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Research article

Does sugammadex facilitate recovery after outpatient tonsillectomy in children?

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KEYWORDS

Sugammadex;
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Abstract *Introduction:* Sugammadex is an efficient reversal agent at any time, after neuromuscular blockade. It provides complete reversal for light or deep block facilitating rapid airway control and decreases anesthesia recovery period in outpatient surgeries in children.
Patient and methods: After ethical committee approval, informed consent and sample size calculation, 70 patients planned for outpatient total bilateral tonsillectomy were divided randomly into 2 groups. Group S (n = 35) received 2 mg/kg sugammadex to reversing NMB achieved by rocuronium. Group N (n = 35) received 0.05 mg/kg neostigmine and atropine sulfate 0.01 mg/kg, and extubation time (time from administration of reversal agent to time of extubation), train-of-four ratio, time to reach train-of-four >0.9, and side effects were recorded.
Results: There was no significant difference in demographic variables. TOF ratio after reversing was a statistically less in group S than in group N ($p < 0.05$). The time when TOF rate exceeded 0.9 and extubation time were less in group S than in group N with significant difference ($p < 0.05$). No adverse effect was recorded in both groups.
Conclusions: Sugammadex has created a novel rapid, effective and reliable retrieval from NMB with rocuronium in children undergoing tonsillectomy with no side effects.

1. Introduction

Tonsillectomy and adenoidectomy in considered one of the most frequent surgeries carried out all over the world. Healthy children undergoing such procedure may be associated with considerable morbidity and death rate [1]. The anesthetic technique use neuromuscular blockers associated with higher complications than other techniques without them. This is due to the development of postoperative residual neuromuscular block, affecting ventilation, airway patency, and hypoxia [2]. The reversal of NMBs is done by acetyl-cholinesterase inhibitors (neostigmine, edrophonium, or pyridostigmine). Undesirable side effects of cholinesterase inhibitors (bradycardia, hypersalivation and bronchoconstriction) can avoided by muscarinic antagonists as atropine. However, side effects of muscarinic antagonists such as blurring of vision, mouth dryness, and increase in heart rate may occur. Cholinesterase inhibitors have difficulty in reversing deeper muscular paralysis [3]. Because of their mechanism of action is based upon the action

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of acetylcholine on motor end plate. At deep neuromuscular blockade, NMBA is present at the motor end plate, but the maximum increase in the amount of acetylcholine to compete with NMBA is expressed [3]. Neostigmine is the most potent and selective cholinesterase inhibitors and not selective as it stimulates both nicotinic and muscarinic systems. Atropine is used to avoid the concomitant side effects [4].

Sugammadex eliminates the effect of steroid formed non-depolarizing muscle relaxants through binding to them. The first study on sugammadex in volunteers is published in 2005 [5]. Sugammadex is an alternative reversal agent to NMB, which was executed by cholinesterase inhibitor. Postoperative residual NMB action and the muscarinic adverse effects are not present with sugammadex, when used to reverse rocuronium induced NMB [6].

Rapid action of Sugammadex attributed to the mechanism of action differs from other reversal agents [7]. More pediatric studies are needed for certification of its use in variety of patients needed to increase the knowledge about the safety and effective use of sugammadex [8]. So we aim to present our use of sugammadex regarding dose and in side effects in the pediatrics. Sugammadex has been used to reverse moderate NMB in various studies and shown very good recovery of motor power [9,10]. Compared with neostigmine administration (0.05 mg/kg), sugammadex recovery time was approximately 13 times faster [11].

2. Materials and methods

This prospective randomized single blind clinical trial in which the participant and their guardian did not know the drug used, was conducted at Zagazig University Hospital, between June 2015 and December 2015, after approval of our hospital ethical committee and written informed consent was obtained from parents or guardian of **70** children.

2.1. The aim of the study

Our aim was to compare the efficacy of sugammadex and neostigmine on reversing neuromuscular blockade in pediatric patients undergoing outpatient tonsillectomy. The primary outcome was to measure the train-of-four ratio after reversing neuromuscular blockers. The secondary outcome is extubation time.

2.2. Rationale

The use of neuromuscular blockers in children was associated with higher complications due to the development of postoperative residual neuromuscular block, affecting ventilation, airway patency, and hypoxia, side effects of cholinesterase inhibitors (bradycardia, hypersalivation and bronchoconstriction) and muscarinic antagonists such as blurring of vision, mouth dryness, and increase in heart rate.

2.3. Randomization

Allocation of subject in one arm of study was done by using physical method (coin): head for one group and tail for the other, until one group is completed, after that all randomly selected subjects will automatically be allocated to the remaining group (randomization with balance).

Seventy healthy children (2–10 years) scheduled for total bilateral tonsillectomy were included in this study, exclusion criteria such as parent refusal, age less than 2 years or more than 10 years, difficult intubation, any neuromuscular disease, any metabolic disorder, known drug hypersensitivity, kidney impairment, liver impairment, congenital heart disease and history of malignant hyperthermia were not included.

Patients received no premedication, when they attended operating theater; basic monitoring was carried out by the following: ECG (HR), blood pressure cuff to record (MAP), and capnography and SpO_2 values. An intravenous cannula was inserted in peripheral vein of the upper limb. Anesthesia was started with fentanyl (1 mice/kg) analgesia, propofol (1–2 mg/kg) and rocuronium (0.6 mg/kg) for intubation. Ventilation was provided by facemask with 100% and their neuromuscular block was monitored in other limb using the TOF-Watch® SX (Organon, Dublin, Ireland), by stimulation of the ulnar nerve and activity of the adductor pollicis muscle. Two electrodes were positioned near the wrist and the ulnar nerve till recovery to a TOF ratio of 0.9 and then maintained with isoflurane.

Neuromuscular blocking effect was monitored clinically by increase in respiration frequency and disruption to respiration curve, and with the onset of muscular movements. Another bolus dose of rocuronium, 0.2 mg/kg, was injected during surgery. At end of procedure isoflurane was discontinued and TOF monitoring started. On the reappearance of **T2** in ***1st group (Group N)***, patients received reversal by neostigmine (0.05 m/kg) and atropine sulfate 0.01 mg/kg according to body weight. In ***2nd group (Group S):*** reversal was by 2.0 mg/kg sugammadex.

Two anesthesiologists were available during procedure: one was in charge of anesthesia (induction, tracheal intubation, reversal of muscle relaxant, extubation and recovery), while the other was in charge of recording all variables. In both groups **the primary outcome** was to evaluate recovery time from neostigmine or sugammadex administration until recovery of the TOF ratio to 0.9% was recorded and **the secondary outcome** extubation time from reversal from NMB to extubation was recorded.

Adverse effects such as bradycardia, hypotension, arrhythmia, nausea, vomiting, rash, or postoperative recurrence of neuromuscular blockade were recorded and patients' oxygen saturation and breathing in the recovery area were monitored for at least 2 h.

2.4. Statistical analysis

Sample Size: In study by Kara et al. 2014, TOF ratio at extubation was 76.95 ± 31 in Neostigmine group versus 96.35 ± 21.34 in Sugammadex group, at a power analysis of β-error = 0.8 and α-error = 0.05, and 35 patients per study group were needed as the appropriate sample size to find significance difference between the studied drugs.

Continuous variables were checked for normality by using Shapiro-Wilk test. Mann Whitney *U* test was used to compare two groups of non-normally distributed data. Percent of categorical variables were compared using the Pearson's Chi-square test. All tests were two sided. $p < 0.05$ was considered

statistically significant. All data were analyzed using Statistical Package for Social Science for windows version 18.0 (SPSS Inc., Chicago, IL, USA), MedCalc for windows version 13 (MedCalc Software bvba, Ostend, Belgium) and Microsoft Office Excel 2010 for windows (Microsoft Cor., Redmond, WA, USA).

3. Results

Table 1 shows no statistical difference in the demographic data and time of surgery of the studied groups.

Table 2 shows no significant differences between 2 groups in time for applying neostigmine or sugammadex after the last NMB and time from the last NMB to extubation. There was a statistically non-significant difference in group S regarding extubation time than group N ($p < 0.05$).

Table 3 shows no significant differences in TOF ratio before reversing. TOF ratio after reversing was a statistically significant in group S than in group N ($p < 0.05$). The time when TOF rate exceeded 0.9 was less in group S with significant difference ($p < 0.05$).

4. Discussion

High doses of NMB was administered in children to get the same NMB relaxation as in adults, as children have a different efficacy than adults because of larger extracellular area in children than in adults, and the NMB creates lower plasma concentrations in children due to spread of NMB in the extracellular area [12]. Sugammadex is completely different mechanism from anticholinesterase. Its effects are independent from acetylcholine concentration and nicotinic or genus Muscarinic sensory receptor. Sugammadex is effective particularly on the steroid formed NMB such as rocuronium and vecuronium [13]. It forms a cyclodextrin build with steroid NMB relaxant being a reaper binder decreasing the NMB present in plasma and in the nicotinic receptors. For this cause, the side effects are noticed with muscarinic receptor affection with anticholinesterase not presented with sugammadex [13].

We have used 2 mg/kg sugammadex, and assess the of NMB effect with TOF after Sorgenfrei et al. [14] who compared different doses of sugammadex with a placebo and observed time to reach 0.90 TOF ratio was significantly shorter

Table 1 Demographic data of the studied groups.

Demographic data	Control group (N) ($n = 35$)	Sugammadex group (S) ($n = 35$)	p-value
Age (years)	5.42 ± 2.23	5.64 ± 2.41	0.693*
Gender			
Male	16 (45.7%)	17 (48.6%)	0.811§
Female	19 (54.3%)	18 (51.4%)	
Weight (kg)	15.24 ± 8.92	14.42 ± 10.65	0.728*
Time of surgery (min)	33.62 ± 8.51	31.97 ± 4.75	0.315*
Rocuronium (mg)	9.12 ± 5.34	8.64 ± 7.59	0.760*

n = Total number of patients in each group; quantitative data were expressed as the mean ± SD; qualitative data were expressed as a number (percentage).
* Mann Whitney U test.
§ Chi-square test; $p < 0.05$ is significant.

Table 2 The times from last NMB, reversal agent administration to Extubation.

Time	Control group (N) ($n = 35$)	Sugammadex group (S) ($n = 35$)	p-value
Time for applying neostigmine or sugammadex after the last NMB (min)	25.54 ± 21.36	25.84 ± 21.45	0.953*
Time from the last NMB to extubation (min)	29.14 ± 20.34	26.23 ± 22.32	0.571*
Extubation time (min)	4.21 ± 1.18	1.25 ± 0.59	< 0.001*

n = Total number of patients in each group; quantitative data were expressed as the mean ± SD.
* Mann Whitney U test; $p < 0.05$ is significant.

Table 3 The TOF ratio evaluation.

TOF ratio	Control group (N) ($n = 35$)	Sugammadex group (S) ($n = 35$)	p-value*
TOF ratio before reversing	39.16 ± 20.65	32.54 ± 20.84	0.186
TOF ratio after reversing	83.21 ± 1.16	91.25 ± 0.56	< 0.001*
The time when TOF rate exceeded 0.9 min	1.64 ± 2.59	0.41 ± 0.58	0.007*

n = Total number of patients in each group; quantitative data were expressed as the mean ± SD.
* Mann Whitney U test; $p < 0.05$ is significant.

with sugammadex doses larger than 2 mg /kg. Schaller et al., and Hogg et al., showed that doses larger than 2 mg/kg sugammadex are efficient [15,16]. TOF ratio is a reliable objective method to assess residual NMB. Safety of spontaneous ventilation was approved when TOF ratio is $\geqslant$0.9, so we can guarantee normal muscle functions [17].

We compared neostigmine with sugammadex reverses the medium NMB obtained with rocuronium; TOF ratio after reversing was 91.25 ± 0.56 in sugammadex and 83.21 ± 1.16 in neostigmine group. The time to reach 0.90 TOF ratio in sugammadex and neostigmine reversal was found to be 0.41 ± 0.58 min in sugammadex group and 1.64 ± 2.59 in neostigmine group, in agreement with the study by Khuenl-Brady et al. [18] who compared the time to reach 0.90 TOF ratio in sugammadex and neostigmine reversal was found to be 1.4 min with sugammadex 4 mg/kg and 17.6 min with neostigmine in a randomized multicentre study where it was applied to reverse the medium NMB obtained with rocuronium in adults.

Blobner et al. [11] reported that 11% of patients in the neostigmine group reached the 0.90 TOF ratio in 5 min and 98% of the patients in the sugammadex group using 2 mg/kg reached the 0.90 TOF ratio in 5 min. Jones et al. [19] reported that the time to reach 0.90 TOF ratio was 18 times shorter with sugammadex than with neostigmine in routine reversal of deep NMB. Plaud et al. [9] reported that sugammadex was 10 times faster in efficiency. It is now accepted that sugammadex is more effective than ordinary drugs, cholinesterase inhibitors in the recovery of NMB with rocuronium [20,21]. Our observations in our study are supportive of the studies that extubation time was found to be 1.25 ± 0.59 min in sugammadex group and 4.21 ± 1.18 in neostigmine group making fast, easy and safe NMB reversal, in agreement with the study by Kara et al. [22].

No side effects were reported in both groups in agreement with the study by Plaud et al. [8] who reported that sugammadex use in children group is effective, safe and reliable drug without hypersensitivity findings with dosing 2 mg/kg.

5. Conclusion

Sugammadex has created a novel rapid, effective and reliable retrieval from NMB with rocuronium in children undergoing tonsillectomy with no side effects.

Conflict of interest

The authors declare that there are no conflict of interests.

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