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Randomized cross-over clinical trial comparing two pharmacokinetic models of propofol using entropy indices☆

Oscar Leonardo Mosquera-Dussán[a], Andrés Cárdenas[a], Daniel Alfonso Botero-Rosas[a,*], Andrés Yepes[a], Henry Oliveros[a], Rubén Henao[b], Fernando Ríos[a]

[a] Grupo PROSEIM, Facultad de Medicina, Doctorado en Biociencias, Universidad de La Sabana, Chía, Colombia
[b] Grupo Calidad, Seguridad, y Educación en Salud, Socciedad Colombiana de Anestesiología y Reanimación (S.C.A.R.E.), Bogotá D.C., Colombia

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ABSTRACT

Introduction: There are two different pharmacokinetic models (Marsh and Schnider) for the administration of total intravenous anesthesia with propofol, the parameter differences could have some impact over the depth of anesthesia.
Objective: To determine if there is a significant difference in the variability of depth of anesthesia suggesting that one model is superior in achieving a more stable and predictable depth of anesthesia during surgery.
Methods: A cross-over clinical trial was conducted on 16 healthy patients programmed for upper or lower limb ambulatory orthopedic surgery. Patients were randomly assigned to (i) effect site target controlled infusion of propofol with Marsh model at a target concentration of 2.5 μg/ml for 20 min, a 20 min washout, then propofol was administered with Schnider model at the same effect site target for the reminder of the surgery, or (ii) the reverse sequence. Differences in variability of depth of anesthesia, were assessed by comparing records of spectral entropy indices during surgery through an unpaired *t*-test.
Results: There was no evidence of significant difference in the mean variances of either spectral entropy indices between the two models (*p*-value: 0.57 for State Entropy, *p*-value: 0.51 for Response Entropy).
Conclusion: The study suggests that both pharmacokinetic models are equivalent in terms of stability of depth of anesthesia. It is important to keep testing determinants of the efficacy of the models in different types of population because their behavior according to individual characteristics of patients or variables such as cost-effectiveness could end up tilting the scale.

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* *Corresponding author at*: Facultad de Medicina, Doctorado en Biociencias, Universidad de La Sabana, Campus del Puente del Común, Km. 7, Autopista Norte de Bogotá, Chía, Colombia.
E-mail address: daniel.botero@unisabana.edu.co (D.A. Botero-Rosas).

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Ensayo clínico cruzado y aleatorizado para comparar dos modelos farmacocinéticos de propofol usando índices de entropía

Palabras clave:
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RESUMEN

Introducción: Hay dos modelos farmacocinéticos diferentes para la administración de la anestesia total intravenosa con propofol (Marsh y Schnider), las diferencias entre los parámetros podrían tener algún impacto sobre la profundidad anestésica.

Objetivo: Comparar la variabilidad de la profundidad anestésica durante administración de infusión de propofol con los modelos de Marsh y Schnider para determinar si hay diferencias significativas que sugieran que uno de los modelos es superior en lograr una profundidad anestésica más estable y predecible.

Métodos: Estudio clínico cruzado, controlado y aleatorizado llevado a cabo en 16 pacientes programados para cirugía ambulatoria de ortopedia. Los pacientes fueron asignados aleatoriamente a i) infusión controlada por objetivo de propofol con el modelo de Marsh a una concentración objetivo en sitio de efecto de 2.5ug/ml durante 20 minutos, 20 minutos de periodo de lavado, seguido de infusión de propofol con modelo de Schnider a la misma concentración objetivo; o ii) la secuencia inversa. La diferencia en variabilidad de profundidad anestésica fue evaluada mediante la comparación de registros de índices de entropía con una prueba t no pareada.

Resultados: No se encontró evidencia de diferencias significativas de la varianza media en los índices de entropía espectral asociada a los modelos (valor-p: 0.57 para entropía de estado, valor-p: 0.51 para entropía de respuesta).

Conclusión: El estudio sugiere que ambos modelos son equivalentes en términos de estabilidad de profundidad anestésica. Es importante continuar estudiando la eficacia de los modelos en diferentes tipos de población, dado que su comportamiento según características individuales de los pacientes o variables cómo costo-efectividad podrían inclinar la balanza.

Introduction

Currently, there are multiple efficacious anesthetic agents, inhaled as well as intravenous, and both types allow detailed titration and fast recovery with a good safety profile. However, total intravenous anesthesia has been demonstrating possible advantages over inhaled techniques, regarding not only safety during surgery and post-operative well being but also in terms of convenience of the administration technique in some specific circumstances (airway intervention, neuroanesthesia) and other issues like environmental impact. This is why total intravenous anesthesia has been gaining popularity in clinical practice, especially since the introduction of propofol, its use is increasingly widespread.[1–4]

There are two pharmacokinetic models for the administration of total intravenous anesthesia (TIVA) with propofol, Marsh and Schnider models, which take into account interactions between body compartments to modify infusion rate and, in theory, maintain a constant plasmatic concentration.[5] Although there is no evidence of clinically important differences between the two models, neither is it clear which of the two is able to predict more accurately the plasma concentrations, it is evident that they differ in the calculations of compartment volumes as well as diffusion velocity between them, which results in significant differences in total propofol dose administered, infusion velocity, and therefore estimated plasma and effect site concentration,[6] differences that could have some impact over the depth of anesthesia. Table 1, presents respective equations for each model implemented in the *B.Braun Space Infusion Pumps*,[7] corresponding parameters are: V1, distribution volume for central compartment. V2, V3, distribution volume for fast and slow peripheral compartments. k10, velocity constant for elimination rate. k12, k13, velocity constants from central compartment to peripheral compartments. k21, k31, velocity constants from peripheral compartments to central compartment.

As of today, there is no gold standard to quantitatively measure the state of consciousness and the depth of anesthesia, ordinarily their monitoring is based on judgment of the anesthesiologist, based on variables of autonomic activity, respiratory cycles and pupil size.[10] However, there has been important progress in the analysis of electroencephalographic signals by techniques like bispectral index (BIS)[11] and spectral entropy indices (M-Entropy)[12] which have demonstrated good correlation with sedation levels evaluated clinically and different steps of anesthesia.[13,14] The M-Entropy module, particularly the Response Entropy (RE) index, was considered a better predictor of patient response to painful stimuli than BIS.[15] This is why entropy measurement can be considered an indirect sign of depth of anesthesia, and allows a type of monitoring able to detect variations even within the same plane of anesthesia which makes it an ideal tool to evaluate dynamically and quantitatively the real repercussions of