Journal of Anesthesia & Clinical Research

Mogahed et al., J Anesth Clin Res 2017, 8:10
DOI: 10.4172/2155-6148.1000769

Research Article Open Access

Sugammadex Efficacy for Rapid Reversal of Rocuronium Induced Neuromuscular Blockade in Pediatric Rigid Bronchoscopy Regardless the Depth of Anesthesia

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Received date: October 06, 2017; **Accepted date:** October 20, 2017; **Published date:** October 23, 2017

Abstract

Background: Bronchoscopy may be either rigid or flexible. Rigid bronchoscopy is usually done for diagnosis and treatment of intra and/or extra luminal obstruction in the airway for adults and children, anaesthesia for bronchoscopy poses unique challenges for the anaesthesiologist. This procedure needs specific technical precision because both the anaesthesiologist and operator share the same working space, that is, the airway. Pediatric rigid bronchoscopy needs a deep level of general anesthesia with a good (profound) muscle relaxation for a short time, with the modern anesthetic muscle relaxant rocuronium Bromide and its unique rapid onset it gives chance to be used in challenging airway procedures like rigid bronchoscopy and with the its newly advent of selective reversal, sugamadex, encourage its use in pediatric rigid bronchoscopy as it is usually performed for Foreign body removal.

Aim: The aim of this study is to compare the efficacy of sugammadex and neostigmine for reversal of neuromuscular blockade induced by rocuronium for facilitating interventional rigid bronchoscopy and having awake child with good adequate muscle power and good ability to protect airway reflexes.

Methods: This study was done on 100 patients ASA1-11 underwent rigid bronchoscopy for foreign body aspiration, we compared the efficiency of both neostigmine and the newly selective reversal agent; sugamadex in recovery of the patients, hemodynamics, and the presence of any side effects.

Results: Our results showed that no significant changes between two groups in Table 1, Table 2, Table 3 i.e. heart rate, arterial blood pressure and O_2 saturation (%) during all period of study i.e. Base line, Strating study drug, 2 min, 5 min, 10 min. But in Table 4, Table 5, Table 6 i.e. Time (in min) from administration at study drug until recovery (TOF>0.9) , extubation time in min (from administration at study drug until extubation), Recovery time (from administration at study drug until Aldrete score more than 9) the time was significantly shorter in group (1) when compared with group (2) which was (3.6 ± 2.6, 3.9 ± 2.6 and 7.3 ± 1.9) in group (1) and (15.12 ± 1.85, 15.85 ± 1.85 and 19.59 ± 2.3) in group (2). In Table 7, there was no significant difference in the side effects between both groups.

Conclusion: Sugammadex achieved significantly faster recovery of rocuronium-induced neuromuscular block when compared with neostigmine regardless the depth of anesthesia. Serious adverse events were less than 1% of patients in both sugammadex and neostigmine, and data showed no differences in risk of serious adverse events between groups. sugammadex was well tolerated.

Keywords: Rigid bronchoscopy; General anesthesia; Muscle relaxants; Rocuronium

Introduction

Rigid bronchoscopy is the gold standard for management of foreign body (F.B.) inhalation in pediatric age group. It requires a deep level of general anesthesia with a profound muscle relaxation for a short time. Thus, muscle relaxants are used intraoperatively to ensure patient relaxation during surgical exposure along with smooth endotracheal intubation [1].

Redistribution, metabolism of the neuromuscular blocking agent (NMBA) administered are the main ways to terminate their effect [2]. At the end of bronchoscopy, acetylcholinesterase inhibitors (e.g. neostigmine) are injected to speed the rate of recovery from non-depolarizing NMBAs. However, such drugs remain as risk factors for complications such as respiratory depression and hypoxemia which are known as residual block [3]. In addition, muscarinic receptors may be activated by using these agents [3].

Recently, newer agents with good pharmacokinetic profile such as sugammadex have become available and helped in early and smooth recovery after general anesthesia [4]. In contrast to acetylcholinesterase inhibitors, sugammadex achieves reversal by encapsulation of rocuronium, resulting in reduction of free rocuronium plasma concentration. This action leads to the removal of NMBDs from the neuromuscular joints to the central compartment through a gradient between the tissue compartment (including the NMJ) and plasma [3].

Pediatric rigid bronchoscopy is safe and effective procedure with short time duration and favorable outcomes. Therefore, the aim of this

study was to compare the efficacy of sugammadex and neostigmine for the reversal of neuromuscular blockade induced by rocuronium. Such results will facilitate the interventional rigid bronchoscopy with awaked child in good adequate muscle power and good ability to protect airway reflexes.

Methodology

Study design and setting

We conducted a prospective, cross-sectional study approved by ethics committee, Faculty of Medicine, Tanta University over 3 month period (may extend) from 30 March 2016 to 30 May 2016.

Study population

A purposeful convenience sample was employed to recruit a total of 100 patients aged 1-3 yrs who underwent rigid bronchoscopy under general anesthesia. Patients were eligible to participate in the study if they had history of foreign body inhalation and fulfill the criteria of American Society of Anesthesiologists Class 1 or 2. Patients who were expected to have difficult intubation due to congenital malformations, those with history of malignant hyperthermia, allergy of any of the study drugs, toremifene or fusidic acid drug intake within 24 h prior to the initiation of the study and history suggestive of any potential contraindications to neostigmine or glycopyrrolate were excluded from the study. In addition, patients who had a significant renal or hepatic dysfunction, neuromuscular disorders that may interfere with neuromuscular blockade and those whose legal guardians refused to consent were also excluded.

Study procedures

All study participants were admitted to the endoscopic unit after fasting for 4-6 h and received oral premedication with 0.5 $mg{\cdot}kg^{-1}$ midazolam solution up to a maximum oral dosage of 15 mg. To prevent any possible transient hypoxemia, 2 1 min^{-1} O_2 was delivered *via* a nasal tube. Patients were continuously monitored using pulse oximetry, ECG and non-invasive blood pressure. Based on those parameters, all participants were subjected to baseline measurements defined as the values measured at the time sugammadex was administered, with subsequent measurements at 2, 5 and 10 min, respectively. Peripheral intravenous lines (I.V) were optimally inserted for all patients at this stage. All patients were received inhalational anesthesia and ventilated manually after obtaining paralysis with rocuronium at dose 0.6 mg/kg, prior to tracheal intubation, with maintenance doses of 0.15 mg/kg as required. The first Train-Of-Four (TOF) ratio was calibrated and measured.

The anesthesia was maintained with sevofluorane 2%, 100% oxygen and opioids (fentanyl 1 ug/kg min) titrated to the desired clinical effect by the attending anesthesiologist. The effect of neuromuscular blocking was evaluated by TOF. We considered sedation sufficiently deep when the patient tolerated the insertion of the endoscopic instrument and inspection of the upper airway without spontaneous movements and/or coughing but with adequate spontaneous ventilation.

Olympus BF-P10 and 3C20 pediatric bronchoscope (Olympus Corporation, Lake Success, NY, USA), with external diameters of 5.0 mm for children and 3.7 mm for younger children was utilized for the current procedure. To minimize the risk of bias, the study was conducted as a single surgeon study, where a single expert E.N.T surgeon performed all the procedures included in the study. Bronchoscope was applied with the aid of laryngoscopy with bronchoscope positioned above carina. The anesthesia circuit was connected to the side hole of the bronchoscope and ventilation was manually controlled using Ayres T-piece. The surgeon was allowed to go to the target bronchus for bronchoscopy and F.B. removal, and if there was any desaturation, the surgeon was asked to go above carina. Following the end of the rigid bronchoscopy procedure and F.B. removal, sevofluorane was interrupted, switched off and turned to 100% oxygen, then we intubated the patient and muscle relaxation was no longer required for surgery.

At this step, patients were randomized equally for one of two groups to compare the effect of sugammadex (Group I) and neostigmine (Group II). Group I (n=50) was received a single IV bolus dose of sugammadex (2.0 mg/kg) within 10 s at reappearance of T1, while in Group II (n=50), the patients were received 0.01 mg/kg atropine and 0.03 mg/kg neostigmine at reappearance of T2.

Primary outcome measures were monitoring of neuromuscular functioning by applying repetitive Train-Of-Four (TOF) electrical stimulations to the ulnar nerve with 15 s intervals and assessing twitch response at the adductor policies muscle. Assessment started since the study drugs have been administrated to recovery of the T4/T1 ratio to 0.9. T1 and T4 referred to the magnitudes (height) of the 1st and 4th twitches, respectively, after TOF nerve stimulation. The T4/T1 Ratio (expressed as a decimal of up to 1.0) indicating the extent of recovery from neuromuscular blockade. In the current study, twitch responses were recorded until the T4/T1 Ratio reached ≥ 0.9, the minimum acceptable ratio that indicated complete recovery.

Secondary outcome measures included extubating and recovery time according to the Aldrete scoring system.

An informed written consent was obtained from legal guardians of the all participating children before commencing the study. Aim of the study, surgical procedures along with potential complications were comprehensively explained to the parents/legal guardians and they were assured of the confidentiality of their data.

Statistical analysis

The sample size was chosen after reviewing many randomized. Control studies on the same subject. The full detailed form is: SPSS 20, IBM, Armonk, NY, United States of America.

Quantitative data were expressed as mean ± standard deviation (SD).

Qualitative data were expressed as frequency and percentage.

1. Independent-samples t-test of significance was used when comparing between two means.

2. Chi-square (χ^2) test of significance was used in order to compare proportions between two qualitative parameters.

Results

Our results showed that no significant changes between two groups in Table 1, Table 2, Table 3 i.e heart rate ,arterial blood pressure and O2 saturation (%) during all period of study i.e., Base line, Strating study drug, 2 min, 5 min, 10 min. But in Table 4, Table 5, Table 6 i.e. Time (in min) from administration at study drug until recovery (TOF>0.9) ,Extubation time in min (from administration at study drug

until extubation), Recovery time (from administration at study drug until Aldrete score more than 9) the time was significantly shorter in group (1) when compared with group (2) which was (3.6 ± 2.6, 3.9 ± 2.6 and 7.3 ± 1.9) in group (1) and (15.12 ± 1.85, 15.85 ± 1.85 and 19.59 ± 2.3) in group (2). In Table 7, there was no significant difference in the side effects between both groups.

Time	Group 1	Group 2	P value
Base line	91.75 ± 6.86	93.10 ± 6.71	0.322
Strating study drug	89.75 ± 4.62	89.90 ± 4.96	0.876
2 min	90.40 ± 3.79	90.85 ± 4.42	0.586
5 min	90.70 ± 6.02	89.45 ± 5.50	0.281
10 min	90.65 ± 6.14	91.90 ± 5.67	0.293

Table 1: Change in heart rate (beat\min) in both group each(n=50) (P value: comparison between G I & G II).

Time	Group 1	Group 2	P value
Base line	89.10 ± 8.41	91.45 ± 8.43	0.151
Strating study drug	87.50 ± 6.13	89.95 ± 6.99	0.065
2 min	87.85 ± 7.77	89.85 ± 6.21	0.158
5 min	88.85 ± 6.89	91.00 ± 6.58	0.114
10 min	89.50 ± 7.19	91.45 ± 6.40	0.155

Table 2: Change in mean arterial blood pressure in both group each(n=50) (P value: comparison between G I & G II).

Time	Group 1	Group 2	P value
Base line	95.350 ± 1.348	95.300 ± 1.342	0.853
Strating study drug	94.950 ± 1.395	94.750 ± 1.164	0.439
2 min	94.850 ± 1.785	94.700 ± 1.625	0.662
5 min	95.950 ± 0.999	96.100 ± 1.294	0.517
10 min	95.000 ± 1.124	95.300 ± 1.147	0.189

Table 3: Change in O2 saturation (%) in both group each(n=50) (P value: comparison between G I & G II).

	Sugammadex group	Neostgmine group	P value
Mean	3.6	15.12	0.001*
SD	2.6	1.85	

Table 4: Time (in min) from administration at study drug until recovery (TOF>0.9) (P value: comparison between G I & G II).

	Sugammadex group	Neostgmine group	P value
Mean	3.6	15.12	0.001*
SD	2.6	1.85	

Table 5: Extubation time in min (from administration at study drug until extubation) (P value: comparison between G I & G II).

	Sugammadex group	Neostgmine group	P value
Mean	7.3	19.59	0.001*
SD	1.9	2.3	

Table 6: Recovery time (from administration at study drug until Aldrete score more than 9) (P value: comparison between G I & G II).

Side effect	Group 1	Group 2	P value
nausea and vomiting	0	1	0.315
Bradycardia	0	0	1
Bronchoconstriction	0	1	0.315
stimulation of salivary glands	0	0	1
Miosis	0	1	0.315
recurrence of block	0	1	0.315
movement of limbs or body	1	1	1
coughing during anesthesia	1	0	0.315
suckling on the endotracheal tube	1	0	0.315
Tachycardia (as a side effect of Anticholinergic agents)	0	1	0.315

Table 7: Side effects of the study drugs (P value: comparison between G I & G II).

Discussion

In this study, it was found that the use of rocuronium-sugammadex allowed us to have a completely recovered child with adequate force of respiratory muscles and airway reflexes within a significant short time compared to the use of rocuronium-neostigmine. This is in accordance to the strategy of having a child with normal airway reflexes after rigid bronchoscopy.

In Group I, sugammadex was used with a dose of 2 mg/kg at reappearance of T1 i.e. TOFC of 1 and primary outcome was the time from the administration of the study drug till the TOF ratio i.e. T4/T1 more than 0.9 which was 3.6 ± 2.6 which was significantly less when compared to the group 2 i.e. neostigmine group where neostigmine was used with a dose of 0.03 mg/kg at reappearance of T2 and the time was 15.12 ± 1.85. We also found that both extubation and recovery time were 3.9 ± 2.6 and 7.3 ± 1.9, respectively in Group I which were significantly less when compared to group 2 where they were 15.85 ± 1.85 and 19.59 ± 2.3, respectively. The hemodynamic parameters had no significant changes between two groups in Table 1, Table 2, Table 3 during all period of study i.e. base line, strating study drug, 2 min, 5 min, 10 min and were maintained within 20% above or below the preoperative level by using optimal level of inhalational anesthetic and by titration of opioids to the desired clinical effect. Also, there was no

significant difference in the side effects between both groups. Most studies found that in ambulatory surgery, there was an increase in symptoms of PONV after administration of anticholinesterases [4-6].

In our study, neostigmine was used at reappearance of T2 and sugammadex at reappearance of T1.

The present study confirms and extends the recent observation by Sorgenfrei et al., suggesting that sugammadex, administered to reverse a moderately profound rocuronium-induced neuromuscular block, allowed return of the TOF ratio to 0.9 within 5 min [7].

In this context, the previous researchers found that if the reversal agents were used before a muscle relaxant was completely cleared, a phenomenon of recurrence of NMB may occur. This has been demonstrated to occur with sugammadex only when insufficient doses were administered. The underlying mechanism is thought to be related to the redistribution of relaxant after reversal. It may occur when insufficient doses of sugammadex were used which are sufficient for complex formation with relaxant in the central compartment, but insufficient for additional relaxant in peripheral compartments which returned to the central compartment [8-11].

Acetylcholinesterase inhibitors, through acetylcholinesterase, suppress destruction of acetylcholine allowing it to accumulate at neuromuscular joints with subsequent displacement of the NMBA molecules from the binding sites on the nicotinic receptors [12]. Nonetheless, acetylcholinesterase inhibitors agents cannot adequately reverse profound neuromuscular blockade [13,14]. Analogous to the earlier findings of Kopman et al. [13]. In another study only 5 of the 20 patients receiving neostigmine for reversal of rocuronium at a similar degree of neuromuscular blockade were able to achieve a TOF ratio of 0.9 within 30 min [15].

Consistent with other studies [1,3,4,8,16], our findings revealed that the profound neuromuscular blockade can be rapidly and reliably reversed by sugammadex in young children aged 1-3 yrs undergoing rigid bronchoscopy. According to Epemolu et al. [17] modified cyclodextrins like sugammadex form tightly bound 1:1 complexes with aminosteroid-based muscle relaxants and act as encapsulating drugs. The ability of sugammadex to encapsulate rocuronium initially increases the plasma concentration of rocuronium, thereby rocuronium molecules at the neuromuscular junction (i.e., effect site) will be reduced, so the residual neuromuscular blockade will be rapid reversed. In contrast to the preliminary dose-ranging study by Sorgenfrei et al., in our study there is no evidence of a hypotensive effect due to sugammadex when it was administered under steady-state anesthetic conditions [7]. In the current study, sugammadex produced more rapid reversal of such a profound level of rocuronium-induced neuromuscular blockade compared to neostigmine, with subsequent improvement of patient's comfort. Sugammadex, as a modified-cyclodextrin, is a selective relaxant-binding agent forming a tight complex with unbound steroidal NMBA molecules leading to rapid reversal of muscle relaxation thereby preventing their action at the neuromuscular junction [18-20].

Conclusion

Sugammadex achieved significantly faster recovery of rocuronium-induced neuromuscular block when compared with neostigmine regardless the depth of anesthesia. Serious adverse events were less than 1% of patients in both sugammadex and neostigmine, and data showed no differences in risk of serious adverse events between groups. Sugammadex was well tolerated.

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