Reversal of Rocuronium Induced Neuromuscular Block with Sugammadex or Neostigmine in Patients Undergoing Uvulopalatopharyngoplasty

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Abstract

Background: Obstructive sleep apnea syndrome (OSAS) is now considered to be a major public health concern, with significant morbidity and mortality. One of the most common surgical procedures used in OSAS patients is uvulopalatopharyngoplasty (UPPP). The recent introduction of sugammadex, allows the rapid and complete reversal of especially rocuronium-induced neuromuscular blockade.

Methods: 40 patients who are candidated to undergo UPPP had been enrolled in the study. 20 patients as group (A) [sugammadex group] and the other 20 patients as group (B) [neostigmine group]. This prospective, randomized, double-blinded, clinical trial study was designed to compare the efficacy of reversal of neuromuscular blockade induced by rocuronium either by neostigmine or sugammadex.

At the end of surgery, all patients will receive reversal of neuromuscular blockade either by sugammadex 4mg/Kg regarding group (A) or by neostigmine 0.05mg/Kg and atropine 0.02mg/Kg for group (B). Efficacy of the reversal will be assessed by nerve stimulator.

The Primary outcome was to Compare between reversal time of neostigmine and sugammadex [time between administration of the drug and visual loss of fade (train of four ratio of 0.9)].

The secondary outcome was to detect intraoperative complications and to detect successful extubation, reintubation, and failure of extubation in both groups.

Results: Comparison between reversal time of neostigmine and sugammadex was assessed as primary outcome for the study and there was a significant difference between the 2 groups. The patients were also assessed for intraoperative complications and intraoperative laryngeal view, there were no significant differences detected. Also, there was no significant difference detected regarding successful extubation, reintubation, and failure of extubation in both groups.

Conclusion: By comparing the efficacy of reversal of neuromuscular blockade produced by rocuronium either by neostigmine or sugammadex using train of four ratio (TOF), we found a statistically significant difference between neostigmine and sugammadex group. However there was no statistically significant difference regarding intraoperative complications, intraoperative laryngeal view, successful extubation, reintubation, and failure of extubation in both groups.

Key Words: Sugammadex – Neostigmine – Reversal of neuromuscular block – Train of four.

Introduction

OSAS is an extremely common sleep related breathing disorder, and its prevalence has been increasing throughout the world because of obesity and increasing age of the general population [1]. It results in increasing upper airway resistance, reduced blood oxygen levels, fragmentation of sleep and clinical manifestations from snoring alone to obstructive sleep apnea, and cardiovascular and pulmonary complications [2].

One of the most common surgical procedures used in OSAS patients is uvulopalatopharyngoplasty (UPPP) [3]. Perioperative complications of uvulopalatoplasty included difficult intubation, reintubation, postoperative pulmonary edema, postoperative desaturations, and/or need for continuous positive airway pressure [4].

The incidence of postoperative residual neuromuscular blockade is still alarmingly high with the prevalence of a train-of-four (TOF) ratio of less than 0.9 found in the postoperative recovery unit. Recent studies have been able to link even seemingly low levels of residual paralysis (TOF ratio <0.9) with significant impairment of pharyngeal muscle function, hypoxic ventilatory drive and decreased respiratory function in the immediate postoperative period [5].
The recent introduction of sugammadex, has raised hopes to finally overcome the problem of residual neuromuscular blockade [6]. Also, due to its pharmacodynamic profile, sugammadex, in combination with rocuronium, may have the potential to displace succinylcholine as the “gold standard” muscle relaxant for rapid sequence induction [7].

This prospective, randomized, double-blinded, clinical trial study was designed to compare the efficacy of reversal of neuromuscular blockade produced by rocuronium either by neostigmine or sugammadex.

The Primary outcome was to compare between reversal time of neostigmine and sugammadex [time between administration of the drug and loss of visual fade (train of four ratio of 0.9)].

The secondary outcome was to detect intraoperative complications and to detect successful extubation, reintubation, and failure of extubation in both groups.

**Patients and Methods**

After obtaining Local Research Ethics Committee approval and written informed consent, forty patients aged above 18 years with ASA physical status II and III, underwent uvulopalatopharyngoplasty under general anesthesia were included in the study that had been done in Cairo University hospitals (Kasr Al-Ainy) from May 2015 to February 2016. Patients known to have allergy to rocuronium, allergy to sugammadex, patients with ASA more than III, significant renal or hepatic disease were excluded. They were randomly allocated into 2 groups (20 patient in each group) using computer generated number and concealed using sequentially numbered, sealed closed opaque envelope technique. Group (A) have received reversal of neuromuscular blockade by sugammadex, group (B) neostigmine. After induction, the envelope was opened by an anesthetist who prepared the study drug. This anesthetist was not involved in the anesthetic management during surgery or postoperative assessment to insure blinding.

**Preoperative assessment:**

Obstructive sleep apnea syndrome (OSAS) was diagnosed by clinical symptoms and signs, STOP BANG score and polysomnography.

**STOP BANG score is formed of 8 yes or no questions:**

O: Has anyone OBSERVED you stop breathing during your sleep.

P: Do you have or are you being treated for high blood PRESSURE.

B: BMI more than 35kg/m^2.  

A: AGE over 50 years old.

N: NECK circumference >16 inches (40cm).

G: GENDER (Male).

High risk of OSA: ≥5, at risk of OSA: ≥3, no risk of OSA: 0-2 [6].

Polysomnography remains the standard investigation in the diagnosis of sleep-related breathing disorders. Patients were classified on the basis of their AHI (apnea/hypopnea index) using full night polysomnography.

Apnea, was defined as reduction in airflow greater than ≥90% as recorded by oronasal thermistors or nasal pressure cannulas lasting ≥10 sec. Hypopnea was defined as reduction in airflow ≥30% as recorded by nasal pressure cannulas or alternatively by induction of plethysmography or oronasal thermistors lasting ≥10sec with reduction in saturation at least ≥4% from baseline SpO2% prior to the event. Apnea-hypopnea index (AHI) was defined as the number of apnea and hypopnea attacks per hour of sleep, confirmed by electroencephalogram (EEG). Mild OSAS (AHI 5-15), moderate (AHI >15) and severe form (AHI >30).

**Anesthetic technique:**

Upon arrival to the operating room a pulse oximetry, continuous electrocardiogram (ECG), and noninvasive blood pressure measurement device will be connected to the patient. A large bore cannula will be inserted. Anesthesia was induced with IV propofol, 1.5mg/kg, IV fentanyl 1mic/Kg and IV rocuronium 0.6mg/kg. Before intubation, patients were assessed for their laryngoscopic view according to the scale described by Cormack and Lehane:

- Grade 1, most of the glottis is visible;
- Grade 2, only the posterior extremity of the glottis is visible;
- Grade 3, no part of the glottis and only the epiglottis is visible; and
- Grade 4, not even the epiglottis can be seen [8].

Patients were intubated and ventilated with oxygen maintaining ETCO2 at 35-40mmHg. Anesthesia will be maintained with oxygen, isoflurane and rocuronium.
Patients were assessed for any intraoperative complications (e.g., hemodynamic instability; in the form of arrhythmias or changes in blood pressure and respiratory complications; in the form of desaturation, bronchospasm or pulmonary edema).

At the end of surgery, all patients received reversal of neuromuscular blockade either by sugammadex 4mg/Kg regarding group (A) or by neostigmine 0.05mg/Kg and atropine 0.02mg/Kg for group (B). Efficacy of the reversal was assessed by nerve stimulator. Upon appearance of T2, discontinuation of isoflurane was performed either neostigmine-atropine or sugammadex were given to the patients. Adequate return of neuromuscular function was assessed by the TOF guard, using peripheral nerve stimulator.

Extubation was performed at TOF ratio 0.9 (with visual loss of fade) and after performing clinical signs of recovery and after full awaking and ability of the patient to follow verbal commands.

Any adverse events after administration of drugs, were reported. Hemodynamic instability in the form of arrhythmias (tachyarrhythmias >120 bpm or bradyarrhythmias <50 bpm) or blood pressure changes (hypertension >20% of baseline or hypotension <20% of baseline) and oxygen saturation were assessed intraoperatively.

Primary outcome was comparing the reversal time of neostigmine and sugammadex (time between administration of the drug and train of four ratio of 0.9).

The secondary outcome was to detect intraoperative complications and to detect successful extubation, reintubation, and failure of extubation in both groups.

**Sample size:**

Based on two-tailed α error probability of 0.05 and β error probability of 0.2 (power of 80%), a total sample size of 40 patients randomly allocated into two equal groups (20 patients in each group) will have 80% power to detect a clinically significant results. Statistical power calculations was performed using computer program G*Power 3 for Windows. (Franz Faul, Universität Kiel, Germany).

**Statistical analysis:**

Data was summarized and analyzed using SPSS (version 17, USA); and the results (numerical continuous data) were reported as mean ± SD. Ordinal data was reported as median and range. Categorical data presented as frequency. Comparison of the means of the 2 study groups were done by unpaired t-test. Non parametric variables were compared using Mann Whitney test. Categorical data was compared using chi square. For all statistical tests, the level of significance was fixed at the 5% level. A p-value >0.05 indicated no significant difference. A p-value <0.05 indicated significant difference. The smaller the p-value was obtained, the more significant would be the difference.

**Results**

Forty patients were enrolled in this study in Cairo University, Kasr El-Aini Hospital, 20 patients as group (A) [sugammadex group] and the other 20 patients as group (B) [neostigmine group], 31 males and 9 females with no statistically significant difference detected between both groups regarding the gender or age (Table 1).

The forty patients underwent uvelopalato-pharyngeoplasty operation, with no statistically significant difference regarding clinical symptoms and signs and medical history (comorbidities as hypertension, chronic obstructive lung disease, arrhythmias and ischemic heart disease) (Table 1) and (Fig. 1).

Preoperatively, screening by STOPBANG questionnaire and polysomnography were done and there was no statistically significant difference detected between both groups regarding the gender or age (Table 1).

**Table (1):** Demographic data, preoperative assessment of the study groups. Data are presented as mean (standard deviation), and number (frequency).

<table>
<thead>
<tr>
<th></th>
<th>Sugammadex group</th>
<th>Neostigmine group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>47.65 (5.4)</td>
<td>49.65 (5.5)</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (N, %)</td>
<td>16 (80.0%)</td>
<td>15 (75.0%)</td>
</tr>
<tr>
<td>Female (N, %)</td>
<td>4 (20.0%)</td>
<td>5 (25.0%)</td>
</tr>
<tr>
<td>Clinical Symptoms:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild (N, %)</td>
<td>12 (60.0%)</td>
<td>13 (65.0%)</td>
</tr>
<tr>
<td>Moderate (N, %)</td>
<td>8 (40.0%)</td>
<td>7 (35.0%)</td>
</tr>
<tr>
<td>STOPBANG:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No risk (N, %)</td>
<td>8 (40.0%)</td>
<td>10 (50.0%)</td>
</tr>
<tr>
<td>At risk (N, %)</td>
<td>11 (55.0%)</td>
<td>10 (50.0%)</td>
</tr>
<tr>
<td>High risk (N, %)</td>
<td>1 (5.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Polysomnography:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild (N, %)</td>
<td>9 (45.0%)</td>
<td>9 (45.0%)</td>
</tr>
<tr>
<td>Moderate (N, %)</td>
<td>11 (55.0%)</td>
<td>11 (55.0%)</td>
</tr>
</tbody>
</table>
Intraoperatively, laryngeal view and intraoperative complications were taken into consideration as factors that may affect the results. By comparing both groups, there were no significant differences detected (Table 2).

Table (2): Intraoperative laryngeal view and intraoperative complications of the study groups. Data are presented as median (Range), and number (frequency).

<table>
<thead>
<tr>
<th></th>
<th>Sugammadex group</th>
<th>Neostigmine group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laryngeal view (Median, Range)</td>
<td>2 (1-3)</td>
<td>1.5 (1-2)</td>
</tr>
<tr>
<td>Intraoperative complications:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemodynamic instability (N, %)</td>
<td>2 (10.0%)</td>
<td>2 (10.0%)</td>
</tr>
<tr>
<td>Respiratory complication (N, %)</td>
<td>1 (5.0%)</td>
<td>1 (5.0%)</td>
</tr>
<tr>
<td>No complication (N, %)</td>
<td>17 (85.0%)</td>
<td>17 (85%)</td>
</tr>
</tbody>
</table>

A comparison was done in this study between the 2 groups regarding train of four ratio >0.9 [T1:T4 >0.9] as primary outcome for the study. As regarding TOF ratio there was significant difference between the 2 groups (Fig. 2).

However, there was no significant difference detected regarding extubation, reintubation, and failure of extubation in both groups (Fig. 3).

Discussion

Obstructive sleep apnea (OSA), the most prevalent sleep-disordered breathing condition, is defined by repetitive partial or complete upper airway obstruction leading to episodes of breathing cessation during sleep. The prevalence of OSA among the general population aged 30-70 years is 5% in females and 14% in males [9].

A significant proportion of patients with a diagnosis of OSA are not identified by surgeons and anesthesiologists prior to surgery. Although screening questionnaires and clinical screening models have been developed to identify patients with OSA prior to their surgery, careful screening is frequently not implemented before surgery [10].

Neuromuscular blockade agents act longer than the duration of surgery and postoperative residual curarisation affects postoperative respiratory outcome [11].

Studies in surgical patients have demonstrated the dose dependent association between intermediate-acting neuromuscular blocking agents and PRCs, an effect shown to be unyielding despite neostigmine-based reversal at end of surgery [12,13].

Based on the pathophysiology of the disease, patients with OSA should have an increased vulnerability to the effects of neuromuscular blocking agents and reversal agents. However, population-based studies aiming to quantify the effects of residual neuromuscular blockade in patients with and without risk of OSA are currently missing [14].
This study was done on 40 patients, 20 patients as sugammadex group (group A) and the other 20 patients as neostigmine group (group B). There was no statistically significant difference detected between the two groups in the demographic data including gender, age, medical history (comorbidities as hypertension, chronic obstructive lung disease, arrhythmias and ischemic heart disease), clinical symptoms and signs, screening by STOP-BANG questionnaire and polysomnography.

In this study, we found a good correlation between the results of STOP-BANG questionnaire as a simple and sensitive tool for diagnosis of patients with OSAS and polysomnography, the gold standard for diagnosis, which is more complicated and expensive. The sensitivity of STOP-BANG increased especially with those patients with high or at risk of OSAS. This observation was in line with that of Chung and his colleges when they conclude that for identifying severe OSA, a STOP-Bang score of 4 has high sensitivity of 88%. For confirming severe OSA, a score of 6 is more specific [15].

Also, the meta-analysis done by Nagappa and his colleges confirmed the high performance of the STOP-Bang questionnaire in the sleep clinic and surgical population for screening of OSA. The higher the STOP-Bang score, the greater was the probability of moderate-to-severe OSA [16].

In our study, there was no statistically significant difference detected regarding laryngeal view and intraoperative complications as hemodynamic instability or respiratory complications.

The current study shows a statistically significant difference regarding train of four ratio between the 2 groups. The sugammadex group shows a significant decrease in the TOF ratio which agreed with the results of the study that was done by Illman HR et al., in which fifty patients were included, received volatile anesthetics, opioids, and a rocuronium-induced NMB. At end of operation, patients were randomized to receive either neostigmine 50 μg/kg or sugammadex 2mg/kg, when 2 twitch responses were detected after the last dose of rocuronium. Timing of tracheal extubation was based on PNS and loss of visual fade. They concluded that sugammadex in comparison with neostigmine allows a safer reversal of a moderate NMB when relying on visual evaluation of the TOF response [17].

Our results were in line with that of Jones RK et al. Seventy-four patients (37 in each group) were enrolled in their study with ASA I-IV. Patients were randomized to receive sugammadex (4.0mg/kg) or neostigmine (70μg/kg) plus glycopyrrolate (14μg/kg) at the end of operation. The primary efficacy parameter was the time from sugammadex or neostigmine-glycopyrrolate administration to return of the train-of-four ratio to 0.9.

They declared that recovery from profound rocuronium-induced neuromuscular blockade was significantly faster with sugammadex versus with neostigmine, suggesting that sugammadex has a unique ability to rapidly reverse profound rocuronium neuromuscular blockade [18].

A large observational study, done by Della RG et al., in which three hundred fifty-nine patients were enrolled agreed also with the results of the current study as they confirmed that reversal time is faster in patients receiving sugammadex than in those receiving neostigmine [19].

On the other hand, a case reported by Le Corre F et al., concluded that shortly after tracheal extubation, an obese patient experienced respiratory failure necessitating tracheal intubation and an additional dose of sugammadex. This occurred despite initial reversal of neuromuscular blockade with an appropriate dose of sugammadex 2mg·kg·(-1) IV given at two responses to TOF stimulation [20].

Also, the results of our study regarding TOF ratio were against the study of Baumuller E et al., as they concluded that antagonizing rocuronium at TOF > 0.9 with sugammadex 1.0mg/kg did not improve patients’ motor function or well-being when compared with placebo, even though many postsynaptic acetylcholine receptors may still be inhibited upon giving sugammadex. They supported the view that TOFR > 0.9 measured by electromyography signifies sufficient recovery of neuromuscular function [21].

These results were against that of Pongrácz A et al., when they declared that sugammadex, 1.0mg/kg, rapidly and effectively reverses rocuronium-induced block that has recovered spontaneously to a threshold TOF-count-four. Their study included 80 patients undergoing general anesthesia. Neuromuscular monitoring was performed with calibrated acceleromyography. Once rocuronium-induced neuromuscular blockade recovered spontaneously to threshold TOF-count-four, patients randomly received 0.5, 1.0, 2.0mg/kg of sugammadex or 0.05mg/kg of neostigmine. The time between study drug injection and reversal of TOF ratios to 1.0 was measured. Suggamadex group (1mg/kg, 2mg/kg) showed rapid reversal than other groups [22].
In our study, there was no significant difference detected regarding successful extubation, failure of extubation or reintubation between the 2 groups. This may be due to the nature of our operation as many factors may affect the decision of extubation other than the efficacy of motor power as preoperative pulmonary function and postoperative airway edema.

A case of 78-year-old woman underwent an open incisional pulmonary tissue biopsy reported by Kayashima K et al., were against our results. They found that although the rocuronium-induced neuromuscular blockade was reversed by 2.0mg x kg (-1) of sugammadex (train-of-four ratio, nearly 100%), it seemed a little difficult to extubate the patient just after the operation. They suggested that the difficulty was due to the poor pulmonary function of the patient [23].

Limitations: There were several limitations in this study. We didn't study the effect of sugammadex on patients with severe obstructive sleep apnea. Also, we excluded patients with liver or kidney failure and patients with severe comorbidities. Our study depends on visual loss of fade (depends on the subjective evaluation) in comparing the TOF ratio, however the usage of TOF-Watch® SX would be more objective. The approval of sugammadex recently in December 2015 by FDA was a very good step to study more about sugammadex and its effects. From our results, we recommend:

i- Other prospective studies with larger samples of patients are needed to assess the effect of sugammadex on the overall recovery of patients.
ii- Additional studies to evaluate the safety of sugammadex in pregnancy, in patients with renal or liver cell failure and in patients with prolonged Qt interval or coagulopathy.
iii- Further studies are needed to evaluate the effect of sugammadex on the speed of recovery when used with a dose higher than that in our study or in patients undergoing other operations.

Conclusion: In the current study, we aimed to compare the efficacy of reversal of neuromuscular blockade produced by rocuronium either by neostigmine or sugammadex in patients undergoing uvulopalatopharyngoplasty.

We found a statistically significant difference between neostigmine and sugammadex regarding TOF ratio. There was no statistically significant difference regarding successful extubation and hemodynamic stability.


