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Original Contribution

The effect of sugammadex on steroid hormones: A randomized clinical study

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Abstract

Study objective: Sugammadex is an alternative drug to traditional decurarization by cholinesterase inhibitors. It has been examined the effect of sugammadex on steroid hormones in this study.

Design: Randomized clinical trial.

Setting: The study was conducted in a University Teaching Hospital from January 2013 to May 2014.

Patients: Fifty male patients between 18 and 45 years of age with an American Society of Anesthesiology (ASA) class I or II undergoing elective lower extremity surgery were included in this study.

Interventions: Patients were categorized into two groups (neostigmin group, Group N; and sugammadex group, Group S). In addition to standard monitorization, train-of-four (TOF) was also used to monitorize the level of neuromuscular blockade. Standard induction and maintenance of anesthesia were performed. At the termination of surgery, neuromuscular blockade was antagonized using 0.05 mg/kg of neostigmine and 0.01 mg/kg of atropin when spontaneous recovery of neuromuscular blockade occurred with the reappearance of T2 in Group N and using 4 mg/kg sugammadex in Group S.

Measurements: The primary outcome in this study was to determine serum aldosterone, cortisol, progesterone, and free testosterone levels. Three blood samples were obtained in each patient just before and 15 minutes and 4 hours after antagonism,

Main results: No significant differences were found in demographic characteristics between the groups. While there were no differences in serum progesterone levels, patients in neostigmin group had significantly higher cortisol levels at 15 minutes as compared to baseline. Also, patients in sugammadex group had significantly higher serum aldosterone and testosterone levels 15 minutes after antagonism as compared to those in the neostigmine group.

Conclusions: Our findings suggest that sugammadex is not associated with adverse effects on steroid hormones progesterone and cortisol, while it may lead to a temporary increase in aldosterone and testosterone.

1. Introduction

The action of non-depolarizing neuromuscular blocking agents can be terminated either spontaneously or pharmacologically [1]. Sugammadex, a recently introduced agent, represents an alternative to traditional decurarization by cholinesterase inhibitors and negates the effect of steroidal neuromuscular blocking agents through their encapsulation.

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This unique mechanism of action allows quick neutralization of the effect of neuromuscular blocking agents, even if they are administered at intubation doses. Sugammadex is particularly effective in the re-initiation of spontaneous respiration in patients who are not able to be intubated and ventilated through the elimination of muscular paralysis [2–5].

Despite the above-listed advantages of sugammadex, the product label states that concomitant use of toremifen (a selective estrogen receptor modulator) and certain antibiotics (flucloxacilline, fucidic acid) on the day of surgery may result in decreased efficacy of sugammadex, with an additional word of caution on the occurrence of capture reaction with concomitant use of oral contraceptives again on the same day of surgery. Also, skipping the dose in patients receiving flucloxacilline or progesterone is recommended before sugammadex use [6]. In in vitro study, it has demonstrated that dexamethasone inhibited dose-dependently sugammadex reversal [7].

In the present study, our aim was to examine the effect of sugammadex on endogenous steroid hormone levels in patients receiving this agent for the reversal of the neuromuscular blockade of rocuronium, on the basis of the assumption that sugammadex could be associated with encapsulation of other steroidal molecules.

2. Materials and methods

The study protocol was approved by the Local Ethics Committee for Human Research (University Medical School Ethical Evaluation Commission Chairman, 10.01.2013) and ACTRN. The study is a randomized controlled, blinded and parallel clinical trial. After obtaining written/oral informed consent from patients who were scheduled for lower-extremity surgery with an expected duration of surgery ≥ 1 and <3 hours, a total of 50 male patients between 18 and 45 years of age with an American Society of Anesthesiologists physical status class of I-II were included in the study. Exclusion criteria included the following: an ASA III or greater, presence of significant muscular, neurological, psychiatric, hepatic, renal, cardiac, endocrinological (including diabetes mellitus) and peripheral neurological disease, cooperation difficulty, possible difficult intubation, treatment with steroids or hormones, obesity (body mass index >30 kg/m2), use of agents interacting with neuromuscular blocking agents (i.e. magnesium, anti-convulsants, aminoglycosides), a history of hypersensitivity to neuromuscular blocking agents, opioids or other agents used for general anesthesia, and a history of drug or alcohol abuse.

The patients were randomly (allocation ratio was 1:1) assigned into the two following groups based on the sealed envelope method: Group S, sugammadex group (n = 25); and Group N, neostigmine group (n = 25) by an applicator that does not interfere with the patients. After placing the patient on the surgery table the patient was monitored with electrocardiography (ECG), non-invasive blood pressure (NIBP) measurement, and peripheral oxygen saturation (SpO2). An intravenous access route was established on the arm with no neuromuscular monitorization using a 20 G cannula and physiological saline infusion was commenced.

In all patients, prior to the induction of anesthesia, two electrodes were placed on the ulnar nerve trajectory after cleansing the forearm skin by alcohol in order to provide neuromuscular monitorization by TOF device. The acceleration transducer was placed on the thumb, the remaining four fingers were fixed on the arm board, thus allowing free movement of the thumb. In order to maintain a skin temperature above 33 C in the monitored arm, cotton pads were used. The TOF device (TOF-Watch®S, Organon, Ireland) was set at 2 Hz and 0.2 ms with 10-sec stimulation intervals.

After pre-oxygenation with 100% O_2 for 3 minutes, anesthesia was induced with 2 mg/kg of propofol, 0.6 mg/kg of rocuronium, and 1 μgr/kg/min remifentanyl. At the time of no-response to TOF stimulation after induction, endotracheal intubation was performed for mechanical ventilation at a target end-tidal carbon dioxide ($ETCO_2$) value between 35 and 40 mmHg.

Anesthesia was maintained with 2 to 2.5% sevoflurane in a 50%:50% mixture of O2 and dry air. At the time of response to TOF stimulation (re-appearance of T2), additional doses of rocuronium (0.15 mg/kg) were administered. For analgesia, remifentanyl infusion at a dose of 0.5 to 5 μgr/kg/min was given according to patient's need.

At the termination of surgery, sevoflurane was stopped and 100% O_2 inhalation was started. After obtainment of at least 2 responses to TOF stimulation, reversal of neuromuscular blockade was achieved with 0.05 mg/kg neostigmine and 0.01 mg/kg of atropine sulfate (Group N) or 4 mg/kg of intravenous sugammadex. At the time of awakening from anesthesia the TOF values and durations for which antagonists were administered and the time to a TOF ratio of 0.7, 0.8 and 0.9 after antagonism were recorded in both groups. Patients with a TOF ratio greater than 0.9 who have spontaneous respiration and adequate muscular power were extubated and transferred to the recovery room.

For steroid-hormone assays, a total of three blood sampling was performed just before sugammadex/neostigmine

Table 1 Demographic data of groups (mean ± SD).

	Group N (n = 25)	Group S (n = 25)
Age (year)	28.96 ± 8.32	33.04 ± 9.15
Weight (kg)	76.04 ± 9.77	76.08 ± 11.10
ASA (I/II)	16/9	19/6
Operation duration (minute)	103.80 ± 38.27	102.60 ± 39.45
Total rocuronium dose (mg)	56. 64 ± 13.28	58.60 ± 15.91
TOF 0.7 (min)	116.80 ± 67.49	56.00 ± 31.62 *
TOF 0.8	155.20 ± 76.87	72.80 ± 41.18 *
TOF 0.9	196.80 ± 80.96	81.60 ± 40.79 *

* : P < .001, Group N was compared to Group S.