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Editorial

Characterizing depth of anesthesia during target-controlled infusions: Not an easy job☆

La caracterización de la profundidad de la anestesia durante las infusiones controladas a objetivo: No es un trabajo fácil

*Eric B. Rosero**

Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center at Dallas, United States

Availability of powerful intravenous hypnotics and opioids with specific pharmacokinetic profiles, including rapid onset and short duration of action[1] has allowed the development and popularization of total intravenous anesthesia (TIVA). Due to its safety, rapid titrability, quick recovery with better operating room efficiency, and a low incidence of nausea and vomiting,[2,3] TIVA has become a valid alternative to inhaled general anesthesia. There are several modes of TIVA administration that range from the simple intermittent injection of small boluses of hypnotics with or without opioids to the infusion of anesthetics using complex computerized infusion pumps. Target-controlled infusion (TCI) TIVA consists of the administration of intravenous anesthetics according to their pharmacokinetic profiles in order to maintain desired concentration of the drugs in the central compartment (effect-site concentration). Computerized infusion devices equipped with software that continuously controls the infusion rates of the drugs are used for this purpose. The software includes pharmacokinetic models derived from studies involving volunteers with diverse demographic characteristics. The models are mathematical algorithms used to predict the plasma concentration of a drug after the administration of a bolus or after an infusion of varying duration. The TCI system uses the pharmacokinetic models to calculates the dose regimen for each drug, which usually consists of a bolus dose delivered to fill the central compartment (plasma), a constant infusion rate equivalent to the elimination rate, and two exponentially decreasing secondary infusions to equilibrate the amount of drug transferred to the peripheral compartments of distribution. The pharmacokinetic models most frequently used for propofol TCI are the Marsh and the Schnider models.[4,5] Hemodynamic stability, recovery time, and discharge time may be improved by the use of TCI compared with manual administration of TIVA.[6,7] Furthermore, the depth of hypnosis and analgesia can be adjusted promptly and efficiently by changing the target concentration on the TCI devise without any need for mathematical calculations, comparable to changing the desired concentration of an inhaled anesthetic by just turning the dial of the vaporizer. However, TCI techniques also have several limitations, mainly related to inter-patient differences in pharmacokinetics, which may lead to poor performance of the models in prediction of target concentrations.[8]

In this issue of the Colombian Journal of Anesthesiology, Mosquera-Dussán et al.[9] present the results of a cross-over randomized clinical trial on ASA I class patients undergoing elective orthopedic surgery of the upper or lower extremity. The authors compared variability of depth of anesthesia when either the Marsh or Schnider pharmacokinetic models were used for TCI TIVA. In this original and novel study, the investigators used rigorous methodological research techniques to address their question whether there is a significant difference

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* *Correspondence to*: 5323 Harry Hines Blvd., Dallas, TX 75390-9202, United States.
E-mail address: Eric.Rosero@utsouthwestern.edu

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in variability of depth of anesthesia between the two pharmacokinetic models. Only ASA I class patients were included in the study, which probably allowed more homogeneous results by avoiding variability attributed to different patient comorbidities. An AB|BA cross-over design was used as a strategy to decrease the number of subjects needed for the study without reducing statistical power, while randomization was employed in an attempt to eliminate the effect of confounders. Spectral entropy was used to define the primary outcome of the study. Spectral entropy is a technique derived from electroencephalography used for monitoring depth of anesthesia. Two indices, the state entropy (SE) and the response entropy (RE), are calculated mainly from frontal electroencephalography (EEG) and electromyography, respectively. In general, high values in the indices indicate a conscious and alert state and low values indicate deeper levels of hypnosis. The concept of entropy is similar to monitoring with bispectral index (BIS), and studies have demonstrated acceptable correlation between BIS and entropy.[10]

Although the study is novel, the outcome measure selected by the investigators limits the capability of the study to answer the question whether any of the two pharmacokinetic models is superior in providing a more stable or less variable depth of anesthesia in patients undergoing surgery. It is known that indices derived from frontal EEG are not perfect predictors of depth of anesthesia. Multiple factors like frontal/facial muscular movement and tone, use of electro cautery or warming blankets during surgery, type of anesthetic, and presence of neurologic disorders may affect the reading of entropy or BIS monitors. Therefore, variability in the SE and RE readings can be due to these types of artifacts instead of true variation in depth of anesthesia. In this aspect, there is some evidence that intraindividual variability is smaller for BIS monitoring compared with SE or RE.[11] In their report, Mosquera-Dussán et al. studied patients undergoing orthopedic surgery under general anesthesia preceded by a regional block. Orthopedic interventions commonly cause movement, vibration, and pounding on the anatomy of the patient, factors that can introduce artifacts to the entropy reading. Similarly, incomplete blocks of the upper or lower extremity may have caused selective changes in the variability of the entropy readings due to different levels of surgical stimulation between the blocked and non-blocked areas. Inclusion of patients having either only upper extremity or lower extremity surgery would have been preferable to improve the comparability within the sample.

A concerning issue about the cross-over design used by the investigators is the inclusion of a washout period within the same anesthetic procedure. This is rarely seen in anesthesia research. Propofol was stopped during surgery after the end of the infusion period with the first pharmacokinetic model. From the methods section of the paper, it is evident that remifentanil was continued during this period. However, as remifentanil is not an anesthetic, the washout period creates serious concerns about the possibility of patient awareness. The authors do not describe the administration of any other hypnotic during this phase. Washout periods are usually designed to have duration equivalent to several half-lives of the study drug. The appropriate duration of the washout period for the study could have been inappropriate, as the investigators used plasma levels calculated from the TCI device and not from direct plasma measurements of propofol concentration. Therefore, the results of the study could have been confounded by carry over effects.

The increment in the number of ambulatory procedures is contributing to a parallel increase in the popularity of TCI TIVA in a growing number of countries. Therefore, research efforts like that performed by Mosquera-Dussán et al. aimed to improve our knowledge on the topic are commendable. Improvements in the pharmacokinetic models for TCI TIVA are necessary and depend on our better understanding of the inter-individual pharmacokinetic variability of patients. However, it is also necessary to invest research efforts in improving our current understanding of the mechanisms of anesthesia and analgesia and in finding better methods that predict accurately the depth of anesthesia.

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Conflicts of interest

The author has no conflicts of interest to declare.

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