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Rocuronium reversal: sugammadex versus neostigmine in asthmatic patients undergoing open cholecystectomy

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Abstract: Sugammadex is a new selective relaxant binding drug that provides a rapid decrease in free rocuronium in the plasma and also at the nicotinic receptor that helps in proper awakening of patients, which is extremely helpful for minimizing postoperative respiratory complications. The aim of this study is to compare the recovery profile of sugammadex versus neostigmine in asthmatic patients undergoing open cholecystectomy.

Methods: This study included 60 patients of ASA physical status II, aged 45–55 years with controlled bronchial asthma undergoing open cholecystectomy. General anesthesia was induced with propofol (2–3 mg/kg), fentanyl 1 μg/kg, and then rocuronium 0.6 mg/kg was administered to facilitate tracheal intubation (train of four (TOF) guarded). Muscle relaxation was maintained throughout the procedure with additional bolus doses of rocuronium 0.15 mg/kg which were administered upon appearance of the second twitch in TOF to maintain neuromuscular block during surgery. Patients were allocated randomly into two equal groups: (group I) received sugammadex 4 mg/kg, and (group II) received neostigmine 0.05 mg/kg and atropine 0.02 mg/kg (group II) as a reversal agent. Assessment of pulmonary function tests on the day before and 30 min after extubation was made. In addition capillary hemoglobin oxygen saturation was measured as well as the reversal time.

Results: The reversal time showed highly significant differences between the two groups: 2.5–3 min in group I versus 21–25.3 min in group II. Pulmonary function tests (PFT) and number of patients unable to perform sustained head elevation for 5 s showed non-significant differences between the two groups.

Conclusion: This study showed that the benefits of sugammadex are superior to those of neostigmine in reversing rocuronium-induced neuromuscular blockade in asthmatic patients undergoing open cholecystectomy.

Keywords: Sugammadex, Neuromuscular blocker antagonists, Nerve stimulator, Asthma, Lung function

Introduction

Neostigmine is a cholinesterase inhibitor that is commonly used to reverse the residual effects of nondepolarizing neuromuscular blocking agents at the end of surgery. Although it is generally considered to be safe and effective for reversing the residual block, it may cause undesirable side effects through stimulation of muscarinic receptors such as bradycardia, bronchospasm, increased airway secretions, and also airway resistance (Van Vlymen and Parlow 1997; Booij et al. 2002); therefore, neostigmine should be used with caution in asthmatic patients (http://emc.medicines.org.uk/medicine/20888/SPC/Neostigmine+Methylsulphate+Injection+BP+2.5mg+in+1 ml/#CLINICAL_PRECAUTIONS n.d.). Although muscarinic antagonists such as atropine are often co-administered with neostigmine to counteract cardiopulmonary side effects, it is associated with adverse effects such as blurred vision, dry mouth, and tachycardia (Feinberg 1993). Also there are other limitations to neostigmine use such as incomplete reversal from deep residual block and emesis (Kim et al. 2002; Caldwell 1995).

Therefore, there is a need for another reversal drug with rapid onset of action and the same efficacy or even better irrespective to the degree of residual neuromuscular block and with better side-effect profile (Hunter and Flockton 2006).

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Sugammadex (Bridion) is a newly developed agent for reversing neuromuscular block (NMB) induced by either rocuronium or vecuronium. It is a cyclodextrin molecule that encapsulates steroidal non-depolarizing neuromuscular blocking agents (NDBAs). As a result it can reverse profound block and can be given for immediate reversal without the need to wait for partial recovery, (even recovery that could take place after a few minutes) (Gijsenbergh et al. 2005). This may be beneficial for the patients requiring rapid sequence induction of anesthesia or facing difficult intubation as it allows immediate reversal of relaxation which enables the use of large doses of rocuronium in the knowledge that should a "cannot intubate-cannot ventilate" situation occurs, the block will be reversible. The use of sugammadex in this situation avoids the potentially serious adverse effects of the currently used agent succinylcholine as anaphylactic and allergic reactions, cardiac arrest, myalgia and malignant hyperthermia (Chambers et al. 2010). As it is a modified-γ-cyclodextrin compound, its mechanism of action does not result in stimulation of the cholinergic nervous system (Bom et al. 2002), thus avoiding undesirable side effects of routinely used anticholinesterases that need the addition of muscarinic antagonist (Donati 2008).

Aim

The aim of the study was to compare the recovery profile in asthmatic patients undergoing open cholecystectomy reversed by conventional anticholinesterase such as neostigmine versus the novel one, sugammadex.

Patients and methods

After obtaining approval from our institution's Ethical Committee and informed consent from all patients, this study was conducted in Ain Shams University hospitals. The study included 60 patients aged 45–55 years of ASA physical status II with controlled bronchial asthma who were on regular medications with mild to moderate obstructive pattern in the pulmonary function test (PFT) and undergoing open cholecystectomy. They were allocated randomly into two equal groups using a computer-generated system to receive either sugammadex 4 mg/kg (group I), or neostigmine 0.05 mg/kg and atropine 0.02 mg/kg (group II) as a reversal agent to the muscle relaxant.

Obese patients (BMI > 35), those with neuromuscular, cardiac, hepatic, renal diseases, those with severe obstructive respiratory pattern, and patients with history of difficult intubation or suspected to be difficult were excluded from this study.

Preoperative investigations were done in the form of ECG, chest radiograph, complete blood picture, liver, kidney function, and PFT. None of the patients received premedication. An intravenous line was inserted, and basic monitors were applied upon arrival to the operating room (ECG, pulse oximeter for O_2 saturation values, end-tidal carbon dioxide, and non-invasive blood pressure). The neuromuscular function of the adductor pollicis muscle was monitored by using the TOF-Watch_ SX acceleromyograph (Organon Ireland Ltd. Co., Dublin, Ireland). After induction of anesthesia TOF tracing was stabilized by administering 1 min of repetitive TOF stimulation followed by a 5-s, 50-Hz titanic stimulation, and then another 3–4-min period of repetitive TOF stimulation. Calibration of the transducer of the acceleromyograph and determination of the supramaximal threshold were done by using the CAL2 mode. TOF stimulation at the predetermined supramaximal threshold (at a pulse width of 200 s and a frequency of 2 Hz) was repeated every 15 s. All these data were transferred via an interface to a laptop computer in the operating room in areal time.

A BIS monitor strip (BIS X, Aspect medical system, Norwood, Massachusetts, USA) was applied to the patient forehead of the dominant hemisphere according to the guidelines of the manufacturer.

General anesthesia was induced with propofol (2–3 mg/kg), fentanyl 1 μg/kg, and then rocuronium 0.6 mg/kg was administered to facilitate tracheal intubation when complete block occurs. Ventilation was controlled to maintain end tidal CO_2 at 30–35 mmHg. Anesthesia was maintained with 50% oxygen in air and 1.5% isoflurane. Additional bolus doses of rocuronium 0.15 mg/kg were administered upon appearance of the second twitch in TOF to maintain deep profound neuromuscular blockade during the duration of surgery (1–2 post-tetanic response). By the end of the surgical procedure, discontinuation of isoflurane was performed; then, patients received either sugammadex (Bridion: Merck & Co, Kenilworth, NJ, USA) 4 mg/kg (group I) or neostigmine 0.05 mg/kg and atropine 0.02 mg/kg (group II) as reversal agent.

The test drug was injected upon appearance of the second twitch in response to TOF stimulation. Both were prepared in 10-ml syringe by a resident who was blind to the type of drug injected.

Patients were extubated when TOF ratio reached 0.9 and after full recovery. Clinical signs of recovery were assessed immediately after extubation including level of consciousness (awake and oriented = 3, arousal with minimal stimuli = 2, responsive only to tactile stimulation = 1). Orientation was assessed, then clinical assessment of muscle strength using (5-s head-lift test, 5-s hand-squeeze test) (Sacan et al. 2007). Reversal time was defined as the time from administration of the test drug till TOF ratio of 0.9 was recorded. The number of patients who were unable to perform a sustained head lift for 5 s was also recorded.

Pulmonary function tests were performed in the sitting position by the same technician who was blinded to the patient allocation group, on the day before surgery and 30 min after extubation. The following variables were recorded: forced expiratory volume in first second (FEV1), forced vital capacity (FVC), and peak expiratory flow rate (PEFR); all parameters were measured using a Microlab 3000 series bedside spirometer (Micro Medical Ltd, Rochester, UK). Also capillary hemoglobin oxygen saturation SpO_2 was measured using a DatexCardiocap pulse oximeter (Datex, Helsinki, Finland) after breathing room air for 10 min.

Statistical analysis The sample size of this study was based on data from previous studies, PASS 11 was used for sample size calculation, where a sample size of 27 per group will achieve 80% power to detect a difference of 15.0 min in reversal time between the 2 groups with estimated group standard deviations (SD) of 10.0 and 3.0 min and with a significance level (alpha) of 0.05000 using a two-sided two-sample *t* test, 30 patients per group were included to replace any missing data.

The statistical analysis was performed using SPSS software package version 17 (Chicago, IL). Data were expressed as mean values ± SD, median (interquartile range IQR) and numbers *n* (%). Student's *t* test was used to analyze the parametric data, Mann-Whitney test for non-parametric data and categorical variables were analyzed using the χ^2 test, with *p* values < 0.05 considered statistically significant.

Results

Sixty asthmatic patients undergoing open cholecystectomy were successfully enrolled in this study, 30 in each group; the variables in demographic data did not show any statistically significant difference between the two groups with respect to age, weight, height, sex and duration of operation (Table 1).

As regards PFTs, there were no statistically significant differences between the sugammadex group and neostigmine group either before surgery or 30 min after extubation; (*p* value for FVC was 0.19, for FEV1 was 0.12, for PEFR was 0.64, and for SpO_2 was 0.47). In contrast, PFTs parameters, except SpO_2, differed significantly 30 min after extubation from those before surgery. FVC at 30 min after extubation was 46.5 ± 2% of the preoperative value for sugammadex group and 44.5 ± 3.6% in the neostigmine group; FEV1 and PEFR 30 min after extubation were 45 ± 2% and 47 ± 2.9% respectively for sugammadex group while they were 43.2 ± 2.8% and 45 ± 4.9% of the preoperative values respectively for neostigmine group compared with 100% before surgery. Lastly, for sugammadex group SpO_2 30 min after extubation was 95.3 ± 1% compared with 97.5 ± 0.6 % before surgery and for neostigmine group it was 95.1 ± 1.7% after extubation compared with 96.7 ± 0.4% before surgery and all were non-significantly different when compared between groups and between pre and postoperative values in the same group (Table 2).

Table 1 Demographic data

	Group S (*n* = 30)	Group N (*n* = 30)	*p* value
Age (years)	48.1 ± 4.3	47.9 ± 4.2	0.88
Weight (kg)	80.1 ± 5	82 ± 4.4	0.09
Height (cm)	167 ± 5	165.8 ± 7.8	0.52
Sex (M/F)	15/15	18/12	0.6
Duration of operation (min)	66.87 ± 2.5	65.8 ± 2.5	0.09

Values are expressed as mean ± SD or ratio
p > 0.05 was considered statistically non-significant

The reversal time was highly significantly different between the two groups; the sugammadex group reached a TOF of 0.9 in a mean time 2.7 (2.5–3) minutes versus 23 (21–25.3) minutes in the neostigmine group (*p* value < 0.001) (Table 3).

There were no significant differences between the two groups regarding number of patients unable to perform sustained head elevation for 5 s (only one in sugammadex group versus three in neostigmine group) (*p* > .5).

Discussion

This study was done to evaluate the efficacy and safety of sugammadex versus neostigmine in patients with pulmonary diseases. It was associated with a more rapid and complete reversal of profound rocuronium-induced neuromuscular block with fewer postoperative respiratory complications.

It is well known that patients with pre-existing pulmonary diseases have an increased risk of perioperative pulmonary complications (Bremerich 2000; Groeben 2004; Wong et al. 1995; Smetana 1999). General anesthesia, the anesthetic drugs and the process of surgery may all have an effect on the respiratory system.

Sugammadex which is a modified γ-cyclodextrin form that tightly binds 1:1 complexes with aminosteroid-based muscle relaxants and act as chelating or encapsulating drug. The ability of sugammadex to encapsulate rocuronium increases the latter plasma concentration, thereby reducing the number of rocuronium molecules at neuromuscular junction leading to rapid reversal of residual neuromuscular blockade (Sacan et al. 2007). This means that there is no direct interaction with cholinergic system and this obviates the need for anticholinergic drugs as glycopyrrolate and atropine.

Neostigmine, which is the most widely used acetylcholinesterase inhibitor and is the logical comparator for sugammadex, should be used with caution in asthmatic

Table 2 Pulmonary function tests (%)

	Group S (n = 30)		Group N (n = 30)		p value
	Before	After (% of before)*	Before	After (% of before)*	
FVC	100%	46.5 ± 2†	100%	4 4.5 ± 3.6†	0.19$^{\bullet}$
FEV1	100%	45 ± 2†	100%	43.2 ± 2.8†	0.12$^{\bullet}$
PEFR	100%	47 ± 2.9†	100%	45 ± 4.9†	0.64$^{\bullet}$
SpO2 (%)	97.5 ± 0.6	95.3 ± 1$^{\bullet}$	96.7 ± 0.4	95.1 ± 1.7$^{\bullet}$	0.47$^{\bullet}$

Values are expressed as mean ± SD
$^{\bullet}p > 0.05$ was considered statistically non-significant comparison between the two study groups after surgery
$^{\dagger}p < 0.001$ was considered statistically significant in the same group between after and before surgery
*This is as regards all pulmonary functions except for SpO_2

patients as its parasympathomimetic action may cause bronchospasm.

Our study showed that sugammadex 4 mg/kg was generally well tolerated in asthmatic patients, and this coincides with the study done by Amao et al. (Amao et al. 2012) who showed that sugammadex 2 and 4 mg/kg was also well tolerated in patients with underlying pulmonary diseases.

Other non-sugammadex studies have investigated the incidence of perioperative bronchospasm in both general population and in those with history of pulmonary disease. In those without a history of pulmonary disease, the incidence was close to 0.17% (Olsson 1987). The same study done by Olsson et al. (Olsson 1987) proved that the incidence may reach 2.2% in patients with pulmonary disease.

As regards other side effects; the study done by Sacan et al. (Sacan et al. 2007) found that no evidence of hypotensive effect of sugammadex when administered under steady-state anesthetic conditions. Mean arterial pressure (MAP) and heart rate (HR) values remained stable during the entire post-reversal observation period. About symptoms of PONV (postoperative nausea and vomiting); most studies suggest an increase in these symptoms after administration of antichoinestrases in patients undergoing ambulatory surgery (Ding et al. 1994; Lovstad et al. 2001). However, in our study, sugammadex was generally well tolerated.

The study also focused on the benefits of ensuring a rapid and complete reversal of profound block; it demonstrated that sugammadex was associated with much faster reversal time (2.5–3) minutes versus (21–25.3) minutes for neostigmine, which is almost 10 times faster.

Table 3 Number of patients incapable of head lifting and reversal time

	Group S (n = 30)	Group N (n = 30)	p value
No. unable of head lift	1	3	0.6
Reversal time (min)	2.7 (2.5–3)	23 (21–25.3)	< 0.001

This is important to avoid the hazards of undetected postoperative residual neuromuscular block in postanesthesia care units.

TOF ratio of 0.9 was considered the standard for neuromuscular recovery after neuromuscular blockers (Khuenl-Brady Karin et al. 2010). The test drug was injected upon appearance of the second twitch; the time interval between injecting the test drug and TOF ratio of 0.9 is considered as the reversal time. These parameters coincide with those studied by Fuchs-Buder et al. (Fuchs-Buder et al. 2007) which detected the same results as ours.

Another previous study had shown that sugammadex at doses of 4 and 8 mg/kg was able to reverse profound neuromuscular block produced by rocuronium in a mean time 1.7 min (Rex et al. 2009). Also, Amao et al. (Amao et al. 2012) proved that there was a trend towards faster recovery of neuromuscular block with sugammadex at 4 mg/kg than 2 mg/kg dose group (1.8 min versus 2.1 min) for recovery of TOF ratio of 0.9.

In the present study the reversal agent was administered as the volatile agent was discontinued to allow assessment of the reversal time without being influenced by the volatile agents as the later can potentiate the neuromuscular junction and this can potentially slow down the reversal process. This is contradictory to a study conducted in 2010, in which the volatile agent had been continued until TOF ratio reached 0.9 (Khuenl-Brady Karin et al. 2010). Also, Sacan et al. (Sacan et al. 2007) administered sugammadex in the presence of volatile agent. However, a BIS monitor was used to exclude the risk of awareness in the current study and patients were excluded if the BIS was 60 or more before injecting the reversal agents and isoflurane was resumed.

Conclusion

The use of sugammadex in reversing profound rocuronium-induced neuromuscular block is superior to neostigmine in asthmatic patients undergoing open cholecystectomy. Further studies are needed to weigh the cost-benefit relationship in the use of sugammadex in routine clinical practice.

Abbreviations
ASA: American society of anesthesiologists; BIS: Bispectral index; BMI: Body mass index; ECG: Electrocardiogram; FEV1: Forced expiratory volume in first second; FVC: Forced vital capacity; HR: Heart rate; IQR: Interquartile range; MAP: Mean arterial pressure; NDBAs: Non-depolarizing neuromuscular blocking agents; NMB: Neuromuscular block; PEFR: Peak expiratory flow rate; PFT: Pulmonary function tests; PONV: Postoperative nausea and vomiting; SD: Standard deviations; SpO_2: Oxygen saturation; TOF: Train of four

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Authors' contributions
The idea of the research belongs to the first author NG. NG also participated in the design of the study and performed the statistical analysis. TY conceived of the study, participated in its design and clinical data collection and coordination. HA helped to draft and participated in clinical data collection. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The study was approved by the ethical and scientific committees of the department of Anesthesia, Faculty of Medicine, Ain-Shams University 2015 and after obtaining a written informed consent from the patients.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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