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" REVERSAL OF VECURONIUM INDUCED NEUROMUSCULAR BLOCK WITH SUGAMMADEX USING TRAIN OF FOUR MODE IN PATIENTS UNDERGOING SURGERIES UNDER GENERAL ANESTHESIA"

Anaesthesiology

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ABSTRACT

BACKGROUND: Sugammadex is a modified γ-cyclodextrin, "SU" stands for sugar and "gammadex" stands for structural molecule gamacyclodextrin. It can reverse profound neuromuscular blockade and can be given for immediate reversal without waiting for the natural recovery. In a dose of 1.0 mg/kg. It can reverse Rocuronium-induced neuromuscular block which has spontaneously recovered to a train-of-four count of four. In this prospective single arm interventional clinical study, we investigated whether 1mg/kg of Sugammadex can also reverse Vecuronium induced neuromuscular blockade at a similar level of block.

METHODS: Thirty one patients of 18-70 years of age who were scheduled to undergo general surgery and gynaecological procedures were enrolled. All patients received standard general anaesthesia with propofol, sevoflurane, fentanyl, and vecuronium. Neuromuscular function was monitored with acceleromyography (Stimupod xavant technology. Hague, Netherlands). Once the neuromuscular function recovered spontaneously to four twitches in response to train-of-four stimulation, patients were administered 1 mg/kg of Sugammadex I.V. Time from study drug injection to normalized train-of-four ratio 0.9 and the incidence of incomplete reversal within 30min were the primary outcome variables. Secondary outcome was the incidence of reparalysis with normalized train-of-four ratio less than 0.9.

RESULTS: We observe that at 0 min, less than 5 percent had complete recovery of neuromuscular function, while at 5th minute, almost 97% of patients had complete recovery which maximizes to 100 percent in 15 minutes. The same total recovery is maintained until 30 minutes without any reparalysis.

CONCLUSIONS: Sugammadex in a dose of 1.0mg/kg, reversed a threshold train-of-four count of four in vecuronium induced neuromuscular block without any reparalysis.

KEYWORDS

Sugammadex, Vecuronium, neuromuscular block, train-of-four, general anesthesia

INTRODUCTION

Sugammadex is a modified γ-cyclodextrin, compund[1]. It is used for immediate reversal without the need to wait for the natural recovery[2]. It binds, encapsulates and thereby decreases the concentration of unbound neuromuscular blocking agents like Rocuronium, and Vecuronium at the neuromuscular junction (NMJ) and reverses neuromuscular blockade (NMB)[3].Vecuronium is an aminosteroid muscle relaxant structurally similar to rocuronium[4] and has lesser side effects[5] . In a study by Harper et al and his colleagues suggamedex 4 mg/ kg^{-1} rapidly reversed rocuronium-induced neuromuscular blockade in patients with severe renal impairment but safety experience is insufficient for its use[6]. Another study by Cammu et al concluded that suggamedex can reverse the neuromuscular function in heart failure patients in hemodynamically stable conditions, but it requires longer reversal times than the normal patients.[7]

In comparison to rocuronium, there are few studies conducted with vecuronium. Study by Catia Real[8] (2015) concluded that in accidental extubation sugammadex 2mg/kg^{-1} was used instead of neostgmine which could reverse the NMB faster.. Theoretically, a sugammadex dose as low as 0.5mg/kg is enough to encapsulate all vecuronium molecules present in the body at any time after the administration of vecuronium 0.10 mg/kg[9].

In this study we intend to evaluate the reversal effect of vecuronium using sugammadex in a dose of 1mg/kg, from the time of injecting sugammadex to normalize a train-of-four ratio of 0.9 using a neuromuscular junction monitor. We also observed the incidence of incomplete reversal and recurrence of NMB within 30 minutes.

MATERIAL AND METHODS

The study was conducted after approval from the institutional ethical committee. The study was undertaken in the department of anesthesia in collaboration with central research laboratory of a tertiary care medical college hospital. This was a prospective, interventional, single arm clinical study. We enrolled 31 patients of either sex aged between 18 and 50 years, belonging to ASA class I-III scheduled to undergo laparoscopic surgery under general anesthesia. Patients with neuromuscular disorders, history of malignant hyperthermia, renal dysfunction, allergy to narcotics, epilepsy, chronic kidney disease, chronic liver disease, patients with suspected difficult airway, bronchial asthma, significant hepatic dysfunction, glaucoma and allergy to the drugs used in this study, were excluded. Pregnant women and patients who were smokers and alcoholics were also excluded.

Data was collected in specially designed case record form [CRF]. We collected demographic data, disease data, treatment data, pre-anesthetic medication data, data of vecuronium dose and time of administration and Sugammadex dose and time of administration.

After informed consent an 18gauge IV cannula was inserted in large vein of the forearm. Patients were premedicated with Inj. Midazolam 2mg IV and 0.2mg of glycopyrrolate IV. Mandatory physiological monitoring of the patients was instituted. In addition Neuromuscular monitoring was instituted using Stimpod acceleromyography ,Stimpod xavant technology, Hague Netherlands(Fig 1). The forearm and the fingers were immobilized, and surface skin electrodes was

placed over the ulnar nerve proximal to the wrist. A TOF mode of NMJ stimulation was started and repeated every 15s for 3 min followed by a 5-s tetanic train of 50 Hz to stabilize the signal. Two minutes later automatic calibration was carried out to set the supramaximal current intensity and to calibrate the device. General anesthesia was induced with fentanyl 1-2 µg/kg, propofol 1-2 mg. vecuronium was given at 0.1 mg kg^{-1}. Patients were maintained with sevoflurane 2MAC in oxygen and nitrous oxide.

Fig 1: Stimpod acceleromyography (Stimpod xavant technology) Hague Netherlands.

Patient's respirations were assisted until the injection of NMJ Blocker. Patient's oxygen saturation, temperature and end tidal carbon dioxide levels were kept near normal levels. Once the neuromuscular recording is stable, Inj.vecuronium 0.10 mg/kg was injected IV, and the trachea was intubated when the muscle response to TOF stimulation disappeared(train of four count was none). If surgical relaxation is necessary, top up doses of vecuronium 0.015 to 0.02 mg/kg were administered when one to two twitches to TOF stimulation returned. The TOF stimulation was set to deliver automatically at every 30-s interval. Anaesthesia was maintained with sevoflurane 2-2.5 MAC along with oxygen and nitrous oxide. At the end of surgery when four twitches in response to TOF stimulation reappeared at three consecutive TOF measurements (a threshold TOF count of four), anesthesiologist injected sugammadex (Merck Sharp&Dohme Co.,Inc NSW Australia) 1 mg kg^{-1} intravenously(IV).

Criteria Of Reversal Of Nmj Block And Recurrent Nmj Block:
Adequate reversal was achieved with TOF ratio 0.9 in 5 min or less.

Once the TOF ratio reached at least 0.9 (unchanged during 3min), inhalational anesthetic sevoflurane was discontinued and the trachea was extubated when the patients emerged from anesthesia. Patients were kept under observation in the PACU room for one hour. Patients were placed in the semi recumbent position and oxygen therapy using nasal cannula was commenced. Here all the mandatory physiological monitoring along with acceleromyography were continued. We observed for any residual paralysis using NMJ monitor. Patients were shifted out of PACU once they met the discharge criteria.

Adequate reversal
We defined adequate reversal as achievement of normalized TOF ratio of 0.9 in 5 min or less.

Incomplete reversal
was defined as failure to reach TOF ratio of 0.9 within 30 min after administration of reversal agent. Also, the incidence of recurrent neuromuscular block was studied. If found, rescue reversal was given using 2-4mg/kg of sugammadex and when the patients reached TOF ratio of 0.9, then the endotracheal tube was extubated. When the NMJ was completely recovered the person was taken into post anesthesia care unit (PACU).

Statistical Analysis
All the data were entered into Microsoft excel sheet before analysis. The data was analyzed using descriptive statistics like mean, standard deviation, percentage and frequency distribution. Statistical package "R" version 3.4.3 was used for analysis. For every TOF ratio computed, a 90% confidence intervals were estimated from normal distribution and is shown as error bar on the measurement.

RESULTS

We enrolled total of 31 patients in the study, who have undergone laparoscopic surgeries under general anesthesia. We have patients between the age group of 18-70 years, Majority of the patients were in the age group of 36 to 45 years [41.9%]. Male predominance [77.4%] was more in our study [Fig 2].

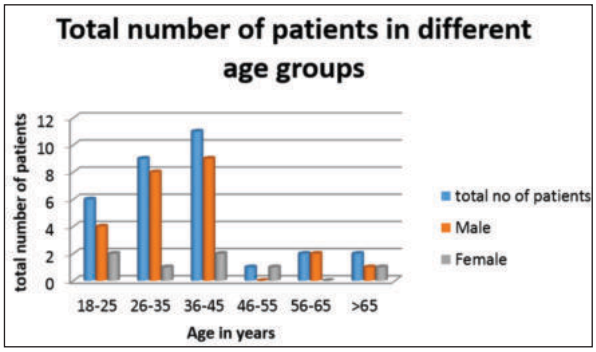
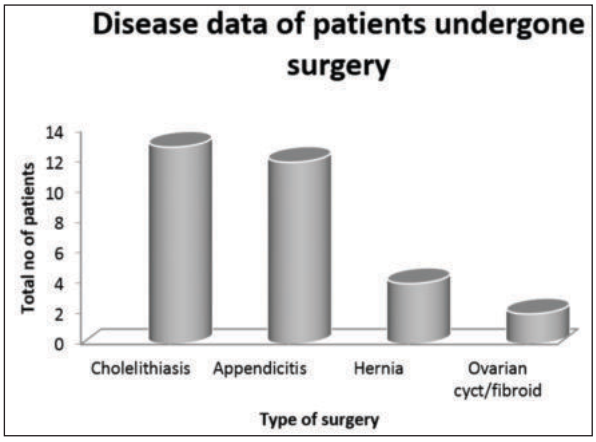


Fig 2: Age and Gender wise distribution of patients

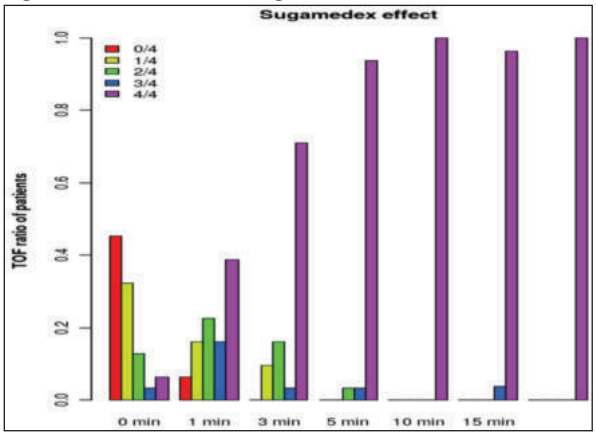
Patients who underwent surgery were diagnosed with conditions like cholelithiasis [41.9%], appendicitis [38.7%], hernia [12.9%], ovarian cyst/fibroid [6.45%] Fig 3. Majority of the patients reported to the outpatient department (OPD) with complaints of pain in the abdomen [58.06%].

Fig 3: Disease Data of patients who underwent surgery



TOFC (train of four count) of patients:
In fig 4, we observed the number of twitches in response to TOF stimulation(TOFC) at various time points to look for the recovery after administering sugammadex. TOFC are represented by different bars, with 4/4 indicating complete recovery. We observe that at 0 min, very few patients (less than 5 percent) had TOFC of 4/4, while at 5th minute, almost 97%(n=29/30) of patients had TOFC count of 4/4. In 3%(n=1/30) of patients TOFC was3/4 and it reached 4/4 at 10th minute. This TOFC was maintained until 30 minutes and beyond without any reversal of NMB.

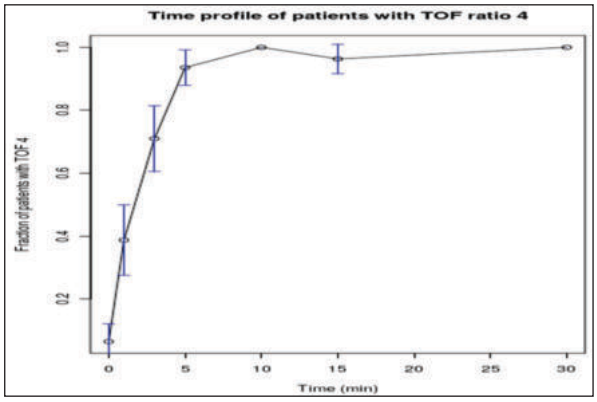
Fig 4: TOFC and TOF ratio of sugammedex at different time intervals.



Time profile of patients with TOF ratio at different time points:
In fig 5, the time profile of patients with TOF ratio is represented in the graph with standard errors to confirm the complete recovery. The error

bars represent a 90% confidence interval around mean. In this plot we observe that all the patients achieved TOF ratio of >0.9 and showed complete recovery in 5 minutes after administering sugammadex within statistical uncertainties. The slight dip observed at 15 minutes is due to single patient displaying a TOF ratio of 0.95 and gradually reaching a TOF ratio of 1 (one) by 30 minutes.

Fig 5: Time profile of patients with TOF ratio at different time points



DISCUSSION

In this study we evaluated whether sugammadex 1.0 mg/kg adequately reverses a vecuronium- induced neuromuscular block that spontaneously returned to a TOF count of four. In our study sugammadex 1.0 mg/kg adequately reversed the block in each patient. We did not find any case of residual paralysis in our study. These results support our hypothesis that a vecuronium-induced neuromuscular block can adequately be reversed with lower sugammadex doses similar to a rocuronium-induced block using a threshold TOF count-of-four in the NMJ monitor without any side effects. In our study we also observed small dose is effective without escalating cost. It may reduce the cost of the required drugs used in anesthesia, if re intubation is required for repeat surgery soon after extubation[11,12].. We tried to decrease the cost of sugammadex for reversal[10] by using 1mg/kg. There are concerns that clinically smaller doses than normal might result in inadequate reversal of neuromuscular block or residual paralysis[13,14] In the literature very few studies have investigated the effect of low-dose sugammadex on the reversal of shallow and moderate rocuronium induced NMB under sevoflurane anaesthesia in a dose of 0.25,0.5,1 and 2 mg/kg[10,15].

A multicenter study[16] investigated the dose–response relationship for the reversal of rocuronium- and vecuronium-induced neuromuscular block with sugammadex 0.5, 1.0, 2.0, and 4.0mg/kg under sevoflurane anesthesia. In their study recovery times to TOF ratio 0.9 were shorter in the rocuronium group compared to the vecuronium group, and the difference was highly sigmificant in a dose of 0.5 mg/kg. In the same study seven patients had recurrence of the NMB block where in dose of sugammadex was 0.5mg/kg. In one case recurrence of NMB occurred after the recommended dose of 2.0mg/kg. Similarly, Duvaldestin etal[17] observed recurrence of neuromuscular block in five patients in the rocuronium group who were administered 0.5-1mg/kg of sugammadex. Eleveld[18]*et al.*12 observed the recurrence of NMB when they tried to reverse a deep rocuronium induced NMB with sugammadex in a dose of 0.5mg/kg. In our study, we have not encountered any case of recurrence of NMB.

Some studies[10,15,16,17,18] have shown that low-dose sugammadex is unsuitable to reverse moderate or deep rocuronium- or vecuronium-induced neuromuscular block. It has been explained on the basis of sugammedex and NMBA complex formation and molecular weight. The complex formation of sugmmadex with NMBA and its breakdown into constituent molecules depends on the degree of the two substances to associate and to dissociate[19]. As we know that sugammadex is more selective for rocuronium than for vecuronium (Ka = 1.79×107 mol/L and 5.72×106 mol/L, respectively)[20], hence the complex formation is slower with vecuronium than with rocuronium. As Kd of vecuronium is 0.17 μM compared to rocuronium 0.055 μM[20,21], so higher relative sugammadex concentrations are required for complex formation with vecuronium compared with rocuronium. Hence sugammadex 0.5mg/kg was limited in reversing the residual effect of vecuronium, in contrast to what was previously found with rocuronium[10]. It is reported that sugammadex/vecuronium concentration ratio, not the absolute number of vecuronium molecules in the body, appears to be the driving force for the reversal of vecuronium block[3] Therefore, sugammadex 1.0mg/kg and 2.0mg/kg were effective, whereas 0.5 mg/kg was not effective.

It is less likely that residual concentrations of sevoflurane can enhance the block in the postoperative period. It is also unlikely that the metabolite of vecuronium can cause reparalysis as the doses were too small. In our study neither mild, moderate or severe postoperative residual paralysis nor recurrence of NMB occurred in any of our patients.

Limitation of this Study

In this study we used acceleromyographic measurements of neuromuscular transmission. It may overestimate the recovery of NMB. We had set the supramaximal current after calibration to improve the accuracy of measuring the neuromuscular transmission.

Perioperative hypothermia may increase skin impedance and may limit the appropriate interpretation of evoked responses to TOF stimulation.Measuring the plasma concentrations of sugammedex, vecuronium, or degradation products like 3-desacetylvecuronium would have helped in accuracy but this was beyond the scope and limitation of the study. Explanation of the results obtained was based on published data, presumptions about the mechanism of reversal and postoperative recurrent neuromuscular block. Due to ethical reasons the placebo control was excluded from the comparison of the reversal times. Large scale randomized studies are required to confirm our results.

CONCLUSION

In our study sugammadex 1 mg/kg, reversed vecuronium-induced NMB under train of four mode of neuromuscular junction monitoring and we did not encounter any case of residual paralysis or recurrent neuromuscular block. None of the patient had any side effects.

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Conflict of interest: None

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