randomized, double-blinded, multi-center controlled trial. *Chin Med J* 2011;12422:3664-3669.