

THE ROLE OF SUGAMMADEX IN RESIDUAL MYOPLEGIA CONTROL IN FAST TRACK EXTUBATION PROTOCOL OF PATIENTS AFTER OPERATIONS WITH CARDIOPULMONARY BYPASS

UDC 616.77:616.12-089.168.1/5-032:612.13
Received 6.02.2012



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The aim of the investigation was clinical assessment of sugammadex (Bridan) use efficiency for early activation of patients after open-heart operations with cardiopulmonary bypass.

Materials and Methods. We analyzed the results of sugammadex (Bridan) treatment of 30 patients after open-heart operations under cardiopulmonary bypass. Among them there were 17 male and 13 female aged from 25 to 62 years (mean age 49.4±5.3 years). Cardiopulmonary bypass time was from 50 to 129 min (mean time 78.9±10.4 min), aortic compression time — from 38 to 111 min (mean time 62.1±8.2 min). We studied clinical progression of postperfusion period, acid-base composition and blood gases, the change of central hemodynamics indices and TOF index (neuromuscular conduction index). Total dose of the administered drug was 4.3–6.9 mg/kg.

Results. The recovery of a good muscle tone and autonomous breathing was observed immediately after the drug injection in 29 patients (96.7%). TOF index (neuromuscular conduction index) increased from 0.23±0.03 to 0.92±0.01 ($p \leq 0.05$) within 3–5 min after the drug administration. The drug had no effect on the changes of central hemodynamics indices, contributed to rapid and full recovery of muscle tone and autonomous breathing in patients. Extubation was performed in operating room, and activation time was 30–120 min (on average 47.0±10.4 min). 27 patients (90.0%) stayed in the intensive care unit (ICU) for 18 h on average, three patients stayed in ICU for 2 days due to the continuous cardiac pacing. The complication resulted from sugammadex usage was delayed vomiting (40–50 min after the drug administration) in 3 patients.

Conclusion. The use of sugammadex (Bridan) for fast track extubation protocol of patients after cardiosurgical interventions with cardiopulmonary bypass is feasible and very efficient.

Key words: cardiosurgical interventions; early activation in cardiosurgery; sugammadex.

Anesthetic resuscitative modalities providing quickest possible cessation of artificial ventilation of the lungs (AVL) after operations with cardiopulmonary bypass (CPB) are considered abroad as the main component of the so called “fast-track cardiac surgery” promoting hospital stay reduction, treatment process improvement, and cost-saving treatment. In this country such technical approach is generally referred to as fast track extubation protocol, and ALV cessation is considered to be the key point of postoperative recovery of patients’ physical activity [1–5].

One of the basic components of fast track extubation protocol of patients after operations with CPB is timely and complete muscular block correction. Waiting on the completion of neuromuscular relaxant action means just unreasonable waste of time, and the use of anticholinesterase

drugs presents the risk of severe hemodynamic disorders that is undesirable for patients who underwent an open-heart operation.

A new medication, sugammadex, binding molecules of amino-steroid non-depolarizing muscle relaxants, turns a new page in anesthesiology [6]. Sugammadex is the first medication of a new group of cyclodextrins. They are called a group of selective substances binding muscle relaxant molecules. The size and shape of sugammadex molecule make it possible to act as “synthetic” receptor (“molecule-guest”) that encapsulates amino-steroid neuromuscular relaxants (Vecuronium bromide, Rocuronium bromide) resulting in muscle relaxant dissociation from nicotinic acetylcholine receptors. It is confirmed by the fact that sugammadex administration leads to the increase in

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rocuronium plasma concentration (free, and as a part of a complex).

The result of sugammadex-rocuronium complex formation is the rapid decrease of free rocuronium effective plasma concentration. It produces gradient of muscle relaxant concentrations between plasma and neuromuscular synapse. As a result of back diffusion, muscle relaxant leaves H-cholinoreceptor, and neuromuscular conduction recovers.

Currently, there are only single reports about sugammadex use in cardiac anesthesia [7], and it has given rise to the present research.

The aim of the investigation was clinical assessment of sugammadex (Bridan) use efficiency for fast track extubation protocol of patients after open-heart operations with cardiopulmonary bypass.

Materials and Methods. Sugammadex (Bridan) was used in the treatment of 30 patients after open-heart operations with CPB performed in Nizhny Novgorod Specialized Cardiological Clinical Hospital (Russia) in 2011. Among the patients there were 17 male and 13 female aged from 25 to 62 years (mean age 49.4 ± 5.3 years), with body mass from 58 to 93 kg (mean weight — 74.3 ± 6.7 kg). Table 1 shows clinical characteristic of the patients.

After complex clinical functional examination, all patients underwent the following operative interventions: aortic valve replacement — 7 (23.3%); mitral valve replacement — 7 (23.3%); tricuspidal valve replacement — 1 (3.3%); mitral valve replacement + tricuspid valve plastic correction — 8 (26.8%); mitral valve plastic correction + tricuspid valve plastic correction — 2 (6.7%); tricuspid valve plastic correction — 1 (3.3%); coronary artery bypass grafting — 3 (10.0%); aortic valve replacement + coronary artery bypass grafting — 1 (3.3%). CPB time was 50–129 min (mean time — 78.9 ± 10.4 min), aortic cross-clamping time — 38–111 min (mean time — 62.1 ± 8.2 min).

We used different anesthetic management schemes (Table 2).

As anesthetic induction 15 patients received midazolam (0.1 mg/kg) and propofol (2 mg/kg) intravenously, and 15 patients — sevoflurane inhalation. Administration of Esmeron (0.1 mg/kg) was followed by tracheal intubation, and then — AVL by Primus ventilator (Drager, Germany). Volume control ventilation was performed in 26 patients, and pressure control ventilation was used in 4 patients. For AVL we used air-oxygen mixture with $FiO_2 = 0.5$.

Before CPB in 22 patients anesthesia was maintained by sevoflurane inhalation (1–4 vol.%), in 8 patients — continuous intravenous infusion of propofol (2–3 mg/kg/h), and there were used reduced fentanyl dosages of $3.1 \pm 0.2 \mu\text{g/kg/h}$. Total myoplegia was achieved by continuous intravenous Esmeron infusion at the rate of 0.4 $\mu\text{g/kg/h}$.

During CPB sevoflurane (2–3 vol.%) was administered via a vaporizer which was connected to the oxygenator gas supply line (19 patients), in 11 patients — by continuous intravenous infusion of propofol (2–3 mg/kg/h) with fentanyl (3 $\mu\text{g/kg/h}$) added.

After CPB, cardiac recovery, and stabilization of hemodynamics, we excluded fentanyl from anesthetic

Table 1

Clinical characteristics of the operated patients

Index	Number of patients	
	Absolute number	%
One-valve heart diseases	14	46.7
Multi-valve heart diseases	10	33.3
Coronary artery disease (CAD)	3	10.0
Valvular heart diseases + CAD	1	3.3
Infective endocarditis	2	6.7
Congestive heart failure:		
II A	15	50.0
II A–B	12	40.0
II B	3	10.0
NYHA class:		
III	27	90.0
IV	3	10.0

Table 2

Main anesthetic management schemes

Medications used for anesthesia	Number of patients	
	Absolute number	%
Anesthetic induction:		
Dormicum + propofol + Esmeron	15	50.0
Sevoflurane inhalation + Esmeron	15	50.0
Before CPB anesthesia was maintained by:		
Sevoflurane + fentanyl + Esmeron	22	73.3
Propofol + fentanyl + Esmeron	8	26.7
Anesthesia during CPB:		
Sevoflurane + fentanyl + Esmeron	19	63.3
Propofol + fentanyl + Esmeron	11	36.7
Anesthesia after CPB:		
Sevorane + Esmeron	22	73.3
Propofol + Esmeron	8	26.7

scheme, and anesthesia was maintained by sevoflurane inhalation (1–2 vol.%) in 22 patients, and by intravenous propofol infusion (2 mg/kg/h) in 8 patients against the background of total myoplegia by Esmeron, we decreased its dosage up to 0.2–0.3 mg/kg/h.

CPB was performed on “Stockert” machine (Germany) with oxygenators “Niproval” (Japan) in normothermic conditions, with perfusion flow of 2.5–2.6 L/min/m². Ultrafiltration was used during CPB in 20 patients, and average volume of the removed fluid was from 1.5 to 2.5 l.

To protect myocardium, we induced crystalloid cardioplegia by Consol solution using an additional pump of heart and lung machine in 25 patients. In 5 patients we used constant ante- and retrograde coronary perfusion and performed the operation on “a beating” heart with aortic cross clamping.

We stopped sevoflurane inhalation, infusion of propofol and esmeron after sternum closure and suturing subcutaneous fat. After the operation a patient was covered by warm drapes, constant warming was kept by warm mattress; continuous aspiration system was used for postoperative bleeding control, followed by gastric lavage, then we set to a patient’s activation. Bridan

was administered in an average dose of 4 mg/kg. On awakening and return of spontaneous breath, a patient was changed over Pressure Support with gradual pressure support reduction. When appropriate consciousness and spontaneous respiration recovered, we controlled the indices of pulmonary mechanics, acid-base balance, blood gases. In case the patients had satisfactory indices, they were extubated and transferred to intensive care unit (ICU) for case follow-up. There were studied clinical course of the postperfusion period, acid-base balance, blood gases, the change of central hemodynamic parameters and TOF index (neuromuscular conduction).

The findings were statistically processed using software package "Statistica 6.0". We calculated arithmetic mean of a set sample (M), standard deviation (s), error in arithmetic mean (m) and Student t-test. The values were presented as $M \pm m$. The reliability of degree (p) was determined according to confidence coefficient and degree of freedom for tables. The differences of the findings were considered to be statistically significant if $p < 0.05$.

Results and Discussion. There were studied the character of cardiac recovery after ischemia, cardiac rhythm disturbances in post-perfusion period (Fig. 1), the necessity and dosages of catecholamines (Fig. 2). The great majority of patients were noted to have a favorable type of cardiac recovery, we used small doses of catecholamine after CPB. At the end of the operation 20 patients had no inotropic support, and 10 patients — low rate of their administration that indicated a good recovery

of myocardial contractility function after cardioplegic arrest and stable indices of central hemodynamics. Moreover, no significant intraoperative blood loss (total blood loss did not exceed 500 ml (5.8 ml/kg), and hemoglobin level was over 100 g/L in 25 patients), a good diuresis rate, stably good level of blood gases and saturation (HbO_2 — 99–100%, p_aO_2 — 180–250 mm Hg) after CPB enabled to start fast track extubation protocol in all patients. The presence of atrioventricular block (3 patients) and infrequent atrioventricular nodal rhythm (2 patients) were not contradictions to the technique, since appropriate cardiac pacing in these patients provided steady dynamics. 3 patients required blood transfusion, and they received 400 ml of packed red blood cells to correct blood loss (after the transfusion Hb level was over 100 g/L). The control of activated coagulation time, partial thromboplastine time, and INR (international normalized ratio) in post-perfusion period made it possible to maintain close control over coagulation. Infusion therapy of post-perfusion period included fresh frozen plasma transfusion, the correction of electrolytic and voluminal imbalance by albumin infusion (200–300 ml), K-Mg aspartate, hydroxyethyl starch products, saline solutions. Glucose level was corrected.

The indications to using of fast track extubation protocol were the following: 1) a favorable type of cardiac recovery; 2) small doses of inotropic support therapy at the moment of CPB termination; 3) no significant intraoperative blood loss; 4) good diuresis rate; 5) stably good level of blood gases and saturation (HbO_2 — 99–100%, p_aO_2 — 180–

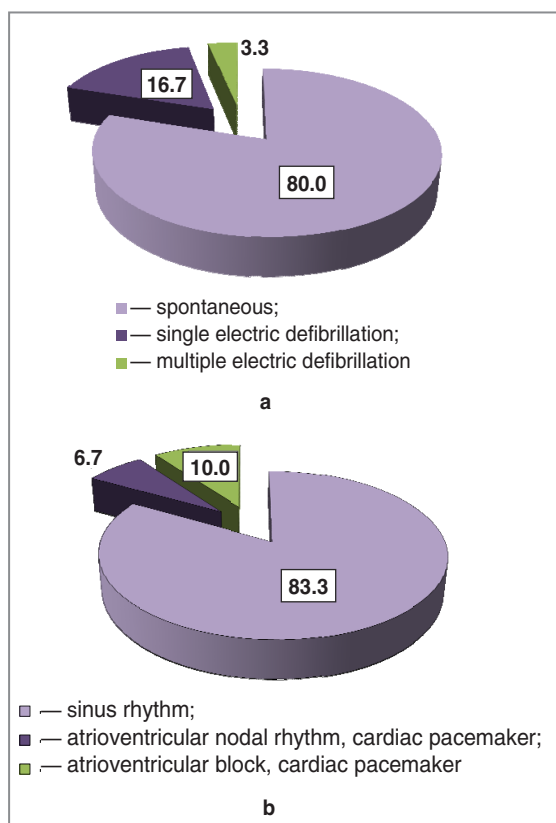


Fig. 1. The character of cardiac recovery (a) and cardiac rhythm disturbances (b) after cardioplegia

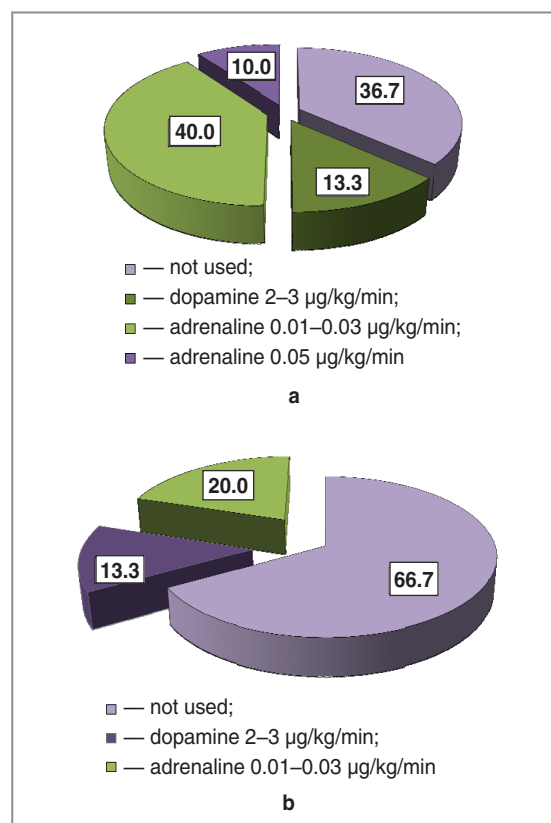


Fig. 2. The use of catecholamines after CPB (a) and at the end of the surgery (b)

250 mm Hg) after CPB. The assessment these factors enabled to set to the technique of fast track extubation in all patients.

The total dose of sugammadex (Bridan) administered was from 4.3 to 6.9 mg/kg (average dose — 5.5 ± 1.2 mg/kg). The recovery of good muscular tone was noted immediately after the drug injection in 29 patients (96.7%). Only one female patient showed delayed muscular activation start (on the average, 10 min later), which was still to the extent recommended by a manufacturer. Spontaneous respiration was restored immediately after the medication administration in 28 patients (93.3%), and only in two patients — 10 min later. TOF index (neuromuscular conduction) increased from 0.23 ± 0.03 to 0.92 ± 0.01 ($p \leq 0.05$) within 3–5 minutes after sugammadex administration. Moreover, there were the patients who recovered consciousness, opened eyes and could come in contact immediately after the medication administration. Not all researchers recognize this effect, some of them do not reveal significant improvement in patients' consciousness, and prove it by bispectral (BIS)-index studies. However, we recorded the significant consciousness improvement in 28 patients (93.3%). It should be noted that sugammadex administration was not accompanied by the changes in cardiac rhythm, and the levels of arterial and central venous pressure. Table 3 shows the data on clinical condition of the patients during the activation.

For intraoperative AVL we used air-oxygen mixture with FiO_2 — 0.5 in volume control mode in 26 patients, and pressure control mode — in 4 patients. On surgery completion, $\text{p}_a\text{O}_2/\text{FiO}_2$ ratio, a predictor of fast track extubation ineffectiveness, was calculated in all patients [1]. If the ratio is less than 300, a recruitment maneuver is recommended. The alveoli were "opened" under AVL with pressure control, reaching maximum pressure in airway (31.6 ± 1.2 cm of water column) and positive end-expiratory pressure (PEEP) (16.4 ± 0.4 cm of water column). An average $\text{PaO}_2/\text{FiO}_2$ value after the first maneuver was 152 mm Hg. At the attempt of activation its value did not differ from those recorded before the maneuver. All patients were extubated in the operating room within 47.0 ± 10.4 (30–120) minutes after injecting sugammadex. The basic parameters of hemodynamics, acid-base balance, gas exchange are shown in Table 4.

27 patients (90.0%) stayed in ICU for 18 h on average, three patients stayed for 2 days due to the continuous cardiac pacing. The complication resulted from sugammadex usage was delayed vomiting (40–50 min after the drug administration) in 3 patients. In this regard, when sugammadex is administered, we recommend preventive use of antiemetic drugs.

The monitoring of neuromuscular block level before extubation is to be an essential component of an anesthesiologist's work.

Saving on sugammadex (Bridan) dosage is impossible due to recurarization risk in case inadequately small doses are used.

Sugammadex is the medication of choice for rapid neutralization of muscle relaxant in case of failed intubation or impossibility of appropriate ventilation performance.

Table 3

Clinical condition of patients during fast track extubation

Index	Number of patients	
	Absolute number	%
AVL intraoperative mode:		
by volume	26	86.7
by pressure	4	13.3
AVL mode during activation:		
Pressure support ventilation + PEEP	30	100.0
$\text{paO}_2/\text{FiO}_2$ at the end of the surgery	290–450	386.0 ± 24.0
the use of a recruitment maneuver	6	20.0
$\text{paO}_2/\text{FiO}_2$ before extubation	320–450	391.0 ± 19.0
Extubation, min	30–120	47.0 ± 10.4

Table 4

Basic hemodynamic parameters, acid-base balance, gas exchange during the stages of fast track extubation protocol

Parameters	Before Sugammadex administration	Before extubation
BP mean, mm Hg	70.5 ± 1.8	$77.9 \pm 1.4^*$
Heart rate	91.3 ± 2.1	92.4 ± 1.9
Central venous pressure, mm Hg	10.5 ± 0.3	9.1 ± 0.6
Esophageal T, °C	36.9 ± 0.1	36.2 ± 0.2
ΔT , °C	0.4 ± 0.1	0.3 ± 0.1
$\text{paO}_2/\text{FiO}_2$	330 ± 15	344 ± 11
paCO_2 , mm Hg	35.7 ± 0.5	$38.2 \pm 0.4^*$
Arterial blood pH	7.41 ± 0.1	7.43 ± 0.1
BEa, mmol/L	-0.8 ± 0.1	-0.2 ± 0.1
P_vO_2 , mm Hg	37.8 ± 1.0	37.7 ± 0.9
HbO _{2v} , %	67.3 ± 1.5	67.0 ± 1.8
Hemoglobin, g/L	92 ± 0.3	$105 \pm 0.5^*$
Total protein, g/L	52.1 ± 0.9	$65.8 \pm 1.1^*$

* — statistically significant difference of values in different phases, $p \leq 0.05$.

The medication is to be used only when Rocuronium or Vecuronium are used as muscle relaxants.

Conclusion. The use of sugammadex (Bridan) appeared to be very effective for fast track extubation protocol of patients after cardiopulmonary bypass. It had no effect on the changes of central hemodynamic indices contributing to rapid and full recovery of muscle tone and autonomous breathing of patients.

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