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Variability of anesthetic depth in total intravenous anesthesia vs balanced anesthesia using entropy indices: a randomized, crossover, controlled clinical trial

Variabilidad de la profundidad anestésica en anestesia total intravenosa vs. anestesia general balanceada usando índices de entropía. Un ensayo clínico aleatorizado, cruzado y controlado

Keywords: Entropy, Intraoperative Awakening, Anesthesia, Propofol, Sevoflurane, Crossover, Clinical Trials

Palabras clave: Entropía, Despertar intraoperatorio, Anestesia, Propofol, Sevoflurano, Cruzado, Estudios clínicos

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Abstract

Introduction: Total intravenous anesthesia (TIVA) and balanced anesthesia (BA) are the most commonly used anesthetic techniques. The differences are the variability of the depth of anesthesia between these techniques that might predict which one is safer for patients and presents a lower risk of intraoperative awakening.

Objective: To determine whether a difference exists in the variability of depth of anesthesia obtained by response entropy (RE).

Methods: A crossover clinical trial was conducted on 20 healthy patients receiving upper or lower limb ambulatory orthopedic surgery. Patients were randomly assigned to (a) target-controlled infusion of propofol using the Schnider model at a target concentration of 2.5 μg/mL for 15 minutes and a 10-minute washout, followed by sevoflurane administration at 0.8 minimal alveolar concentration (MAC) for the reminder of the surgery, or (b) the reverse sequence. Differences in the variability of the depth of anesthesia using RE were evaluated using paired t-test.

Results: The treatment effect showed no significant difference in the average values of RE, during TIVA = 97.23 vs BA 97.04 ($P = 0.39$). Carry Over (−4.98 vs 4.08) and Period (100.3 vs 94.68) effects were not significantly different.

Conclusion: The present study suggests that both anesthetic techniques are equivalent in terms of the stability of the depth of anesthesia. It is important to keep testing the determinants of the

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efficacy of different populations because the individual behaviors of patients might ultimately tip the scale.

Resumen

Introducción: La anestesia total intravenosa (TIVA, por sus siglas en inglés) y la anestesia balanceada (AB) son las técnicas anestésicas más comúnmente utilizadas. La diferencia está en la variabilidad de la profundidad de la anestesia entre estas dos técnicas, lo cual pudiera predecir cuál es más segura para los pacientes y representar un menor riesgo de despertar intraoperatorio.

Objetivo: Determinar si existe alguna diferencia en la variabilidad de la profundidad de la anestesia obtenida según los índices de entropía de respuesta (ER).

Métodos: Se llevó a cabo un estudio clínico cruzado en 20 pacientes sanos que se sometieron a cirugía ortopédica ambulatoria de miembros superiores o inferiores. Los pacientes se asignaron aleatoriamente así: a) infusión controlada por objetivo (TCI, por sus siglas en inglés) de propofol, utilizando el modelo Schnider a una concentración objetivo de 2,5 μg/mL durante 15 min y un período de lavado de 10 minutos, seguido de la administración de sevoflurano a 0,8 de concentración alveolar miínima (CAM) durante el tiempo restante de la cirugía; o b) la secuencia inversa. Las diferencias en la variabilidad de la profundidad de la anestesia utilizando entropía de respuesta se evaluaron utilizando la prueba t pareada.

Resultados: El efecto del tratamiento no mostró ninguna diferencia significativa en los valores promedio de entropía de respuesta (ER) durante TIVA = 97,23 vs. AB 97,04 ($P=0,39$). Los efectos de arrastre (-4,98 vs. 4,08) y período (100,3 vs. 94,68) no fueron significativamente diferentes.

Conclusiones: El presente estudio sugiere que ambas técnicas anestésicas son equivalentes en términos de estabilidad de la profundidad de la anestesia. Es importante continuar probando los factores determinantes de eficacia en las distintas poblaciones, ya que el comportamiento individual de cada paciente pudiera finalmente inclinar la balanza.

Introduction

Intraoperative awakening is a postoperative complication associated with different manifestations, such as sleep disorders, episodes of depression, generalized anxiety, fear of hospital environments, and posttraumatic stress disorder.[1–4] The incidence of intraoperative awakening widely varies from 1:600 to 1:17,000 patients.[5,6] To avoid intraoperative awakening, cortical activity monitoring via electroencephalography (EEG) is used. Systems such as the bispectral index (BIS),[7] entropy recordings (M-Entropy),[8,9] and auditory evoked potentials[10] have guided the knowledge of the patient's degree of unconsciousness.

The EEG is a signal that changes randomly over time, without evidencing a fixed repetitive pattern, so that for its study the entropy analysis has been introduced which quantifies the complexity of the EEG waveform. Physiologically, a greater synchronism of brain wave rhythms represents a transition from wakeful states to sleep states. The EEG record of an anesthetized patient generally changes from low amplitude and high frequency during the waking state, to a greater amplitude and low frequency when a patient is in a deep plane of anesthesia (this occurs with most anesthetics except ketamine). Entropy is a measure of the random distribution of a system, a highly random system has high entropy. The entropy concept is introduced to quantify the degree of disorder and complexity of the EEG. Entropy units are presented as a percentage, 100% being the maximum degree of irregularity and zero being the minimum degree. Generally, the values in wakefulness are around 90% and for deep anesthesia the values are between 40% and 60%. There are 2 types of Entropy record: state entropy (SE), which records only the waves of brain electrical activity; Response Entropy (RE), it includes in addition to the EEG activity record, muscle activity.

Spectral entropy quantifies variations in cortical electrical activity measured using EEG and frontal activity measured using electromyography. In general, these recordings and BIS have shown strong correlations with levels of anesthetic depth as clinically evaluated across different stages.[11,12] The B-Aware study[13] demonstrated how the use of anesthetic depth monitoring via BIS reduces the incidence of intraoperative awakening by up to 82%.[14–16] Some studies, however, have used the M-Entropy module, particularly the RE index, as a better predictor of patient response to painful stimuli than BIS;[17] therefore, it can be considered an indirect indicator of anesthetic depth.

The clinical parameters for evaluating anesthetic depth are inadequate. However, the use of electroencephalographic monitoring is limited by its high cost. According to current recommendations, this type of monitoring is reserved only for patients under total general intravenous anesthesia or those with a higher risk of adverse results, such as intraoperative awakening or excessive anesthetic depth.[18]

The current literature does not include studies evaluating the variability in anesthetic depth by comparing balanced anesthesia (BA) with total intravenous anesthesia (TIVA). As such, the major objective of this research was to determine the technique that ensures the lower variability of anesthetic depth to reduce the risks of intraoperative awakening and increased morbidity with excessive anesthetic depth.

Materials and methods

A 2-period crossover clinical trial was conducted. Once the protocol was approved by the ethics committee of Clinica de La Universidad de la Sabana; the patients were enrolled between September 2017 and January 2018. Protocol was previously registered at Clinical trials (Protocol ID: 003-2017).

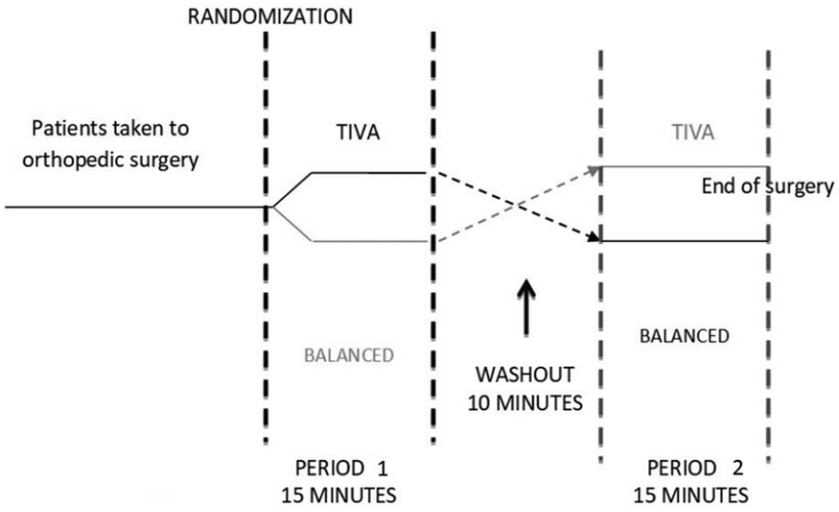

Figure 1. Cross over design.
Source: Authors.

Each of the patients was randomly assigned to either TIVA with propofol and remifentanil or to BA with sevoflurane and remifentanil, in ratio 1:1. Each patients group received anesthesia with TIVA or BA, for 15 minutes (Fig. 1). The washout period was for 10 minutes. Random numbers generated using a table in Excel were distributed to the anesthesiologist before surgery in opaque envelopes for to determine the anesthesia kind in the begin.

Patients were older than 18 years and met the criteria for American Society of Anesthesiologists physical status classification I (ASA I). All patients were scheduled for minor outpatient orthopedic surgery, excluding those who did not sign the informed consent document and those who had a history of using medication affecting the central or autonomic nervous system (e.g., benzodiazepines, beta blockers, calcium antagonists, and alpha-2 agonists). No changes were made to the original protocol.

Calculation of sample size

In order to calculate the sample size, the variability values of the anesthetic depth and its standard deviation were taken from previous works, the entropy records for the TIVA and BA techniques was determined. Using these values, the required sample size calculation was projected to determine the variabilities obtained for the TIVA and BA techniques (4.81 and 5.34, respectively) with an alpha of 0.05, a power of 0.8, and a correlation between the groups of 1; the difference in the variability between groups was established as 10 unit. As a result, an n of 20 patients was obtained in Eq. (1). No data were lost.

$$n = \frac{\left(z_{1-\frac{\alpha}{2}} + z_1 - \beta\right)^2}{d^2} + \frac{Z^2_{1-\frac{\alpha}{2}}}{2} = 20 \quad (1)$$

Source: Authors from.[19]

Procedure

The selected patients were monitored via electrocardiography, non-invasive blood pressure, pulse oximetry, capnography, and EEG. Then, regional anesthesia was established via a femoral, popliteal, or supraclavicular nerve block according to the anatomical site of the surgical procedure, guided by ultrasonography and confirmed by neurostimulation. Doses of 0.75% levobupivacaine and 1% lidocaine without epinephrine were administered with the dose adjusted by weight, verifying the absence of pain, paresthesia, dysesthesia, and pressure control during the administration of the local anesthetic. The success of the procedure was confirmed by evaluating the motor block of the relevant extremity.

After the confirmation of the block, according to the randomization for the TIVA/BA group, the induction of anesthesia was performed with remifentanil using a Target-Controlled Infusion (TCI) system at a dose of 5 μg/mL, with a subsequent bolus of propofol at a dose of 2 mg/kg. Once the anesthetic plane was reached, airway management was performed with a laryngeal mask. For maintenance, propofol infusion was adjusted by TCI at a dose of 2.5 μg/mL, and remifentanil infusion was continued at the same initial dose (period 1).

Patients assigned to the BA/TIVA group received induction with remifentanil using a TCI system at a dose of 5 μg/mL and sevoflurane at 6 vol% with a 5-L/min flow of

fresh gases. Once the anesthetic plane was reached, airway management was performed with a laryngeal mask. For maintenance, the vaporizer dial was adjusted to 2 vol% with a flow of 1 L/min. Remifentanil infusion was continued at the same induction dose (period A).

Based on the pilot test described previously, 10 minutes was determined as the washout period for both techniques. In the TIVA/BA group, the infusion of propofol was suspended after 15 minutes had elapsed since the surgical incision. For the BA/TIVA group, sevoflurane was discontinued, and the flow of fresh gases was increased to 5 L/min after 15 minutes following the surgical incision.

The time from the induction of anesthesia until the surgical incision was 20 minutes on average for all patients, which avoided the pharmacological effect of the dose of the drug administered during the induction. At the end of the washout period, the alternate anesthetic technique was initiated through the end of the surgery (period B).

The recording periods for the analysis of each anesthetic technique had an equal duration of 15 minutes for both periods 1 and 2. These records of the SE and RE indices were obtained every 5 seconds from the M-Entropy device using Datex/Ohmeda Collect (MATLAB R2018b. The Mathworks. INC) serial communication acquisition software for later processing offline in MATLAB.

Statistical analyses

In crossover studies, the following 3 effects must always be analyzed: (1) the effect due to the interventions, (2) the period effect, and (3) the carryover effect. Then, the respective null hypotheses were proposed to evaluate each of the 3 effects (Table 1). Student's t-test was used for paired data with an alpha of 0.05 and a power of 0.8. STATA 14.0 was used to analyze the data (Table 2).

Results

Randomization and patient flow during the study are described in the following flowchart (Fig. 2).

The demographic characteristics described in Table 1 were identified in the sample analyzed (n = 20 patients). In general, the sample consists of all young ASA I patients; the majority (65%) were men, the most performed procedure was knee arthroscopy, and the surgical times were brief (median = 87 minutes).

Based on the analysis of the monitoring of each patient, the averages of the variability measurement for each period and each treatment were determined. Four averages were obtained (Table 3), where X_1 corresponds to the average of the variability of the patients who started with the TIVA technique in period 1, Y_1 corresponds to the average of the variability of the patients who started with the BA technique in period 1, X_2 corresponds to the average of the variability of the patients who were switched to the BA technique in period 2, and Y_2 corresponds to the average of the variability of the patients who were switched to the TIVA technique in period 2.

These results were analyzed based on the approach of the 3 hypotheses considered for the crossover experiments previously mentioned in the statistical analyses section. For the analysis, a paired Student's t-test was applied to evaluate each of the effects, obtaining the following differences for each contrast: the treatment effect showed no statistically significant difference between the average values of RE, during TIVA (97.23) vs BA (97.04) with $P = 0.39$. The Carry Over effect was discarded (−4.98 vs 4.08) and the period effect too (100.3 vs 94.68), the P values were 0.27 and 0.20, respectively (Table 4).

Discussion

Our study did not find differences between the 2 anesthetic techniques with regard to the effect of the variability in depth of consciousness. These findings also extended to the period effect and the carryover effect.

No information is available on the variability of anesthetic depth in the medical literature. Mosquera-Dussan et al[20] was the first to study this depth using 2

Table 1. General characteristics of the sample.

Characteristics	n = 20
Age (years)	
Median	37
IQR	31.45–48
Gender	
Male (n [%])	13 (65%)
Female (n [%])	7 (35%)
BMI	
Median	24.2
IQR	22.5–26.6
Surgical time (min)	
Median	87
IQR	77.7–93.5
Types of procedures	
Complications	None

BMI = body mass index, IQR = interquratile range.
Source: Authors.

Table 2. The null hypotheses for each effect.

Types of effects	Null hypothesis
Treatment effect	$\overline{X}_1 + \overline{Y}_2 \cong \overline{Y}_1 + \overline{X}_2$
Carryover effect	$\overline{Y}_1 - \overline{X}_1 \cong \overline{X}_2 - \overline{Y}_2$
Period effect	$\overline{X}_1 + \overline{Y}_1 \cong \overline{Y}_2 + \overline{X}_2$

Source: Authors.

Table 3. Average effect of the cortical activity variability for the 2 treatments in the different periods.

	Treatment (TIVA)	Treatment (BA)
Period 1 Mean (SD)	$X_1 = 47.4$ (13.8)	$Y_1 = 46.6$ (9.2)
Period 2 Mean (SD)	$Y_2 = 47.7$ (14.1)	$X_2 = 50.9$ (12)

BA = balanced anesthesia, TIVA = total intravenous anesthesia.
Source: Authors.

pharmacokinetic models for propofol, which did not significantly differ in clinical effect.

Although Hasak et al[12] demonstrated a discrepancy between clinical reasoning and the level of anesthetic depth due to entropy, hemodynamic parameters are still used to determine the level of anesthetic depth and patient awareness during the transoperative period. Above due mainly to the cost of the monitoring devices necessary for the recording of anesthetic depth, as well as the lack of training in the interpretation of the EEG signals associated with BIS and entropy techniques.

On the other hand, by guiding the use of BA using entropy, El Hor et al[21] found that the consumption of anesthetics can be reduced. These authors evaluated the effect of entropy on inhalational anesthetic consumption, finding a significant reduction in sevoflurane consumption compared with standard clinical practice (5.2 ± 1.4 vs 3.8 ± 1.5 mL/h; $P = 0.0012$). Gorban and Shchegolev[22] evaluated monitoring of inhalation anesthesia at low flows in high-risk surgeries with entropy, finding that an adequate concentration of anesthetics was associated with fewer hemodynamic changes.

The knowledge of anesthetic depth during various procedures determines, among other factors, the clinical outcomes of the patient because this knowledge helps to control superficiality and excessive depth.[23] This result

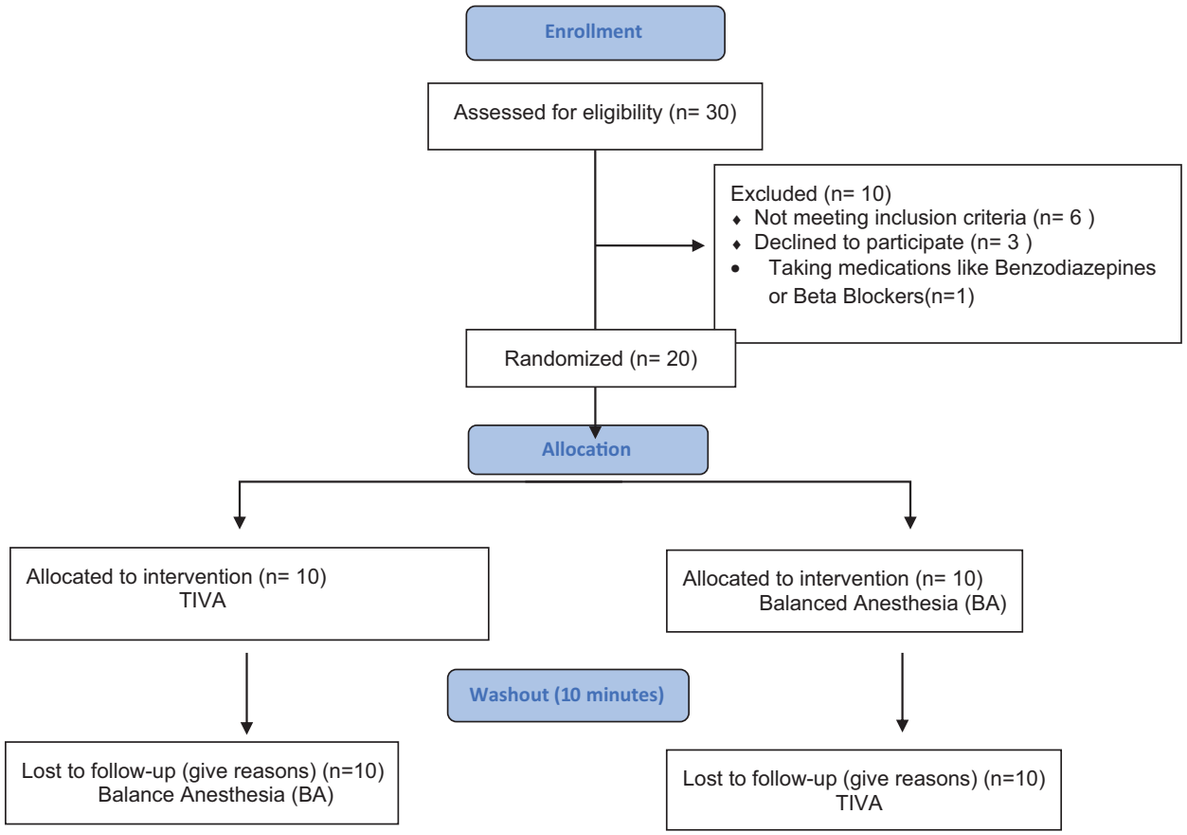

Figure 2. Flowchart.
Source: Authors.

Table 4. Comparison of the average values of the RE index across the different periods and treatments.

Types of effects	Average values	*P* value*
Treatment effect $X_1+Y_2 \cong Y_1+X_2$	52.64+45.29≅47.66+49.38 97.23≅97.042	0.39
Carryover effect $Y_1-X_1 \cong X_2-Y_2$	47.66–52.64≅49.38–45.29 −4.98≅4.083	0.27
Period effect $X_1+Y_1 \cong Y_2+X_2$	52.64+47.66≅45.29+49.38 100.3≅94.681	0.20

ANOVA = analysis of variance, RE = response entropy.
Source: Authors.
* ANOVA probability value >F.

was shown by Vakkuri et al,[9] whose choice of anesthetic agents, administration routes, pharmacokinetic models, and other characteristics was modifiable.

The lack of differences in the present study suggests that the 2 anesthetic techniques are interchangeable regarding the depth of consciousness and that the choice of the technique should be based on other parameters, such as type of procedure, cost, and adverse events.

The design used for this study shows the strength of reducing biological variability while homogenizing the population about the type of procedure, the characteristics of the population, comorbidities, and the use of a peripheral block to guarantee the state of analgesia and immobility during the procedure.

Limitations of this clinical trial are related to its external validity, as it did not include patients with comorbidities that might alter the pharmacokinetics of anesthesia or more complex surgical procedures, the results of which might be a greater variability in depth.

Having found no differences between the 2 anesthetic techniques in the depth of consciousness as assessed by the entropy index, we conclude that these techniques can be used safely at the recommended doses. Future investigations should include patients with different age ranges and comorbidities to increase the reliability of the results. There were no adverse events.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The research was approved by the Bioethics Committee of the Universidad de La Sabana Clinic, through act 0122018. The authors have obtained the written informed consent of the patients or subjects. The authors declare that the confidentiality of the information has been kept.

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Conflicts of interest

The authors have no conflict of interests regarding the publication of this article.

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