Doxapram shortens recovery following sevoflurane anesthesia

[Le doxapram hâte la récupération après une anesthésie au sévoflurane]

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Purpose: A randomized, double blind controlled trial was undertaken to investigate the effect of doxapram on recovery times and bispectral index following sevoflurane anesthesia.

Methods: Upon completion of surgery under sevoflurane anesthesia, 60 adult patients were randomly allocated to receive either doxapram hydrochloride 1 $mg \cdot kg^{-1}$ *iv* or saline placebo. Clinical recovery from anesthesia was assessed by time to eye opening on verbal command, hand squeezing on command, time to extubation, and the Aldrete recovery score. Bispectral index values, systolic blood pressure, and heart rate were recorded at baseline (before anesthesia), during surgery, and every minute for 15 min after administration of the study drug.

Results: Time to eye opening was shorter in the doxapram group compared with the control group (6.9 ± 2.2 min *vs* 9.9 ± 3.1 min, $P < 0.05$). Mean bispectral index scores were also higher in the doxapram group compared with the saline placebo seven to eight minutes following administration of the study medication ($P < 0.05$). More rapid emergence was associated with a greater increase in heart rate with doxapram ($P < 0.05$ compared with placebo), but no differences in systolic blood pressure responses were observed in comparison with placebo.

Conclusion: We conclude that doxapram 1 $mg \cdot kg^{-1}$ hastens early recovery from sevoflurane anesthesia, and this arousal effect correlates with higher bispectral index values.

***Objectif** : Examiner l'effet du doxapram sur les temps de récupération et l'index bispectral à la suite d'une anesthésie au sévoflurane par une étude randomisée, contrôlée et à double insu.*

***Méthode** : L'opération complétée sous anesthésie au sévoflurane, 60 patients adultes répartis au hasard ont reçu 1 $mg \cdot kg^{-1}$ de chlorhydrate de doxapram iv ou un placebo de solution salée. La récupération clinique de l'anesthésie a été évaluée par le moment de l'ouverture des yeux ou de la réaction à une commande verbale, la possibilité de serrer la main sur demande, le temps d'extubation et le score de récupération d'Aldrete. Les valeurs de l'index bispectral, la tension artérielle systolique et la fréquence cardiaque ont été enregistrées avant l'anesthésie, pendant l'opération et à chaque minute pendant 15 min après l'administration du médicament.*

***Résultats** : Le temps écoulé avant l'ouverture des yeux a été plus court avec le doxapram qu'avec le placebo (6,9 ± 2,2 min vs 9,9 ± 3,1 min, $P < 0,05$). Les scores moyens de l'index bispectral ont été aussi plus élevés avec le doxapram sept à huit minutes après l'administration du médicament expérimental ($P < 0,05$). Un retour à la conscience plus rapide a été associé à une plus grande élévation de la fréquence cardiaque avec le doxapram ($P < 0,05$ comparé au placebo), mais aucune différence intergroupe de tension artérielle systolique n'a été observée.*

***Conclusion** : Nous concluons que 1 $mg \cdot kg^{-1}$ de doxapram accélère la récupération après une anesthésie au sévoflurane. Cet effet est corrélé par les valeurs plus élevées de l'index bispectral.*

DOXAPRAM is a respiratory stimulant with effects on both peripheral and central chemoreceptors.[1–5] In addition, doxapram is also a central nervous system (CNS) stimulant and has been shown to hasten the recovery from general anesthesia with barbiturates, ether, cyclopropane, halothane and methoxyflurane.[6–10] However, its effect on sevoflurane, an inhalation anesthetic with a low blood/gas solubility coefficient and rapid recovery, has not been determined. Furthermore, the effect of doxapram on bispectral index (BIS), a widely used clinical monitor for objectively evaluating the hypnotic effect of anesthesia[11,12] and the early recovery

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phase of sevoflurane anesthesia, is also unknown. The objective of the present study was to investigate the effect of doxapram on early clinical recovery and BIS in patients following sevoflurane anesthesia.

Methods

Following Hospital Ethics Committee approval of the protocol for this double-blind, randomized prospective study, written informed consent was obtained from 60 adult patients of ASA class I and II physical status. Enrolled patients had no cardiovascular, pulmonary, or neurological diseases, and were scheduled for elective orthopedic surgeries of the lower extremities. No premedication was given. Upon arrival in the operating room, usual monitors were applied to each subject, including a precordial stethoscope, continuous electrocardiogram, peripheral pulse oximeter, non-invasive blood pressure monitor, and an end-tidal CO_2 monitor. In addition, after cleansing the skin with alcohol, a disposable BIS electrode was placed on the patient's forehead and connected to the BIS monitor (Ultraview Bispectral Index Module, Aspect Medical System, Natick, MA, USA). The BIS values, signal quality index and electromyograph bar graph were monitored continuously, and recorded at one-minute intervals throughout the study period.

After recording baseline vital signs and BIS values, anesthesia was induced with thiopental 4 $mg \cdot kg^{-1}$ *iv* and fentanyl 100 µg *iv*. Endotracheal intubation was facilitated with succinylcholine 1 $mg \cdot kg^{-1}$ *iv*. After intubation the inspiratory and expiratory concentrations of oxygen and sevoflurance were monitored. Anesthesia was maintained with sevoflurane 2–3% end-tidal concentration with oxygen, titrated to maintain BIS scores in the range of 45–50. Incremental doses of atracurium 0.1 $mg \cdot kg^{-1}$ *iv* were given as required to maintain adequate muscle relaxation. No additional opioid was used during surgery. During the last 30 min of the operation no further muscle relaxant was administered, and anesthesia was continued with assisted ventilation to maintain end-tidal CO_2 values between 35–40 mmHg. Five minutes prior to anticipated completion of surgery, sevoflurane was discontinued and the patient's lungs were ventilated with 100% oxygen at a fresh gas flow rate of 5 $L \cdot min^{-1}$. Guided by a train-of-four neuromuscular blockade monitor (TOF-Guard, Organon Teknika BV, Boxtel, Netherlands) reversal of residual neuromuscular block was achieved with neostigmine 0.05 $mg \cdot kg^{-1}$ *iv* and atropine 0.01 $mg \cdot kg^{-1}$ *iv*.

Patients were next randomly divided into two groups of equal size according to a computerized randomization table. The control Group C patients (n = 30) received normal saline *iv*, and Group D patients (n = 30) received doxapram 1 $mg \cdot kg^{-1}$ *iv* (Nhwa Pharma Corporation, Xuzhou, China) in identically appearing syringes. Study medication or placebo was administered by a dedicated research assistant who was blinded to the syringe contents, which were administered immediately after discontinuation of sevoflurane. Recovery from anesthesia was assessed by a blinded anesthesiologist. The following parameters were evaluated: eye opening on verbal command; hand squeezing in response to verbal command, and time to extubation of the trachea after discontinuation of the anesthetic gas. Heart rate, systolic blood pressure, BIS values, and SpO_2 values were determined before, and every five minutes during surgery, then every minute after the injection of the study drugs for 15 min. End-tidal CO_2 concentration and end-expiratory concentration of sevoflurane were also recorded from the time of study drug injection to the time of extubation. Aldrete recovery scores[13] were recorded upon arrival in the postanesthesia care unit (PACU) and at the time of discharge from PACU. Patients were questioned specifically about any recall or awareness during anesthesia or any abnormal psychological feeling during emergence.

The primary end-point of this study was defined as the time to achieve eye opening to verbal command. Applying an *a priori* power analysis, at least 22 patients had to be enrolled in each treatment group to provide 80% power to detect a difference at α = 0.05. Data are expressed as mean and standard deviation. Demographic data and Aldrete scores were analyzed by the Chi-square test. Bispectral index values, end-tidal CO_2, end-expiratory sevoflurane concentration, heart rate, and systolic blood pressure were analyzed by repeated-measures analysis of variance (ANOVA) and the Newman-Keuls test was applied when ANOVA was significant. Times to eye opening, response to verbal command, and extubation were also compared using repeated-measures ANOVA. Data are presented as mean ± standard deviation, and statistical significance was assumed when $P < 0.05$.

Results

All enrolled subjects completed the study protocol. Demographic characteristics were similar between groups (Table I). Groups were also comparable with respect to duration of anesthesia, end-tidal CO_2 values, and end-tidal sevoflurane concentrations (Table I). No patient received any medication during the course of anesthesia, which was not specified by the study protocol.

Mean times to eye opening, hand squeeze to command, and extubation of the trachea were signifi-

TABLE I Demographic and clinical data

	Control (n = 30)	*Doxapram (n = 30)*
Age (yr)	38.6 ± 9.7	38.8 ± 11.0
Gender (M/F)	16 / 14	15 / 15
Body height (cm)	159.2 ± 6.7	160.5 ± 5.3
Body weight (kg)	56.6 ± 9.1	58.9 ± 12.6
Hematocrit (%)	37.6 ± 3.5	38.5 ± 4.3
Anesthesia duration (min)	169.5 ± 53.5	166.6 ± 73.6
End-tidal CO_2 at tracheal extubation (mmHg)	35.6 ± 4.3	36.1 ± 5.1
End-tidal sevoflurane at tracheal extubation (%)	0.20 ± 0.05	0.18 ± 0.07

M = male; F = female.

TABLE II Recovery parameters

	Control (n = 30)	*Doxapram (n = 30)*
Eye opening (min)	9.9 ± 3.1	6.9 ± 2.2*
Response to command (min)	10.6 ± 3.1	7.6 ± 2.1*
Extubation of trachea (min)	11.2 ± 3.8	8.7 ± 2.4*

* $P < 0.05$ when compared with control group. Value expressed as mean ± standard deviation.

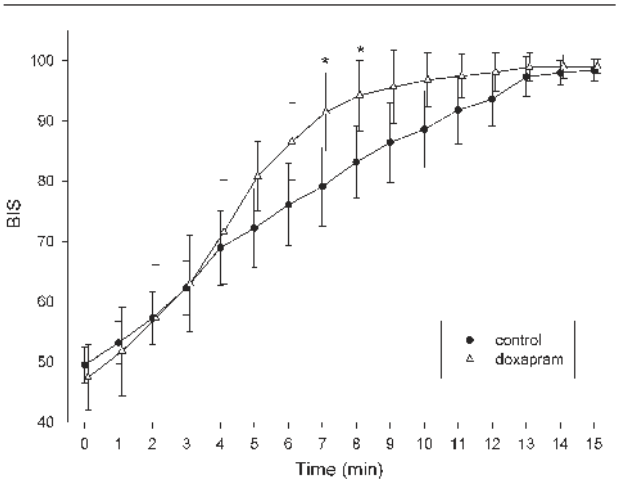

FIGURE 1 Changes in bispectral index (BIS) after injection of study drug. * $P < 0.05$ when compared with placebo.

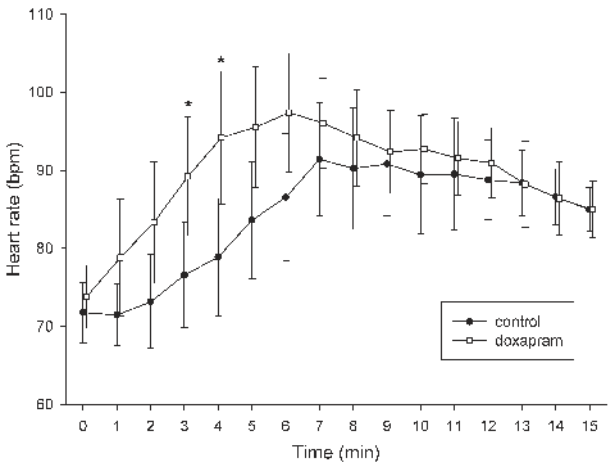

FIGURE 2 Changes in heart rate after injection of study drug. *$P < 0.05$ when compared with placebo.

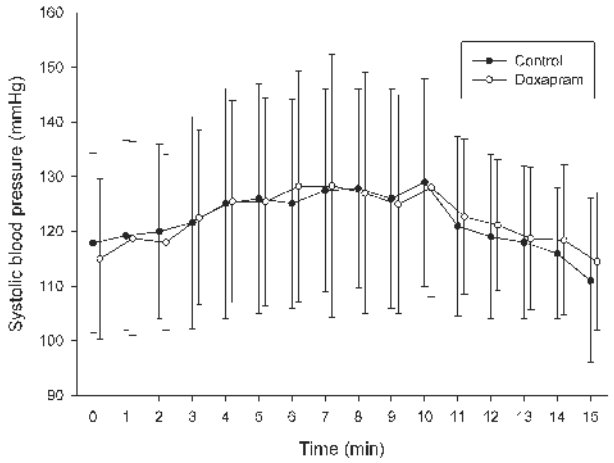

FIGURE 3 Changes in systolic blood pressure after injection of study drug.

cantly shorter in the doxapram group ($P < 0.05$) in comparison with placebo (Table II). Mean BIS scores were similar in doxapram and control groups prior to administration of the study drug. While BIS scores recovered rapidly upon discontinuation of sevoflurane, BIS scores were significantly higher in the doxapram group compared with placebo seven to eight minutes post-drug administration ($P < 0.05$). Beyond nine minutes, there were no differences in mean BIS scores between groups (Figure 1).

Following injection of study medication doxapram was associated with a significantly higher heart rate compared with the placebo group three to four minutes post-injection ($P < 0.05$, Figure 2). Changes in systolic blood pressure were similar in the two groups during emergence from anesthesia (Figure 3).

Aldrete recovery scores were similar in the two groups and all patients were discharged from PACU

uneventfully, and fully awake. No patient experienced recall or awareness during anesthesia, or any unpleasant feeling upon awakening. No adverse effects were observed. Specifically, excitation, hallucinations, and anxiety reactions were not observed in any patient.

Discussion

The main finding of this study is that doxapram 1 $mg \cdot kg^{-1}$ *iv* hastens early recovery from sevoflurane anesthesia, and is associated with more rapid recovery of BIS values.

Doxapram is a central and peripheral respiratory stimulant and a nonspecific CNS stimulant. It is presently approved for the treatment of acute respiratory failure, postoperative respiratory depression, neonatal apnea of prematurity, and postanesthetic shivering. In the 1970s and up to the 1980s doxapram was not infrequently used as an analeptic antagonizing the hypnotic and/or respiratory depressant effects of sedatives such as diazepam, opioids, barbiturates and inhalation anesthetics commonly used at that time.[10,14,15] With the introduction of selective antagonist drugs it is now well recognized that antagonism of opioids should be achieved with either naloxone or naltrexone, and antagonism of benzodiazepines can be achieved with flumazenil. However, there is a paucity of useful agents with reasonable safety profiles to antagonize the CNS depressant effects of inhalational anesthetics. Physostigmine has been used in the past, but this drug is now no longer available.

Recently, Turan *et al.* demonstrated that aminophylline 5 $mg \cdot kg^{-1}$ *iv* hastens recovery from sevoflurane anesthesia.[16] Sevoflurane, with a blood/gas coefficient of 0.65, has a rapid induction time and a generally rapid recovery.[17] However, slow recovery following sevoflurane is observed occasionally, and a pharmacological means to hasten recovery in such circumstances, without side effects, might be desirable and clinically useful. It therefore seemed logical to evaluate whether recovery from an inhaled anesthetic with a rapid recovery profile can be modified by a CNS stimulant such as doxapram, and whether BIS values correlate with the observed clinical response .[18,19] Noe *et al.* observed electroencephalogram (EEG) changes indicative of arousal with intraoperative administration of doxapram 0.5 $mg \cdot kg^{-1}$ *iv* at the end of surgery under thiamylal or halothane-N_2O anesthesia. However, these investigators did not elaborate on the specific EEG patterns.[20] Roy and Stullken reported conversion of the EEG to an awake pattern in dogs under steady state halothane anesthesia, within 22 ± 3 sec following administration of doxapram 1 $mg \cdot kg^{-1}$ *iv*.[21] In our study we found that doxapram 1 $mg \cdot kg^{-1}$ *iv* hastened recovery time in patients receiving sevoflurane anesthesia, and this improvement was also reflected in higher BIS scores. The arousal effect of doxapram appears to be directly related to its CNS stimulating effect, since both the end-tidal CO_2 and the end-expiratory concentrations of sevoflurane were similar between groups. The observed changes in BIS values, attaining a significant between-groups difference within seven minutes, coincided with clinical signs of awakening. There were no episodes of recall/awareness or any other psychological reactions possibly related to the administration of doxapram. Of equal importance, there was no "re-narcotization" effect after doxapram's response had dissipated. Aldrete scores in the PACU showed no difference between the doxapram and placebo groups, and all the patients were discharged uneventfully.

A number of adverse effects have been reported with the use of doxapram, most noticeably tachycardia, cardiac arrhythmia, hypertension, hallucinations, excitation, anxiety reactions, and even panic attacks.[7,9,10] More recently, Rosenberg *et al.* described the response of a doxapram infusion in an elderly patient following a laparotomy. The patient suffered a cerebrovascular accident, which the authors postulated may have been related to doxapram administration.[22] In an animal study, Uehara *et al.* demonstrated that a large dose of doxapram (50 $mg \cdot kg^{-1}$) given prior to bilateral carotid artery occlusion accentuates white matter damage in the neonatal rat.[23] This seems to indicate that doxapram in large doses may render the brain more vulnerable to ischemic damage. For our investigation, we elected to use a modest single dose of doxapram 1 $mg \cdot kg^{-1}$ which had previously been shown to be effective in reversing anesthetic effects, without adverse responses.[7–10] However, benefits must always be weighed against potential risks, and we would only consider using small doses of doxapram in patients where recovery from inhalational anesthesia is unexpectedly prolonged.

The clinical significance of our observations must be considered in light of that fact that doxapram is no longer commonly used. We believe that our study provides clinically relevant information regarding the correlation between the BIS and the CNS arousal effect of a CNS stimulant. The BIS has been shown to be a useful guide in monitoring anesthetic recovery without drug intervention.[18,19] and we have been able to demonstrate that BIS reflects changes during recovery from anesthesia following administration of an analeptic drug.

In conclusion, we have shown that administration of doxapram 1 $mg \cdot kg^{-1}$ *iv* hastens early recovery

from sevoflurane anesthesia, without appreciable side effects. The more rapid emergence correlates with higher BIS values when compared to placebo.

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