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EVALUATION OF CYCLODEXTRIN (SUGAMMADEX) FOR REVERSAL OF INTENSE NEUROMUSCULAR BLOCK OF ROCURONIUM AND VECURONIUM, EXPERIMENTAL AND CLINICAL STUDIES

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Abstract

This study evaluated and explored time course, efficacy, relation, safety, changes in heart rate, and blood pressure after a bolus dose of sugammadex or neostigmine for reversal of a prolonged rocuronium and vecuronium induced neuromuscular block.

A total of 60 patients of both sexes, 'ASA' grade I, II and all were scheduled for elective surgery of 30-45 minutes duration. Informed oral consent was obtained from all patients to participate in this study.

The results showed statistically significant progressive decrease of heart rate and blood pressure at 2, 5 and 10 minutes when compared to their basal values before anesthesia, then it starts to gain its normal value at 5 and 10 minutes, regardless the dose of sugammadex (effect of anesthesia). Also, heart rate and blood pressure showed statistically non-significant variance between groups of sugammadex when compared at any time of the study with the neostigmine groups (i.e. no effect of the dose on heart rate).

Key words: Cyclodextrin, Rocuronium, Vecuronium, In-vitro, In-vivo studies.

Introduction

The neuromuscular blocking agent (nmbas) such as rocuronium and vecuroniumare widely used in clinical anesthesia and emergency medicine to facilitate tracheal intubation and artificial ventilation and to allow surgical access to body cavities (Choi *et al*, 2013). Although nmbas has significantly reduced the incidence of the laryngopharyngeal lesion due to tracheal intubation, yet still associated with higher morbidity and mortality compared with anesthetic techniques that don't use (nmbas). This was mainly attributable to the development of postoperative residual neuromuscular blockade, resulting in the hypoventilation, air way obstruction and hypoxia (Della Rocca *et al*, 2013). Reversal of neuromuscular blockade was indicated for the acceleration of patient recovery and prevention of postoperative residual neuromuscular blockade and reduces incidence of severe morbidity and mortality associated with anesthesia management (De Boer *et al,* 2006). Currently, the reversal of neuromuscular blockade is achieved by the administration of acetyl cholinesterase inhibitors as neostimine, edro-

phonium or pyredostigmine (Lorke *et al,* 2013).

The cholinesterase inhibitors have a number of well-known undesirable side effects as the bradycardia, bronchoconstriction, hyper-salivation; abdominal cramps, nausea and vomiting that can be counteracted by co-administration of muscarinic antagonists with side effects as blurred vision, dry mouth, and tachycardia (Lavon and Sagi, 2013). Besides, cholinesterase inhibitors are not capable of reversing deeper levels of neuromuscular blockade (Stoelting, 1999). Thus, there is clearly a clinical need for new reversal agent, with minimal side effects and the capability to reverse neuromuscular blockade effectively, independently of its depth. Sugammadex is a synthetic modified cyclodextrin derivatives designed to bind selectively to the steroidalrocuronium and vecuronium molecules.

The present study was designed to evaluate and explore the time needed to complete the reversal state by sugammadex and neostigmin in neuromuscular blockade by rocuronium and Vecuronium. The study was conducted clinically and experimentally.

Patients, Materials and Methods

This study covered clinical and experimental studies. Clinically, the study was conducted on ASA I, II 60 patients of both sexes of 16-50 year-old, submitted for elective surgeries of different types and durations (30-45) minutes as (appendectomy, hernia repair, diagnostic laparoscopy or ovarian cystectomy).

Those with hepatic, renal and neuromuscular disease and expected difficult intubation were excluded. The patients were randomly divided into four groups, each of 15 according to relaxant/reversal agent. GI (Rs) was paralyzed with Rocuronium and reversed by sugammadex, GII (Rn) was paralyzed with Rocuronium and reversed by neostigmine, GIII (Vs) was paralyzed with vecuronium and reversed by sugammadex and GIV (Vn) was paralyzed with vecuronium and reversed by neostigmine.

Anesthetic technique: All patients were monitored for ECG, heart rate, SPO2, ETCO2, mean arterial blood pressure, and core body temperature. All patients received fentanyl (1-3µg/kg), propofol (1.5-2.5mg/kg). According to randomization schedule, 0.6mg/kg rocuronium or 0.1mg/kg vecorunium followed by intubation after (60-90 sec.). Anesthesia was maintained with isoflurane 1 mac (1.2) with controlled ventilation for all patients. For neuromuscular monitoring the left arm was extended and fixed on an arm rest and the Datexrelaxogram was used to stimulate the ulnar nerve via surface electrode while the correct placement of electrodes was important to insure that the nerve was stimulated with the selected current. At the end of surgery, the neuromuscular function was assessed by TOF ratio and clinically. Sugammadex (2mg/kg) was administered irrespective of the degree of residual neuromuscular block. Neostigmine (70mic/kg & atropine 0.01mg/kg) was administered only when a patient started to wake with TOF 0.9. Patients

were extubated when breath spontaneously. The investigator assess the duration and state of the neuromuscular blockade, the time to complete the reversal neuromuscular blockers and state of reversal with EMCs and clinically. The mean arterial blood pressure, heart rate and side effects reported by the patients in post anesthesia care unit (PACU) were assessed. Onset of action was assessed by time from neuromuscular blocker administration till disappearance of TOF at adductor policies muscle. The duration was defined as the time from disappearance of response to 10% recovery of T1. Recovery time assessed from recovery of T1 till TOF ratio 75%. The intensity of the block was assessed by TOF adductor policies muscle by ulnar nerve stimulation. The time of the reversal agent to be given is the appearance of first response of TOF or DBS more than 25%.

Experimentally: the reversal effect of sugammadex on the neuro-muscular transmission was studied in-vitro using a phrenic nerve diaphragm preparation of adult rats (weight: 200-500gm).The preparation was carried out using the method described by Bülbring (1997). The perfusion fluid used was Kreb's solution saturated with a mixture of 5% CO2 & 95% O2. The preparation was stimulated at a rate of 12 impulses per minute to avoid fatigue of the muscle. The intensity of the stimulus ranged from 3-5 volts for nerve stimulation (indirect), while that for direct stimulation of the muscle was adjusted at a higher voltage, ranged from 30-50 volts. The duration of the stimulus was 500 micro-seconds.

After obtaining normal records to direct and indirect stimulation rocuronium 50 mic./ml was added and the effect and time course of the drug response was noticed.

In vivo ten anesthetized cats of both sexes (weight: 2.5-3.5 kg) were used to study the effect of sugammadex (20 mic/kg) on neuromuscular transmission on gastro-cnemius sciatic nerve after blocked by rocuronium (400mic/kg IV). A cannula was inserted and tied in femoral vein to maintain anesthesia by pento-barbital sodium 30mg/kg. Each cat was kept under artificial respiration through the experiment. The gastro-cnemius sciatic nerve preparation was carried out after Bülbring and Burn (1942). A single shock of 4-6 volts intensity, 1-2 millisecond duration was applied at a rate of 12 impulses per minute.

In order to explain the mechanism of the observed neuromuscular block obtained by rocuronium 50 mic/ml, the sugammadex 20 mic/ml was added in an attempt to reverse the neuromuscular block and its effect on the indirect stimulation of the muscle was recorded. The contractions of the muscle were recorded with a light spring-loaded lever with a sideways-writing point (kymograph). The nerve was usually stimulated at a rate of about 12 shocks per minute by rectangular-wave pulses of about 0-5 m. sec duration.

Results

The results are shown in tables (1, 2, 3 & 4) and figures (1, 2, 3 & 4).

Table 1: Age, sex, weight and height distribution of studied populations

	Group I	Group II	Group III	Group IV	P-value
Age (years)	39 ± 11,2	41.5 ± 8.4	40.3 ± 10	38.3 ± 10.2	> 0.05
Weight (Kg)	75 ± 11	70.4 ± 10.4	74.9 ± 9.4	70.1 ± 9	> 0.05
Height (cm)	171.4 ± 5.9	170.3 ± 4.4	169.1 ± 6.4	172.2 ± 7.1	> 0.05
Sex (male/female)	8 / 7	10 / 5	9 / 6	8 / 7	> 0.05
Anesthesia time (min)	38.8 ± 5.6	39.2 ± 5.3	41 ± 4.7	40.1 ± 4.6	> 0.05

The patients were 35 males (58.33%) and 25 females (41.67) without significant differences between four groups (p>0.05). Regarding age, weight and height, showed no significant variation between included cases.

Table 2: Times (min) from reversal administration to achieve complete reversal state at TOF ratio 0.7, 0.8 and 0.9.

	Group I	Group II	Group III	Group IV	P-value
0,7	1.26 ± 0.229	5.167 ± 0.683	1.067 ± 0.1	4.667 ± 0.516	< 0.001*
0,8	2.529 ± 0.848	11.6 ± 0.99	3.063 ± 0.531	10.5 ± 0.456	< 0.001*
0,9	4 ± 0.433	16.429 ± 1.514	3.375 ± 0.428	14.929 ± 0.784	< 0.001*

* = GI & III significant lower compared to GII & GIV.

The state of neuromuscular block and times from reversal administration to achieve complete reversal state at Train-of-Four (TOF) Ratio 0.7, 0.8, and 0.9, showed significant lower in GI (Rs) and GIII (Vs) than in GII (Rn) and GIV (Vn).

Table 3: Haemodynamic changes after reversal administration.

		Group I	Group II	Group III	Group IV	P-value
MAP	Baseline	76.1 ± 10.1	74.2 ± 11.2	77.2 ± 8.2	75.1 ±10.2	> 0.05
	After 2 min	78.3 ± 13.6	80.2 ± 14.2	75.2 ± 11.8	79.1 ±11.1	> 0.05
	After 5 min	78.2 ± 12.9	77.2 ± 10.9	77.5 ± 12.5	77.2 ± 12.9	> 0.05
	After 10 min	79.2 ± 12.5	76.2 ± 8.2	75.9 ±12.9	75.1 ± 7.4	> 0.05
HR	Baseline	64.1 ± 14.2	67.5 ± 13.2	65.2 ± 17.5	65.2 ± 12.2	0.931
	After 2 min	62.5 ± 15.1	75.5 ± 12.5**	63.2 ± 14.5	74.1 ±11.2**	0.012*
	After 5 min	63.5 ± 17.2	75.1 ± 8.5**	64.2 ± 15.1	76.5 ± 9.1**	0.009*
	After 10 min	66.2 ± 14.5	73.5 ± 8,.7	65.2 ±13.5	74.5 ± 8.1	> 0.05

* = GI & GIII significant higher compared to GII & GIV, ** = significant increase compared to baseline.

Regarding arterial blood pressure (mmHg), there was non-significant difference between groups at base, 2, 5 & 10 minutes but, without significant changes in each separate group at all times. Regarding heart rate, there was significant increase in GII (Rn) and GIV (Vn) at 2 and 5 minutes, and they were significant higher than GI (Rs) and GIII (Vs). At 10 minutes differences were not significant.

Table 4: Side effects reported in different groups.

	Group I	Group II	Group III	Group IV	P-value
Dry mouth	0	10	1	9	< 0.001*
Nausea	0	6	0	7	< 0.001*
Vomiting	0	2	0	2	> 0.05

* = GI & GIII significant lower compared to GII & GIV.

Regarding side effect, there was significant lower incidence of dry mouth and nausea in GI & GIII compared to GII & GIV, without significant difference between them as regard vomiting.

Experimentally no differences were seen in the lag times of rocuronium and vecuronium (16.9±5.3 & 16.9±5.3 respectively). The onset time for rocuronium was significantly less than for vecuronium (37.5±17.9 vs. 61.9±14.9) respectively. No significant difference in recovery between rocuronium and vecuronium after sugammadex, but a significant difference between sugammadex and neostigmine groups.

Fig. 1: Effect of sugammadex on neuromuscular blocking effect of rocuronium and vecuronium on rat hemiphrenic nerve preparation.

Fig. 2: Effect of neostigmine on neuromuscular blocking effect of rocuronium and vecuronium on rat hemiphrenic nerve preparation.

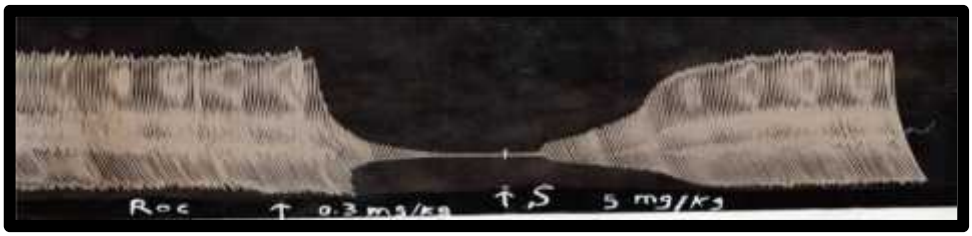

Fig. 3: Effect of sugammadex on neuromuscular blocking effect of rocuronium and vecuronium on cat gastrocaenemius sciatic nerve preparation.

Fig. 4: Effect of neostigmine on neuromuscular blocking effect of rocuronium and vecuronium on cat gastrocaenemius sciatic nerve preparation.

Discussion

Acetylcholinesterase inhibitors, as neostigmine and edrophonium are used for the reversal of non-depolarizing neuromuscular blockade, but risk of side effects, as bradycardia-hypotension, broncho-constriction, hyper-salivation and possibly nausea and vomiting. Anticholinergic drugs, such as atropine or glycopyrrolate, are therefore co-administered to counteract these adverse effects but they may also cause their own side effects such as tachycardia, blurred vision, sedation, and possibly mild confusion, and should be used with care in the elderly and in patients with cardiovascular disease (Khunel-Brady *et al,* 2010).

Sugammadex (Bridion) a modified γ-cyclodextrin that forms tight one-to-one complexes with rocuronium and, to a slightly lesser extent, vecuronium, reducing free plasma concentration of these neuromuscular blocking agents (NMBAs) and rapidly terminating NMB (Naguib, 2007).

Since sugammadex does not act as a reversal agent by its action on receptors but rather by encapsulation in the plasma and possibly extracellular fluid, it is not expected to have such side effects. In general, the safety record of sugammadex has been excellent, with few untoward side effects reported from the various studies in which the efficacy and safety were the primary goals (Mirakhur, 2009).

Sugammadex is given without the need of concomitant administration of any other drugs and provides good cardiovascular stability during the reversal process (Flockton *et al,* 2008). Potential clinical benefits of sugammadex are a fast and predictable reversal of any degree of block not achievable with neostigmine/ atropine. There are also potential benefits in terms of increased patient safety and reduced incidence of residual block on recovery, and more efficient use of health-care resource (Welliver *et al,* 2008).

Because a specific dose recommendation is lacking, the respective dose of 2 mg/kg as a substitute for reversal of any level of neuromuscular block beyond reappearance of T2 was suggested. Rocuronium and vecuronium encapsulation by sugammadex, however, is a one-to-one molecular interaction. It, therefore, would seem feasible that shallow residual neuromuscular blocks would require less sugammadex (Schaller *et al,* 2010).

The present studied patients were randomly assigned for four groups each group consists of 15 patients according to relaxant/reversal agent. 1- rocuronium-sugam- madex (Rs), 2- rocuronium-neostigmine (Rn), 3- Vecuronium-sugammadex (Vs), and 4- vecuronium-neostigmine (Vn). There ages ranged from 16 to 50 years with a M±SD of 40.15±9.14 years while weight ranged from 58 to 87kg with a M±SD of 77.10±6.84kg and finally height ranged from 1.65 to 1.81m with a M±SD of 1.72±0.36m and there was no statistically significant difference between males and females as regard the age, weight or height.

The anesthetic time ranged from 30 to 45 minutes with a mean of 37.44±

2.16 minutes, without significant increase in anesthetic time in males (40.50±3.18) as compared to females (36.4±2.17), and without significant variance between different groups as regard anesthetic time. These results are compatible with the inclusion criteria to evaluate efficacy and safety of sugammadex.

The time of recovery of TOF to 0.7 ranged from 3 to 4 min with a mean of 3.375±0.428 to 4.000±0.433 min. in both sugammadex groups with significant progressive decrease of time of recovery as compared with both neostigmine groups that ranged 14 to 16 min with a mean of 14.929±0.784 to 16.429±1.514 min.

The time of recovery of TOF to 0.8 ranged from 2 to 3 min with a mean of 2.529±0.848 to 3.063±0.531 min in both sugammadex groups with significant progressive decrease of time of recovery as compared to both neostigmine groups that ranged from 10 to 11 min with a mean of 10.500±0.456 to 11.600±0.990 min.

The time of recovery of TOF to 0.9 ranged from 1 to 1.5 min with a mean of 1.067±0.100 to 1.260±0.229 min in both sugammadex groups with significant progressive decrease of time of recovery as compared to both neostigmine groups that ranged from 4 to 5.5 min with a mean of 4.067±0.516 to 5.167±0.683 min.

These results agreed with Pühringer *et al.* (2010) who reported that the geometric mean time to recovery of TOF ratio to 0.9 was significantly faster with sugammadex compared with neostigmine (4.5 minutes vs. 66.2, P< 0.0001) The median range or inter-quartile range time to recovery of the TOF ratio to 0.9 was 3.3 (1.4-68.4 [2.3-6.6]) minutes in sugammadex group vs. 49.9 (46.0-312.7[46.0-96.6]) in neostigmine group. The faster time to recovery was in sugammadex groups. Also, the geometric mean times to recovery of the TOF ratio to 0.7 were significantly faster with sugammadex compared with neostigmine (p<0.0001) 2.6 min with sugammadex vs. 48.8 min with neostigmine. The median range to recovery was 2.5 (1.1-61.9[1.6-3.3]) minutes in sugammadex group vs. 36.4 (27.5-192.7[34.5-67.5]) minutes in neostigmine groups. The geometric mean times to recovery of the TOF ratio to 0.8 were significantly faster with sugammadex compared with neostigmine (P<0.0001) 3.3 min with sugammadex vs. 58.9 min with neostigmine. The median range (inter-quartile range) time to recovery was 2.7 (1.2-65.2[1.8-4.4]) minutes in sugammadex groups vs. 43.9(35.3-250.9 [42.9-79.9]) minutes in neostigmine ones.

In the present study, there was significant progressive decrease of heart rate and blood pressure at 2, 5 & 10 minutes as compared to the basal values before anesthesia, and then started to gain the normal value at 5 & 10 minutes, regardless the dose of sugammadex (effect of anesthesia). Also, the heart rate and blood pressure showed no significant variance between groups of sugammadex when compared at any time of the study with the neostigmine groups (i.e. no effect of the dose on heart rate).

These results agreed with Groudine *et al*. (2007) who reported no clinically significant laboratory abnormalities in terms of hematology, biochemistry, and urinalysis. Besides, no clinically significant changes for systolic and diastolic arterial blood pressure were reported (Hatala *et al*, 2012).

Flockton *et al.* (2008) stated that the lack of any need for a muscarinic antagonist and hence minimal change in heart rate was an advantage of sugammadex. The added, greater stability of heart rate was associated with greater cardiovascular stability and a lower risk of any associated ischemic changes. The lack to use a muscarinic antagonist with sugammadex resulted in mild side-effects as dry mouth, bronchospasm, nausea and vomiting. Also, this study agreed with Sorgenfrei *et al.* (2006) who found no evidence of a hypotensive effect due to sugammadex when administered under steady-state anesthetic conditions. In fact, the MAP and HR values remained stable during the entire post–reversal observation period. Although only 20 patients were studied, this new reversal drug appears to be free of any clinically significant side effects. In the current study, sugammadex was well tolerated without side effects or adverse events, which agreed with an independent systematic review of the efficacy and safety without difference overall in unwanted effects between patients receiving sugammadex or placebo (Abrishami *et al,* 2009).

There were situations in anesthesia practice in which the anesthetist needs to reverse non-depolarizing neuromuscular block very rapid, e.g. when tracheal intubation and /or lung ventilation prove difficult after the administration of non-depolarizing drug such as rocuroniumor in other cases in which the surgical procedure is over, while the patient with a deep neuromuscular blocker, also in cases of anticipated difficult intubation, suxamethonim is the treatment of choice but due to its many side effects, the search for alternative substance is being continued.

In the present work, comparison between sugammadex and neostigmine revealed significant difference between both drugs. The first aspect of comparison was the study of the effect of sugammadexon reverse the relaxant state of rat hemiphrenic nerve. All steroidal muscle relaxants were reversed in less than 1 minute to 90% (Fig 1, 2, 3 & 4) train of four (TOF) or greater, versus the effect of neostigmine showed prolongation of time of recovery up to 8 minutes to 90% train of four (TOF). Also, the effect of sugammadex on gastrocnemius cat sciatic nerve preparation showed neostigmine recovery time from 90% blockade was 6.2 minutes, and recovery after sugammadex was 1.3 minutes.

The present result agreed with Miller and Bometal. (2006). The time to recovery of sugammadex as a reversal agent using mouse and cat models placed mouse hemidiaphragm preparations with the phrenic nerve intact in an oxygenated buffered bath while electrically stimulated isometric contractions were recorded. A 90% blocking dose of common muscle relaxants was administered and paralysis confirmed, and

increasing doses of sugammadex were administered. The return of muscle contraction was measured and timed. The data indicated that aminosteroid muscle relaxants rocuronium and vecuronium were reversed effectively, but rocuronium was the most easily reversed followed by Vecuronium.

Also, the result agreed with Hope and Bom (2001) found that cat gastrocnemius contractions were induced by single twitch stimulation of sciatic nerve. Profound blockade was induced by an intravenous bolus dose of rocuronium. One minute after induction of complete blockade, sugammadex (5mg/kg) Oran equivalent volume of saline was administered. In saline-treated group, 90% recovery occurred after 78.3±15.2 minutes, whereas in the sugammadex occurred after 8.5±2.2 minutes. Thus, the appropriate dose of sugammadex reversed profound block, even when a dose of the NMBA was administered that exceeded normal clinical dose.

Conclusion

The sugammadex was well tolerated without side effects or adverse events in the current study, which agreed with an independent systematic review of the efficacy and safety of sugammadex which showed no difference overall in unwanted effects between patients receiving sugammadex or placebo.

The outcome data proved distinctive advantages over the currently used cholinesterase inhibitors with respect to the speed and completeness of the reversal process, and reduced symptoms of dry mouth nausea and vomiting.

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