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Effect of flumazenil on recovery from general anesthesia with isoflurane: A randomized controlled trial☆

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ABSTRACT

Background and objectives: The inhalational anesthetic isoflurane is widely used in general anesthetics. Its mechanism of action involves interaction with the receptor of gamma-aminobutyric acid (GABA), which is also the binding site for benzodiazepines. Flumazenil, benzodiazepine antagonist, reverses the effects of these drugs in GABA receptors and could therefore also reverse the effect of isoflurane. In anesthesia practice, extubation and early anesthetic recovery reduce morbidity and incidence of complications. The objective of this trial is to determine whether the use of flumazenil may contribute to faster recovery from anesthesia.

Methods: Forty patients scheduled to undergo general anesthesia with isoflurane were enrolled in this prospective, double-blind, randomized trial. Patients were randomized to receive, at the end of anesthesia, flumazenil or placebo as allocated into two groups. The anesthetic technique was standardized. The groups were compared concerning values of cerebral state index (CSI), heart rate, blood pressure and oxygen saturation from the application of flumazenil or placebo until 30 min after injection. Data regarding time to extubation, time to reach 10 points in the Aldrete–Kroulic score (AK = 10) and Vigilance score (VS = 10) was also collected. ANOVA test was applied to analyze the results, considering $p < 0.05$.

Results: Patients receiving flumazenil achieved faster extubation than the control ($p = 0.033$). No differences were observed in values of CSI, the time until AK = 10 and until VS = 10.

Conclusions: Administration of flumazenil at the end of isoflurane general anesthesia resulted in earlier extubation in studied patients.

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El efecto del flumazenil sobre la recuperación de anestesia general con isoflurano: una prueba aleatoria controlada

Palabras clave:
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RESUMEN

Introducción y objetivos: El isoflurano es un anestésico inhalatorio ampliamente utilizado en anestesia general. Su mecanismo de acción involucra el receptor del ácido gamma-aminobutírico. Dicho receptor es también el sitio de acción de las benzodiazepinas. El flumazenil, antagonista benzodiazepínico, podría revertir los efectos del isoflurano. En la práctica, la extubación y recuperación anestésica tempranas reducen la morbilidad e incidencia de complicaciones. El objetivo del estudio es determinar la contribución del uso del flumazenil en la recuperación anestésica.

Métodos: Se realizó un estudio doble ciego, prospectivo, aleatorio de 40 pacientes bajo anestesia general con isoflurano que recibieron flumazenil o placebo según aleatorización previa. La técnica anestésica fue estandarizada. Los parámetros comparados en los 2 grupos fueron frecuencia cardiaca, tensión arterial, saturación de oxígeno y niveles del Índice Biespectral, desde la aplicación del flumazenil y durante los 30 minutos posteriores. El tiempo transcurrido entre la inyección del medicamento y la extubación, así como el tiempo requerido para alcanzar 10 puntos en la Escala de Aldrete-Kroulic y la Escala de Vigilancia, también fueron contabilizados. El análisis de la varianza fue aplicado para comparar los datos, considerando $p < 0.05$.

Resultados: Los pacientes que recibieron flumazenil fueron extubados en menor tiempo que los del grupo placebo ($P = 0.033$). No se observaron diferencias entre los valores del Índice Biespectral y el tiempo necesario para alcanzar 10 puntos en la Escala de Aldrete-Kroulic y la Escala de Vigilancia.

Conclusiones: La administración de flumazenil al final de la anestesia general con isoflurano disminuyó el tiempo a la extubación.

Introduction

Volatile anesthetics are widely used in clinical practice of anesthesia.[1] Isoflurane is one of most used inhalational anesthetics and one of the safest among currently available. Its mechanism of action, as well as the mechanism of all inhalational anesthetics, is still discussed and researched.[2,3] Various experimental studies with isoflurane and also some clinical studies have shown, among other forms of action, their interaction with GABA (gamma-aminobutyric acid) receptor.[4–8] This receptor, described some time ago in brain physiology, is the binding site of various anesthetics such as benzodiazepines and barbiturates.

Isoflurane is an inhalational agent with a blood-gas partition coefficient about 1.46, two times greater than sevoflurane approximately. An anesthetic agent with a high blood-gas partition coefficient will diffuse readily into the blood, thus lowering the alveolar partial pressure and causing a slow induction, with a slow recovery too. To appropriately titrate isoflurane during general anesthesia requires a gas analyzer to know exactly the expiratory concentration of isoflurane. Unfortunately the use of gas analyzer is not common in many hospitals at many countries, and sevoflurane remains an inhalational agent very expensive and not routinely used. These two factors contribute to isoflurane be the most commonly used inhalational agent in general anesthesia with a slowly recovery in many times.

Flumazenil is a drug that acts as an antagonist of benzodiazepines, through interaction with GABA-A receptor.[9] Thus, it could be used to more quickly reverse the hypnotic effect of isoflurane. The literature shows that the use of flumazenil may be beneficial in reversing anesthesia with sevoflurane, but lacks studies with isoflurane in our knowledge.[10–13]

The evaluation of depth of general anesthesia can be performed with the use of hemodynamic monitoring (blood pressure, heart rate, etc.) and, more precisely, using level of consciousness monitors, such as cerebral state index (CSI). These monitors process a single frontal electroencephalographic signal to calculate a dimensionless number that provides a measure of the patient's level of consciousness. The values range from 100 to 0, reflecting the awake state and the absence of brain activity, respectively.[14,15] Using the data provided by CSI monitors, it is possible to dose the administration of anesthetic drugs based on depth of anesthesia and to evaluate its regression.[16]

It is known that general anesthesia is not completely free of risks and that early extubation and recovery from anesthesia reduces the incidence of complications and morbidity, as does early discharge from post-anesthetic recovery unit.[1] The aim of this study was to determine whether the use of flumazenil may contribute to faster recovery from general anesthesia