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Research Article

Can sugammadex improve the reversal profile of atracurium under sevoflurane anesthesia?

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KEYWORDS

Sugammadex;
Reversal of neuromuscular blockade;
Critical respiratory events

Abstract The current prospective comparative study aimed at the clinical outcome of sugammadex reversal of neuromuscular blockade (NMB) and the evaluation of its impact on the frequency of critical respiratory events during sevoflurane anesthesia.

Patients and methods: The study included 100 male patients with mean age of 33.1 ± 7.5 years; 67 patients of ASA grade I, 27 patients of ASA grade II and 6 patients of ASA grade III. Patients were randomly allocated to two equal groups: Group N received reversal of NMB using intravenous (IV) neostigmine (6 μg/kg) and Group S received IV sugammadex (2 mg/kg). After induction of anesthesia, NM function was monitored, at the wrist; using the TOF-Watch-SX. At the end of the surgery, the reversal of NMB assigned for each group was administered at least after 15 min after the last dose of atracurium and NM monitoring was continued until recovery of the TOF T4/T1 ratio to 0.9. Time since injection of the reversal drug till recovery to TOF ratio of 0.9 was recorded and critical respiratory events (CRE) were monitored.

Results: Both groups showed non-significant difference as regards the frequency of patients required top doses of NMBD or the mean number of top doses of NMBD. Time till achievement of TOF ratio of 0.9 was significantly shorter with sugammadex compared to neostigmine. Moreover, mean time to achieve TOF ratio of 0.9 was 2.76 ± 1.5 min with sugammadex, but was 9.78 ± 2 min with neostigmine with significant difference in favor of sugammadex. CRE were recorded in 5 patients (5%); 3 patients with neostigmine (6%) and 2 patients (4%) with sugammadex.

Conclusion: NMB reversal using sugammadex allowed significantly earlier achievement of TOF ratio of 0.9 in significantly higher number of patients with minimally and acceptable respiratory events at PACU in comparison with neostigmine.

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1. Introduction

The problem of residual neuromuscular blockade dates since the introduction of general anesthesia and the use of neuromuscular blockers; earlier studies reported a 6-fold increased risk of death in the perioperative period in association with

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the use of neuromuscular blocking drugs (NMBD) [1]. Thereafter, the advances in manufacturing of NMBD in parallel with development of new inhalational anesthetics promoted the use of general anesthesia and lessened its risks [2,3].

Despite the application of techniques proven to limit the degree of residual paralysis as the use of intermediate-acting NMBD and pharmacological reversal, up to 33–64% of patients have evidence of inadequate neuromuscular recovery on arrival to the post-anesthetic care unit (PACU) [4–6]. Acetylcholinesterase inhibitors, such as neostigmine and edrophonium carry a risk of unwanted effects, such as bradycardia, hypotension, broncho-constriction and hyper-salivation. These side effects were opposed by the concomitant use of anticholinergic drugs, such as atropine or glycopyrrolate, but anticholinergic drugs have their inherent side effects as tachycardia, blurred vision and sedation, and so should be administered cautiously especially in high risk and elderly patients [7–9].

Studies in volunteers have demonstrated that train-of-four (TOF) fade ratios < 0.7–0.9 are associated with upper airway obstruction, inadequate recovery of pulmonary function, reduced pharyngeal muscle coordination, an increased risk for aspiration and an impaired hypoxic ventilatory response [10,11].

Sugammadex, a water-soluble, modified specifically designed γ-cyclodextrin, the first of a new class of selective relaxant binding drugs developed for the rapid and complete reversal of neuromuscular blockade induced by aminosteroid NMBD. Sugammadex acts by encapsulating unbound molecules of NMBD, thus reducing its free fraction and preventing them from binding to nicotinic receptors in the neuromuscular junction thus inducing rapid reversal of their effect [12–14].

Clinical studies of sugammadex in surgical patients have shown that sugammadex provides effective, dose-dependent reversal of both moderate and deep intense rocuronium-induced neuromuscular blockade during propofol maintenance anesthesia. Sevoflurane is widely used in clinical practice and enhances neuromuscular blockade, the safety and efficacy of various doses of sugammadex under maintenance anesthesia with volatile drugs remain largely unknown especially after administration at deep neuromuscular blockade [15–17].

The current prospective comparative study aimed at the clinical outcome of sugammadex reversal of neuromuscular blockade and the evaluation of its impact on the frequency of critical respiratory events during sevoflurane anesthesia.

2. Patients and methods

The current study was conducted at Anesthesia department, Kasr-El-Aini University Hospital since January 2011 till October 2011. After approval of the study protocol by the local Ethical Committee and obtaining written fully informed patients' consent, 100 adult male patients assigned to undergo open abdominal surgical procedures were enrolled in the study. Patients with cardiac, renal or hepatic diseases or sensitivity to used drugs were not enrolled in the study.

Patients were assigned using sealed envelopes, allocated to two equal groups ($n = 50$): Group N included patients who received reversal of NMB in the form of intravenous (IV) neostigmine in dose of 6 μg/kg and 10 μg/kg of atropine while Group S included patients who received reversal of NMB using IV sugammadex in dose of 2 mg/kg.

All patients were premedicated with IV atropine 0.6 mg and midazolam 1–2 mg 5 min before induction of anesthesia. Before induction, patients were preoxygenated and base line mean arterial blood pressure (MAP), heart rate (HR), respiratory rate (RR) and peripheral arterial O_2 saturation (SaO_2) were recorded. Anesthesia was induced with propofol 1.5–2.5 mg/kg and fentanyl 0.5–1 μg/kg. Then, neuromuscular function was monitored, at the wrist; using the TOF-Watch-SX (Schering-Plough Corporation, Swords-Dublin, Ireland). Briefly, according to good clinical research practice in pharmacodynamic studies of NMBD [18], the device was stabilized by using repetitive TOF stimulation for 1 min followed by 50 Hz titanic stimulation given for 5 s and repetitive TOF stimulation for 3–4 min. After calibration of the device atracurium 0.5 mg/kg was given and the trachea was intubated. Then the response to TOF stimulation ceased, top up doses of atracurium of 0.1 mg/kg were used as required upon reappearance of the second twitch (T2) in a TOF to maintain neuromuscular blockade during the operation. Ventilation was controlled and minute ventilation was adjusted to maintain end tidal CO_2 at 35 ± 5 mmHg. Anesthesia was maintained with sevoflurane 2–4%. Lactated Ringer's solution at a rate of 10 ml/kg/hr was given during anesthesia and 2 ml/kg/hr after anesthesia until patients tolerated oral fluids. At the end of the surgery, the reversal of NMB assigned for each group was administered at least 15 min after the last dose of atracurium (with the appearance of the fourth contraction of the TOF) and neuromuscular monitoring was continued until recovery of the TOF T4/T1 ratio to 0.9. Following extubation patients were maintained on supplemental O_2 until awake in the recovery room.

Time since injection of the reversal drug till recovery to TOF ratio of 0.9 was recorded. Critical respiratory events were monitored and included the following items: requirement for intervention for upper airway obstruction, occurrence of hypoxemia categorized according to SaO_2, the presence of manifestations of respiratory distress, need for re-intubation in the recovery room and/or the presence of manifestations of pulmonary aspiration.

2.1. Statistical analysis

Obtained data were presented as mean ± SD, ranges, numbers and ratios and median values. Results were analyzed using Wilcoxon's ranked test for unrelated data (Z test) and Chi-square test. Statistical analysis was conducted using the SPSS (Version 15, 2006) for Windows statistical package. P value < 0.05 was considered statistically significant.

3. Results

The study included 100 male patients with mean age of 33.1 ± 7.5; range: 28–52 years. There were 67 patients of ASA grade I, 27 patients of ASA grade II and 6 patients of ASA grade III. Details of patients' enrollment data are presented in Table 1 showing a non-significant ($p > 0.05$) difference between both study groups.

There was non-significant ($p > 0.05$) difference between both study groups as regards mean operative time and total dose consumed of NMBD (Table 2). Fifty-six patients (56%) required top doses of NMBD; 24 patients (48%) in group N and 32 patients (64%) in group S with non-significant

Table 1 Patients' enrollment data.

Data		Group N	Group S	Total
Age (years)		32 ± 6.7 (29–52)	34.1 ± 8.1 (28–49)	33.1 ± 7.5 (28–52)
Weight (kg)		84.5 ± 5.9 (69–92)	83.2 ± 7.7 (66–93)	83.8 ± 6.8 (66–93)
Height (cm)		167.5 ± 2.5 (165–181)	165.7 ± 3.2 (162–179)	166.6 ± 3 (162–181)
BMI (kg/m^2)		30.1 ± 2.1 (25–33.8)	30.3 ± 2.9 (23.7–35.4)	30.2 ± 2.5 (23.7–35.4)
ASA grade	Grade I	35 (70%)	32 (64%)	67 (67%)
	Grade II	13 (26%)	14 (28%)	27 (27%)
	Grade III	2 (4%)	4 (8%)	6 (6

Data are presented as mean ± SD and number; ranges and percentages are in parenthesis.
A non-significant ($p > 0.05$) difference between both study groups.

Table 2 Operative data.

Data	Group N	Group S
Operative time (min)	95.5 ± 22.4 (60–13	9 ± 20.1 (65–150)
Total dose of NMBD	42.2 ± 2.9 (34.5	1.6 ± 3.9 (33–47)
Number of patients required top doses of NMBD	29 (58%)	31 (62%)
Number of top doses	2.5 ± 1.8 ( )	2.7 ± 1.5 (1–5)

Data are presented as mean ± SD and number; ranges and percentages are in parenthesis.
A non-significant ($p > 0.05$) difference between both study groups.

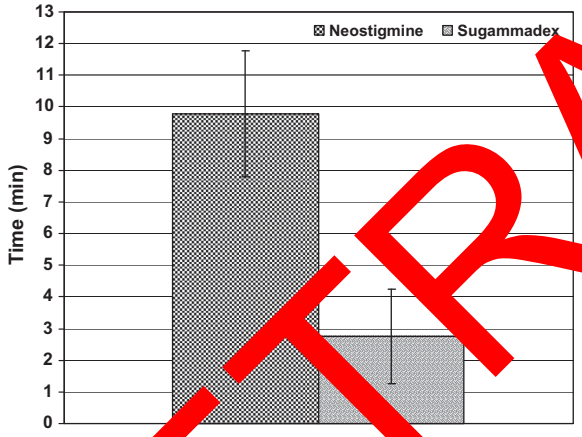

Figure 1 M n (+SD) e till reaching TOF ratio of 0.9.

($p >$ .05) difference between both groups. Mean number of t doses of NMBD, a showed non-significant ($p > 0.05$) ference b tween both groups, (Table 2).

Time till achi ment of TOF ratio of 0.9 was significantly sho ($Z = 6$ 9, $p < 0.001$) with sugammadex compared to neost (Fig. 1). Moreover, only 5 patients (10%) in sug- madex group reached TOF ratio of 0.9 within 3–7 n, 21 patients (42%) reached TOF ratio of 0.9 in range of 3–5 min and 24 patients (52%) reached TOF ratio of 0.9 in less than 3 min with a mean time for patients received sugammadex to achieve TOF ratio of 0.9 of 2.76 ± 1.5 min. On the contrary, only 4 patients (8%) reached TOF ratio of 0.9 within 5–7 min, 23 patients (46%) within 8–9 min, 18 patients (36%) within 10–12 min and 5 patients (10%) achieved TOF ratio of 0.9 within 13–14 min with a mean time for patients received neostigmine to achieve TOF ratio of 0.9 of 9.78 ± 2 min, (Table 3).

All enrolled patients completed the study; CRE were recorded in 5 patients (5%); 3 patients with neostigmine (6%) and 2 patients (4%) with sugammadex. One patient in neostigmine group developed severe hypoxemia with SaO_2 85% despite the oxygenation in line with signs of aspiration and was recovered on application of oral airway, repeated suction, more atropinization and increasing O_2 flow. This patient required additional dose of neostigmine till achieved TOF of >0.9 and was capable of breathing spontaneously. The other

Table 3 euromuscular recovery data.

Data		Group N	Group S
Time to reach TOF ratio of 0.9	<3 min	0	24 (48%)
	3– < 5	0	21 (42%)
	5–7	4 (8%)	4 (8%)
	8–9	23 (46%)	1 (2%)
	10–12	18 (36%)	0
	13–14	5 (10%)	0
	Mean	9.78 ± 2 (5–14)	2.76 ± 1.5 (1.5–7.5)

Data are presented as mean ± SD and number; ranges and percentages are in parenthesis.

two patients in neostigmine group and one patient in sugammadex group developed moderate hypoxemia with SaO_2 of 92%, 93% and 92%, respectively and responded to the application of oral airway and increasing rate of O_2 flow. The 2nd patient in sugammadex group required only jaw thrust with maintenance on O_2 mask till full recovery.

4. Discussion

The problem concerning residual neuromuscular blockade is mostly the development of critical respiratory events (CRE) which usually occur in the post-anesthesia care unit (PACU). The current study showed that the reversal of atracurium using Sugammadex to achieve a TOF ratio of 0.9 took statistically significant less time than with neostigmine in a significantly higher number of patients with an overall lower rate of CRE events. In fact, in the neostigmine group one patient experienced severe hypoxemia.

In hand with the aim of the study and the reported outcome, Murphy et al. [19,20] reported a frequency of residual neuromuscular blockade of 4.5% in the PACU at TOF ratio $\leqslant$0.9 and concluded that incomplete neuromuscular recovery is an important contributing factor in the development of adverse respiratory events in the PACU. Thereafter, Murphy and Brull [21] documented that clinical trials have demonstrated that incomplete neuromuscular recovery during the early postoperative period may result in acute respiratory events (hypoxemia and airway obstruction), delays in trach[illegible]bation, and an increased risk of postoperative pulmona[illegible] complications. Also, Sauer et al. [22] out of their rando[illegible]zed, prospective, placebo-controlled trial conclu[illegible]d that mi[illegible] residual block was associated with hypo[illegible]mia i[illegible]PACU.

Through the present study to exclu[illegible] the imp[illegible]t of gen[illegible] on neuromuscular recovery, all en[illegible]ed patie[illegible]were male so that the difference in the out[illegible]me c[illegible]d be attri[illegible]ed to the type of reversal used. I[illegible]support o[illegible]is opinion, Heier et al. [23] reported sex-relat[illegible]ifferences in t[illegible]elationship between abductor pollicis T[illegible]F ra[illegible]and clinical m[illegible]ures of muscle function used to assess recove[illegible]om neuromuscular block. Also, there was no significant diffe[illegible]e between enrolled patients as regard[illegible]onstitutional, anesthe[illegible]and operative data.

Sugamm[illegible]x was ad[illegible]nistered in a dose of 2 mg/kg; in line with such do[illegible]Makri[illegible]al. [24] reviewed clinical trials concerning dose-depen[illegible]ffect of sug[illegible]mmadex and reported that the sugg[illegible]dose o[illegible]gamma[illegible]x for reversal of shallow block c[illegible]ues up t[illegible]2 mg/kg[illegible]d[illegible]mg/kg for profound level of block.

The us[illegible] dose of sugammadex allowed significant shorter neurom[illegible]ery time compared to neostigmine with a[illegible] time till achievement of TOF ratio of 0.9 of 2.76 min (~1[illegible]). Such duration till recovery coincided with that reported [illegible] Duvaldestin et al. [25] who reported a mean recovery time of 3.[illegible] and 2.8 min with sugammadex 2 mg/kg after rocuronium and vecuronium NMB, respectively. Schaller et al. [26] found sugammadex, 0.22 mg/kg, is able to reverse a TOF ratio of 0.5–0.9 or higher in an average time of 2 min and within 5 min, 95% of patients reach this TOF ratio, while neostigmine, 34 μg/kg, is able to reverse a TOF ratio of 0.5–0.9 or higher within 5 min. Lemmens et al. [27] detected that the mean time to recovery of TOF ratio to 0.9 was 15-fold faster with sugammadex (4.5 min) compared with neostigmine (66.2 min) after profound vecuronium-induced block.

Also, Illman et al. [28] reported a significant time gap between visual loss of fade and return of TOF ratio >0.9 after reversal of rocuronium block by neostigmine compared to sugammadex which allowed a safer reversal of a moderate NMB with significantly shorter times of recovery. Also, Adamus et al. [29] reported that after sugammadex and neostigmine, the respective intervals until TOF ratio $\geqslant$0.90 were 2 and 15.9 min.

In hand with the obtained data, Gaszynski et al. [30] reported a mean time to 90% of TOF for morbid obese patients received rocuronium was 2.7 min w[illegible]madex and 9.6 min for neostigmine with signific[illegible]t differenc[illegible]favor of sugammadex and concluded that [illegible]inistration of [illegible]gammadex provides fast recovery of neuro[illegible]scular functi[illegible]in the morbidly obese, however n[illegible]stigmine[illegible]s not. S[illegible]nsen et al. [31] during rapid seq[illegible]ce induction[illegible]d int[illegible]ation, reported that the media[illegible]me from[illegible]cheal int[illegible]ion to spontaneous ventilation an[illegible]o 90%[illegible]ecovery of the first twitch in TOF were 406 s[illegible]d 518[illegible]succinylc[illegible]ine and 216 s and 168 s with ro[illegible]ronium–sug[illegible]madex[illegible]espectively and concluded tha[illegible]d sequence i[illegible]n and intubation with rocuroni[illegible]follo[illegible]d by reversal with sugammadex allowed earlier re-establishm[illegible]of spontaneous ventilation than with su[illegible]oline.

In support of the efficacy and safety of NMB reversal using sugammadex, its applicability in critical situation. Curtis et al. [32] and Barbo[illegible]and da Cunha [33] presented case reported of patient deterio[illegible]ed from a 'can't intubate, can ventilate' situa[illegible]to a 'ca[illegible]intubate, can't ventilate' situation and rocuronium[illegible]d neuromuscular block was successfully reversed with sugammadex, as evidenced by the restoration of diaphragmatic movement, the ability of the patient to move her limbs, and the presence of a train-of-four nerve stimulation with no fade.

The obtained results concluded that neuromuscular blockade reversal of Atracurium under sevoflurane anesthesia using sugammadex allowed significantly earlier achievement of TOF ratio of 0.9 in a significantly higher number of patients with minimal and acceptable respiratory events at PACU in comparison to neostigmine. Hence, Sugammadex improves the reversal profile of Atracurium under Sevoflurane anesthesia.

Conflict of interest

No conflict of interest to be declared.

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