

Extracorporeal Circulation Interference on Emergence from Anesthesia in Patients Submitted to Myocardial Revascularization

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Summary: Barbosa RAG, Malbouisson LMS, Santos LM, Piccioni MA, Carmona MJC – Extracorporeal Circulation Interference on Emergence from Anesthesia in Patients Submitted to Myocardial Revascularization.

Background and objectives: Extracorporeal circulation (ECC) may change drug pharmacokinetics as well as brain function. The objectives of this study are to compare emergence time and postoperative sedation intensity assessed by the bispectral index (BIS) and the Ramsay sedation scale in patients undergoing myocardial revascularization (MR) with or without ECC.

Method: Ten patients undergoing MR with ECC (ECC group) and 10 with no ECC (no-ECC group) were administered with sufentanyl, propofol 2.0 µg.mL⁻¹ and pancuronium target controlled infusion. After surgery, propofol infusion was reduced to 1 µg.mL⁻¹ and suspended when extubation was indicated. Patients BIS, Ramsay scale and time to wake up were assessed.

Results: The ECC group showed lower BIS values beginning at 60 minutes after surgery (no-ECC = 66 ± 13 and ECC = 53 ± 14, p = 0.01) until 120 minutes after infusion (no-ECC = 85 ± 8 and ECC = 73 ± 12, p = 0.02). Sedation level measured by the Ramsay scale was higher in the ECC group at 30 minutes after the end of the surgery (no-ECC = 5 ± 1 and ECC = 6 ± 0, p = 0.021), at the end of infusion (no-ECC = 5 ± 1 and ECC = 6 ± 1, p = 0.012) and 5 minutes after the end of infusion (no-ECC = 4 ± 1 and ECC = 5 ± 0.42, p = 0.039). Emergence from anesthesia time was higher in the ECC group (no-ECC = 217 ± 81 and ECC = 319 ± 118, p = 0.038).

Conclusions: There was a higher intensity of sedation after the end of surgery and a longer wake up time in ECC group, suggesting changes in the pharmacokinetics of propofol or effects of ECC on central nervous system.

Keywords: Deep Sedation; Extracorporeal Circulation; Pharmacokinetics; Propofol.

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INTRODUCTION

Extracorporeal circulation (ECC) may change plasma concentrations of drugs used during anesthesia for cardiac surgery, as well as cause effects on the central nervous system leading patients to a higher sedation level, which changes patients' emergence from anesthesia time ¹.

Hemodilution, blood loss, fluid mobilization, and hypothermia effects may change drug pharmacokinetics ². A reduction in the hepatic blood flow may change biotransformation of drugs highly extracted by the liver, affecting its elimination ^{3,4}. On the other hand, in the cardiac surgery without ECC, volemic expansion with crystalloids promotes hemodilution and alteration in protein plasma concentrations and in plasma protein binding ⁵⁻⁷. Propofol pharmacokinetics profile favors a quick recovery from anesthesia, and its short action time facilitates administration through continue infusion. Pharmacokinetics software model coupled to the infusion pump allows a drug administration at a rate capable of maintaining a constant plasma concentration using target controlled infusion (TCI). It results in the maintenance of the hypnotic effect for the desirable period of time ⁸, and the quick recovery after infusion interruption ⁹. The ECC effects in patients undergoing myocardial revascularization with ECC or the hemodilution effects in patients undergoing myocardial revascularization without ECC promote pharmacokinetics and pharmacodynamics changes on propofol considered to be controversial ¹⁰⁻¹². The objective of this study was to assess the interference of ECC on emergence from anesthesia in patients undergoing myocardial revascularization with and without ECC, assessing patients postoperative sedation level and wake up time, ad-

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ditionally assessing the correlation between bispectral index (BIS) monitoring and clinical assessment (sedation scale by Ramsay et al.¹³).

METHODS

Study protocol was approved by the institutional Medical Ethics Committee. After clarifications regarding the study's general objectives, patients signed the informed consent form.

Were studied 20 patients with chronic coronary insufficiency, candidates to myocardial revascularization elective surgery, with left ventricle ejection fraction superior to 50%. Patients were randomly allocated in two non-randomized groups according to surgical practice: Myocardial Revascularization with Extracorporeal Circulation Group (ECC Group) (n = 10) and Myocardial Revascularization without Extracorporeal Circulation Group (no-ECC Group) (n = 10).

Pre-anesthetic medication consisted of oral midazolam 0.1 to 0.2 mg.kg⁻¹ dose, 30 minutes before surgery, reaching the maximum dose of 15 mg. Patients were monitored in the surgery room with electrocardiography, pulse oximetry, invasive blood pressure and central venous catheter.

Anesthesia induction was conducted with propofol through specific infusion pump (Diprifusor®, AstraZeneca, USA) with a 30-second infusion initial time and 2.0 µg.mL⁻¹ as the target concentration during the entire surgery, and sufentanil initially infused at the 0.5 µg.kg⁻¹ dose, followed by a 0.5 µg.kg⁻¹.hour⁻¹ continuous infusion through infusion pump (Anne, Abbott®, USA) specially programmed with the patient's weight and the specific drug. Continuous infusion was sustained during the entire surgery. Muscle relaxation was obtained with 0.1 to 0.2 mg.kg⁻¹ pancuronium bromide dose. Manual ventilation was used under mask and tracheal intubation with proper diameter tube, followed by mechanical controlled ventilation (Cicero Dragger®, Germany) with 8 mL.kg⁻¹ current volume, 10 respiratory incursions per minute for the respiratory frequency, I:E ratio = 1:2 and FiO₂ = 0.6 (oxygen, compressed air and PEEP = 5 cm H₂O).

After anticoagulation administration with sodium heparin 500 U.kg⁻¹, ECC started using roller pump or centrifugal pump, with membrane oxygenator and initial perfusion of 1,600 mL Ringer Lactato solution. Perfusion flow was 60 to 80 mL.kg⁻¹.min⁻¹, using moderate hypothermia at 32°C to 34°C and serial gasometry control. During ECC, hypnosis was maintained with target controlled propofol continuous infusion aiming to keep a 2 µg.mL⁻¹ plasma concentration.

At the end of the surgery, propofol target concentration was changed to 1.0 µg.mL⁻¹. It was maintained constant during transportation to the Intensive Care Unit (ICU) until the moment tracheal extubation was indicated. Extubation was indicated when patients were considered to be normothermic, hemodynamically stable, conscious and showing response to verbal commands.

Postoperative sedation intensity was assessed by bispectral index (BIS) and Ramsay sedation scale. Ramsay scale is used to assess patient sedation level. It has been described

by Michael Ramsay as part of a study about Alphaxalone/Alphadolone (Althensin) anesthetic effect published in 1974¹³. It comprehends values to be attributed from 0 to 6, observing responses given by the patient after stimulus:

- Level 1: anxious, restless;
- Level 2: cooperative, orientated, tranquil;
- Level 3: sleepy, responding to commands;
- Level 4: sleeping, brisk response to glabellar or vigorous sound stimulus;
- Level 5: sleeping, sluggish response to glabellar or vigorous sound stimulus;
- Level 6: sleeping, no response to stimulus.

Assessment of postoperative sedation intensity was performed using the BIS and Ramsay sedation scale in different moments:

- 1) At the end of the surgery;
- 2) 5 minutes after the end of the surgery;
- 3) 15 minutes after the end of the surgery;
- 4) 30 minutes after the end of the surgery;
- 5) 60 minutes after the end of the surgery;
- 6) 120 minutes after the end of the surgery;
- 7) at the end of the Propofol infusion.

When patients were hemodynamically stable and normothermic, propofol infusion was interrupted so that the patients could be extubated as fast as possible. Assessment of the BIS and Ramsay sedation scale continued at the moments described as follows in the two studied groups (ECC Group and no-ECC group):

- 1) 5 minutes after the end of the Propofol infusion;
- 2) 15 minutes after the end of the Propofol infusion;
- 3) 30 minutes after the end of the Propofol infusion;
- 4) 60 minutes after the end of the Propofol infusion;
- 5) 120 minutes after the end of the Propofol infusion;
- 6) 240 minutes after the end of the Propofol infusion;
- 7) 360 minutes after the end of the Propofol infusion;
- 8) 480 minutes after the end of the Propofol infusion;
- 9) 720 minutes after the end of the Propofol infusion.

Patient wake up time was also assessed, considered to be the time between the end of the propofol infusion and the moment the patient started to respond to verbal commands.

Groups were compared considering weight, height, body mass index, surgery time, patient intubation time and extracorporeal circulation time in the ECC group.

Statistical analysis

Studied sample size was calculated to detect a reduction in the complete emergence time when sedation is interrupted at 300 minutes in the ECC group and at 200 minutes in the

no-ECC group, considering a standard deviation of 75 minutes in both groups. For this estimation, a test power of 80% and p value = 0.05 were considered, as well as a required sample of at least nine patients in each group. Normal distribution of data was assessed by the Shapiro-Wilk test, and kurtosis and asymmetry tests. Data regarding age, weight, height, body mass index, surgery time, tracheal intubation time and complete wake up time were assessed by the Student t test for non-paired samples. The behavior of BIS values throughout the time in the groups with and without ECC was analyzed using a two-way variance analysis for repeated measures, followed by the Student-Newman-Keuls test to detect differences between the groups at several time-points. The behavior of the Ramsay scale values between the groups were compared at several time-points of interest using the Wilcoxon test, as a result of Ramsay scale's values non-normal distribution. The

Spearman test was used to assess the correlation between BIS and Ramsay sedation scale values. A p value < 0.05 was considered to be significant. All analyses were conducted using the statistical program STATA 11 (STATA Corp™, Tx, USA) and Sigmasat 3.5 (Systat Software Inc.™, Ca, USA).

RESULTS

The two groups were compared considering weight, height, age and body mass index (BMI). Regarding the intubation time and emergence from anesthesia, the ECC group showed to have greater values for these variables, with a significant difference (Table I). The surgery time was greater in the no-ECC group, though showing no significant difference. All patients reported complete amnesia during the surgical procedure. Population BIS mean values were pointed out versus time as illustrated in Figure 1.

Regarding BIS, significant differences were identified between the ECC and no-ECC groups at the following time-points: 60 minutes after the end of the surgery, at the end of the infusion, and 5, 15, 30, 60 and 120 minutes after the end of the infusion, in which the ECC group showed BIS values smaller than the no-ECC group values (Figure 1).

Higher postoperative sedation intensity was observed in the ECC group patients assessed by the Ramsay sedation scale, with a significant difference at the following time-points: 30 minutes after the end of the surgery, at the end of the propofol infusion, and 5 minutes after the end of the propofol infusion (Figure 2).

In all cases, when an association between Ramsay sedation scale and BIS values was identified, such association had been considered to be inversed, i.e., the greater the BIS value was, the smaller was the Ramsay values (Figure 3)

Table I – Patient Demographic Data in MR and TV Groups (mean \pm SD)

	ECC Group	No-ECC Group	p
N	10	10	
Gender	M = 9 F = 1	M = 8 F = 2	
Age (years)	62.20 \pm 8.32	68.50 \pm 6.57	0.0766
Weight (kg)	75.23 \pm 10.55	74.87 \pm 8.17	0.9329
Height (cm)	163.00 \pm 0.04	166.00 \pm 0.10	0.554
BMI	28.14 \pm 4.63	27.58 \pm 2.70	0.7466
ECC Time	79 \pm 23.37		
Surgery Time (min)	277.50 \pm 53.66	287.50 \pm 77.04	0.7527
TI Time (min)	689.00 \pm 123.89	568.50 \pm 119.77	0.0402
Emergence (min)	319.30 \pm 118.99	217.00 \pm 81.38	0.038

ECC: extracorporeal circulation; BMI: body mass index; TI: tracheal intubation.

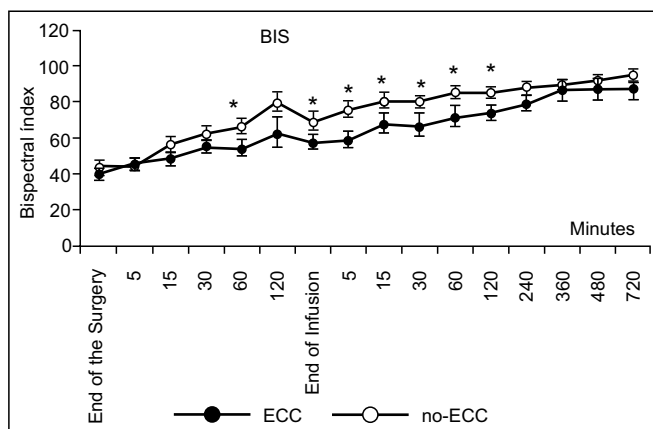


Figure 1 – BIS Mean Profile (\pm SD) according to the group and assessment timepoint.

BIS Behavior throughout the study – Black circles (ECC group) and white circles (no-ECC group).*: p < 0.05. Data presented as mean and standard error.

Table II – BIS and Ramsay Correlation at Some Assessment Timepoints in both Groups

Assessment Timepoint	ECC Group		No-ECC Group	
	I	II	I	II
End of Infusion	-	-	-0.83	0.003
5 min after Infusion	-0.44	0.209	-0.81	0.005
15 min after Infusion	-0.53	0.118	-0.36	0.313
30 min after Infusion	-0.69	0.026	-0.75	0.012
60 min after Infusion	-0.66	0.039	-0.83	0.003
120 min after Infusion	-0.41	0.244	-0.24	0.507

ECC: extracorporeal circulation.

I: Spearman Correlation Coefficient between BIS and Ramsay at some assessment timepoints.

II: Test descriptive level if the correlation is zero.

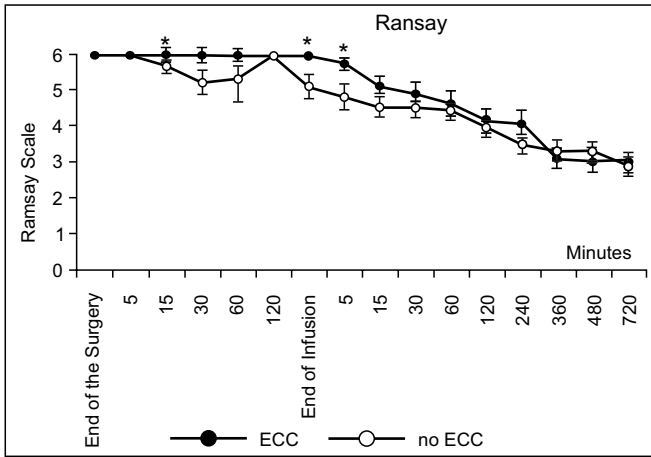


Figure 2 – Concentration Mean Profile (\pm SD) during ECC. Behavior of the sedation deepness according to Ramsay scale throughout the study – Black circles (ECC group) and white circles (no-ECC group).*: $p < 0.05$. Ramsay sedation scale values in groups described in the figure. Data presented as mean and standard error.

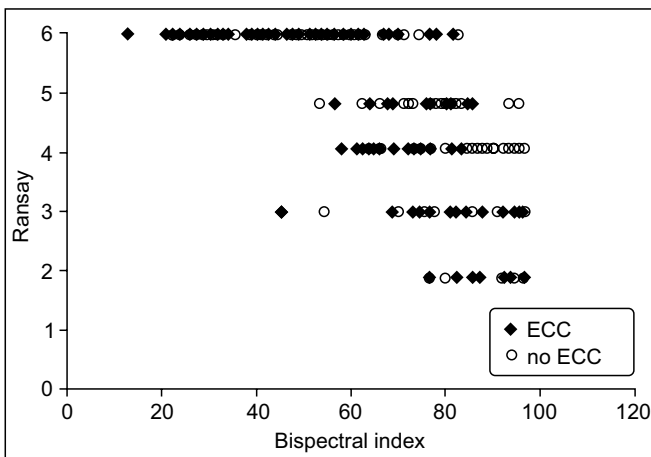


Figura 3 –BIS X Ramsay Correlation (ECC Group and no-ECC Group). Correlation between the bispectral index values and the Ramsay sedation scale values – Black lozenges (ECC group) and white lozenges (no-ECC group).

DISCUSSION

The results obtained showed that the group of patients undergoing myocardial revascularization with ECC differed their behavior regarding the emergence from anesthesia and post-operative sedation intensity after the interruption of the target controlled infusion.

The greater postoperative sedation intensity observed in the ECC group may be justified by hypothermia experienced by the patients in this group and by the central nervous system depression caused by ECC. Hypothermia also causes a reduction in the hepatic blood flow with consequent reduction in propofol metabolism. All these factors may increase patient wake up

time (calculation obtained between the end of the propofol infusion and the moment when the patient first responded to verbal commands) in this group, justifying the greater postoperative tracheal intubation time (Table I). The greatest sedation level observed in the ECC group shows a possible greater central nervous system depression caused by the ECC.

BIS is related to the anesthesia hypnotic component, without considering patient response movements or hemodynamic response to painful stimulus, providing the deepness level of the anesthesia ^{14,15}. In the present study, monitoring results demonstrated an immediate BIS reduction after the anesthesia induction in the two investigated groups, a fact that could be explained by the rapid action start and the rapid distribution of the hypnotic agent to the central nervous system. For the patients with coronary disease assessed in this study, the propofol infused dose was adequate for hypnosis.

The anesthesiologist may define propofol target concentrations that range from 2 to 6 $\mu\text{g}\cdot\text{mL}^{-1}$ for general anesthesia or 0.5 to 1.5 $\mu\text{g}\cdot\text{mL}^{-1}$ for sedation. Pharmacokinetics models of target controlled infusions rapidly reach the desired propofol target concentrations ^{16,17}. However, caution must be taken when administering propofol infusion until the desired effect is obtained due to the subjects' variability regarding propofol pharmacokinetics and pharmacodynamics ¹⁸.

Patient response to propofol during surgery is highly variable and infusion rate and administration dose will be determined according to patients' individual needs. Factors that influence the propofol dose are: age, weight, pre-existing diseases, surgery type and concomitant medical treatments.

The short duration of propofol action of approximately 5 to 8 minutes may be explained by the drug elevated clearance and quick distribution. Propofol concentration at the action site also quickly increases due to the rapid balance reached between plasma and brain concentration (< 3 minutes). These propofol pharmacokinetics features lead to a fast manifestation of the hypnotic effect and loss of consciousness. Notwithstanding the compartmental model chosen, propofol distribution at the action site is considered to be nearly instantaneous, and the drug free fraction controls the pharmacological effect intensity. Preceding studies reported up to a three fold increase in the drug free fraction during cardiac surgery with ECC ⁶. An increase in the free drug fraction of approximately 300% may contribute to ensure a rapid elevation in propofol concentration at the action site, with relevant effect in the pharmacokinetics of this agent.

Some studies have also showed a greater hypnotic effect of propofol as a result of the ECC ¹⁹. For this reason, ECC brain effects may interfere in the hypnosis level.

Results obtained in previous studies confirm that sufentanyl in the low concentrations used does not interfere in the propofol effect measured by BIS ²⁰.

Patient clinical assessment during emergence from anesthesia at the ICU is extremely important during the postoperative time of a cardiac surgery, as it enables patient early extubation. This assessment performed using the sedation scale and also the BIS enables a better follow-up of the patients.

According to the present study, sedation intensity as measured by BIS was greater in the ECC group when compared to the no-ECC group, suggesting changes in the propofol pharmacokinetics or in the ECC secondary effects on the level of sedation.

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