

Intraocular pressure changes associated with tracheal extubation: Comparison of sugammadex with conventional reversal of neuromuscular blockade

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Abstract

Objective: To compare the effects of neostigmine/atropine combination and sugammadex on intraocular pressure during tracheal extubation period.

Methods: The single-blind prospective randomised controlled study was conducted at Ordu University Research and Training Hospital from August to October 2014, and comprised patients who were randomly assigned to 2 groups according to the agent used for reversal of neuromuscular blockade. Group N received 0.05mgkg⁻¹ neostigmine and 0.02 mgkg⁻¹ atropine and the patients in Group S received 2mgkg⁻¹ sugammadex intravenously. Heart rate, mean arterial pressure and intraocular pressure were measured at baseline, before the induction (T1), after the application of reversal agent (T2), and 1 (T3), 3 (T4), 5 (T5) and 10 (T6) minutes after the extubation. SPSS 16 was used for statistical analysis.

Results: There were 36 patients in the study; 18(50%) in each group. There was no significant difference between the groups in terms of age, gender and body mass index ($p>0.05$ each). Intraocular pressure was significantly higher when the baseline level was compared with all measurement intervals in Group N ($p<0.05$ each). In Group S, it showed no significant difference at T2 ($p>0.05$) whereas it was significantly higher at all other measurement intervals ($p<0.05$ each). Intergroup comparisons showed statistically significant difference in heart rate and mean arterial pressure levels at T2 interval which were higher in Group N ($p<0.01$). Intraocular pressure levels at T2 and T3 intervals were significantly higher in Group N ($p<0.01$).

Conclusions: Lower end-extubation intraocular pressure levels were obtained when sugammadex was used as a neuromuscular block reversal agent in comparison with neostigmine-atropine combination. Sugammadex may be a better option for the reversal of neuromuscular blockade and intraocular pressure increase should be avoided in patients with glaucoma or penetrating eye injury.

Keywords: Neostigmine; Anaesthetics; Intraocular pressure; Sugammadex. (JPMA 65: 1219; 2015)

Introduction

Increase in intraocular pressure (IOP) is a serious problem during intraocular surgery. Management of anaesthesia requires the control of IOP in the perioperative period since the IOP rise during open globe conditions like traumatic injury or cataract surgery may cause permanent loss of vision.¹

The main factors affecting IOP are aqueous humour dynamics, choroidal blood volume, central venous pressure and the extraocular muscle tone. IOP may be influenced by several factors related to anaesthesia, including changes in the blood and intrathoracic pressure, some anaesthetic drugs like ketamine and depolarising muscle relaxants, hypoventilation, hypercapnia, drugs affecting the sympathetic and parasympathetic systems such as atropine, epinephrine,

trendelenburg position and laryngoscopy.^{2,3}

IOP may increase due to airway manipulations, rise in blood pressure and ocular blood flow during general anaesthesia process. It is highlighted that these changes in IOP can be faced during recovery period of anaesthesia and tracheal extubation as well as during the course of tracheal intubation.⁴

It is demonstrated that topically or intramuscularly applied atropine may lead to significant increases in IOP, in an animal model. It is, therefore, implicated that it must be avoided if possible or it must be used with caution in patients with glaucoma or in patients who have a predilection for glaucoma.⁵ It has been also shown that combination of atropine/neostigmine has minimal effect on pupil diameter and IOP.⁶

Sugammadex is a γ cyclodextrin agent that selectively binds steroidal neuromuscular blockers such as rocuronium. By making complexes with rocuronium in circulation and at neuromuscular junction, it enables the excretion of the drug in the urine without metabolism.

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Sugammadex gives rise to safe and rapid reversal of deep neuromuscular blockade induced by rocuronium.⁷ Sugammadex is known as a safe drug without any known serious side effects. The common side effects of sugammadex are minimal cough, oral discomfort, hypersensitivity, temporary QT prolongation and temporary (<30 min) activated partial thromboplastin time prolongation.⁸

We hypothesised that the IOP effects of sugammadex used for antagonism of neuromuscular blockade would be less than atropine/neostigmine combination. The current study was planned to test this hypothesis, and to compare the effects of atropine/neostigmine combination and sugammadex on haemodynamic response and IOP during tracheal extubation and early recovery period.

Patients and Method

This single-blind prospective randomised controlled study was conducted at Ordu University Research and Training Hospital from August to October 2014, and comprised American Society of Anaesthesiology (ASA) grade I and II patients aged between 18 and 65 years, who were scheduled to have general anaesthesia with endotracheal intubation for elective surgery. The study was approved by the institutional ethics committee and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all the patients. Patients undergoing laparoscopic surgery, ophthalmic surgery, predicted difficult tracheal intubation (Mallampati III / IV), history of glaucoma, uncontrolled hypertension and cardiovascular disease, body mass index (BMI) >30kg/m², increased intracranial pressure, patients using drugs affecting IOP, surgical positions except supine position were excluded.

None of the patients received premedication. In the operating room, patients were monitored with electrocardiogram (ECG), noninvasive arterial pressure, peripheral oxygen (O₂) saturation (SpO₂) and end-tidal carbondioxide (CO₂) levels (Mindray, BeneView T8, Shenzhen, P. R. China). An intravenous (IV) line of 10 mL kg⁻¹ ringers lactate solution was infused via 20G venous cannula through the dorsum of the non-dominant hand. Using a computer-generated sequence of numbers and a sealed envelope technique, patients were randomly divided into 2 groups: patients who received for reversal of neuromuscular blockade neostigmine/atropine combination were labelled Group N and those who sugammadex were labelled Group S.

IOP values were measured bilaterally via a hand-held tonometer (i-Care TA01i, Tiolat Oy, Helsinki, Finland)

before the induction and the mean of six measurements were recorded as the baseline IOP value. The device was calibrated before each measurement. Neuromuscular monitoring was carried out using TOF Watch SX® (Organon Ltd, Dublin, Ireland) acceleromyography, with skin electrodes located at the ulnar nerve trace for contractions of adductor pollicis muscle.

General anaesthesia was induced by IV 1 mcg kg⁻¹ fentanyl and 2.5mgkg⁻¹ propofol. With the loss of consciousness (loss of eyelash reflex), IV 0.6mgkg⁻¹ rocuronium was applied. Orotracheal intubation was performed when no response was yielded with Train of Four (TOF) stimulation of TOF-Guard device. After intubation the patient was mechanically ventilated in the controlled mode where the end-tidal CO₂ pressure was kept between 35-40mmHg. Anaesthesia was maintained with 2% sevoflurane in 50% O₂/air mixture and 0.2-0.7mcgkg⁻¹ min⁻¹ IV remifentanil infusion. Additional IV bolus of 0.1-0.2mgkg⁻¹ rocuronium was administered during surgical procedure provided that TOF ratio to be 10% or lower. No neuromuscular blocker agent was used if the remaining time to the end of surgery was less than 30 minutes. At the end of the surgery, anaesthetic drug administration was ceased and the patient was manually ventilated with 100% oxygen. Antagonisation of neuromuscular blockade was provided with IV administration of 0.05mgkg⁻¹ neostigmine and 0.02mgkg⁻¹ atropine for the patients in Group N and 2mgkg⁻¹ sugammadex for the patients in Group S when TOF response (T4/T1) had reached 20%. The patients were extubated after aspiration of oropharyngeal secretions with the 90% recovery of TOF value. Additional IV administration of 0.025mgkg⁻¹ neostigmine and 0.01mgkg⁻¹ atropine in Group N and 2mgkg⁻¹ sugammadex in Group S was planned in case of need (should the TOF value stay under 90% after 5 minutes). Quality of the extubation was evaluated by the same clinician on a 5-point scale as defined in literature: 1= no cough and normal breathing; 2= smooth extubation, minimal cough (1 or 2 times); 3= moderate cough (3 or 4 times); 4= severe cough (5 - 10 times) and difficulty in breathing; 5= laryngospasm with severe cough and forced breathing.⁹

Follow-up parameters of heart rate (HR), mean arterial pressure (MAP) and IOP were measured as baseline before the induction (T1), after the application of reversal agent (T2), 1 (T3), 3 (T4), 5 (T5) and 10 (T6) minutes after the extubation. Moreover, extubation time (time to TOF ratio be 90% after administration of the reversal agent), amount of rocuronium and remifentanil consumption during the surgery, type of the surgery and duration of

the surgery were recorded. Complications after the surgery such as nausea, vomiting and shivering were also noted. HR below 50 pulse/min was considered bradycardia and managed with 0.5 mg IV atropine. MAP above 125mmHg was considered hypertension and managed with 0.1mg IV nitroglycerin. Prophylaxis of postoperative nausea and vomiting was carried out by 4 mg IV ondansetron (Ondaren 4 mg/2mL, Vem Ilac, Mecidiyeköy, Istanbul). Intravenous 50mg dexketoprofen (Arveles 50 mg/2 mL, Ufsa Ilac, Topkapi, Istanbul) was

Table-1: Patients characteristics.

	Group N n = 18	Group S n = 18	p
Age (year)	43 (21-64)	42 (21-61)	0.55
BMI (kg / m ²)	25.5 (18-30)	25.0 (19-30)	0.29
Gender (F / M)	8 / 10	7 / 11	0.73
ASA I / II	13 / 5	14 / 4	0.50

Data are presented as median (min-max) or frequencies. BMI: Body mass index, F/M: Female / Male, ASA: American Society of Anesthesiologist.

Table-2: Comparison of heart rate (HR, bpm-1), mean arterial blood pressure (MAP, mmHg) and intra ocular pressure (IOP, mmHg) in all groups.

	HR		MAP		IOP	
	Group N	Group S	Group N	Group S	Group N	Group S
T1	76 (55-89)	73 (62-90)	88 (51-120)	89 (67-107)	13.5 (10-27)	13.5 (8-17)
T2	87 (74-110)* †	69.5 (58-88)	97 (69-128)* †	76.5 (59-119)	21 (16-36)* †	13 (8-25)
T3	95 (66-113)* †	87.5 (63-106)*	106.5(77-166)*	96.5 (86-127)*	26.5 (18-35)*†	21.5 (9-30)*
T4	88.5 (65-96)*	85 (66-110)*	96.5 (78-113)*	103 (79-122)*	21 (12-37)*	17.5 (11-28)*
T5	84.5 (54-98)*	85 (65-110)*	94 (69-110)*	98.5 (70-110)*	18 (10-30)*	14.5 (10-26)*
T6	79 (55-100)	76 (60-100)	91.5 (64-125)	92 (68-112)	16.5 (10-28)*	15 (9-20)*

Data are presented as median (min-max). *: p<0.05 compared with baseline value, Wilcoxon test †: p<0.05 compared with Groups S, Mann-Whitney U. T1: Baseline value, T2: After reversal, T3: First min after extubation, T4: Third min after extubation, T5: Fifth min after extubation, T6: Tenth min after extubation.

administered for postoperative analgesia. Administration of IV 4mg dexamethasone for nausea and vomiting and IV bolus of 1mgkg⁻¹ tramadol for postoperative analgesia were planned as rescue agents. According to an evaluation based on a previous study,¹⁰ 16 patients in each group were required in order to detect 3mmHg IOP change with 90% power and 5% significance in two-way significant interactions (Minitab 13.1 Inc. State College PA, USA). We planned to include 36 patients to allow for dropouts.

Data obtained in the study was analysed with SPSS 16. Descriptive statistics were expressed as median (range) for continuous variables and as frequencies and percentages for nominal variables. Distribution analysis was made with the Kolmogorov-Smirnov test. Age, BMI, rocuronium and remifentanil consumption, extubation time and duration of surgery, HR, MAP and IOP were evaluated with Mann Whitney U test for inter-group comparisons and Wilcoxon test for intra-group comparisons. Chi-square or Fisher exact test was used for categorical data such as gender, ASA physical status, quality of extubation and shivering. P<0.05 was accepted as statistically significant.

Results

Of the 49 patients approached, 13(26.5) had to be excluded, and 36(73.4) represented the final sample who

Table-3: Intraoperative characteristics, frequency of adverse events and quality of extubation in groups.

	Group N n = 18	Group S n = 18	p
Rocuronium consumption (mg)	42.5 (35-60)	42.5 (30-60)	0.61
Remifentanil consumption (µg)	740 (460-960)	730 (420-880)	0.32
Surgery time (min)	45 (30-90)	45 (35-80)	0.68
Extubation time (min)	7 (4-20)	2 (1-8)	< 0.00*
Quality of extubation			0.22
1	7 (38.9)	12 (66.7)	
2	8 (44.4)	5 (27.8)	
3	3 (16.7)	1 (5.5)	
Hypertension	-	1 (5.5)	0.50
Shivering	-	1 (5.5)	0.50
Nausea - vomiting	2 (11.1)	-	0.24

were randomly divided into two groups of 18(50%) each (Figure). There was no significant difference between the groups regarding age, gender, BMI and ASA scores (p>0.05 each) (Table-1).

Intragroup comparisons showed that HR and MAP were significantly higher at T2, T3, T4, T5 intervals than the baseline measurements in Group N (p<0.05), whereas HR and MAP were significantly higher at T3, T4, T5 intervals than the baseline measurements in Group S (p<0.05) (Table-2). In Group N, IOP values were

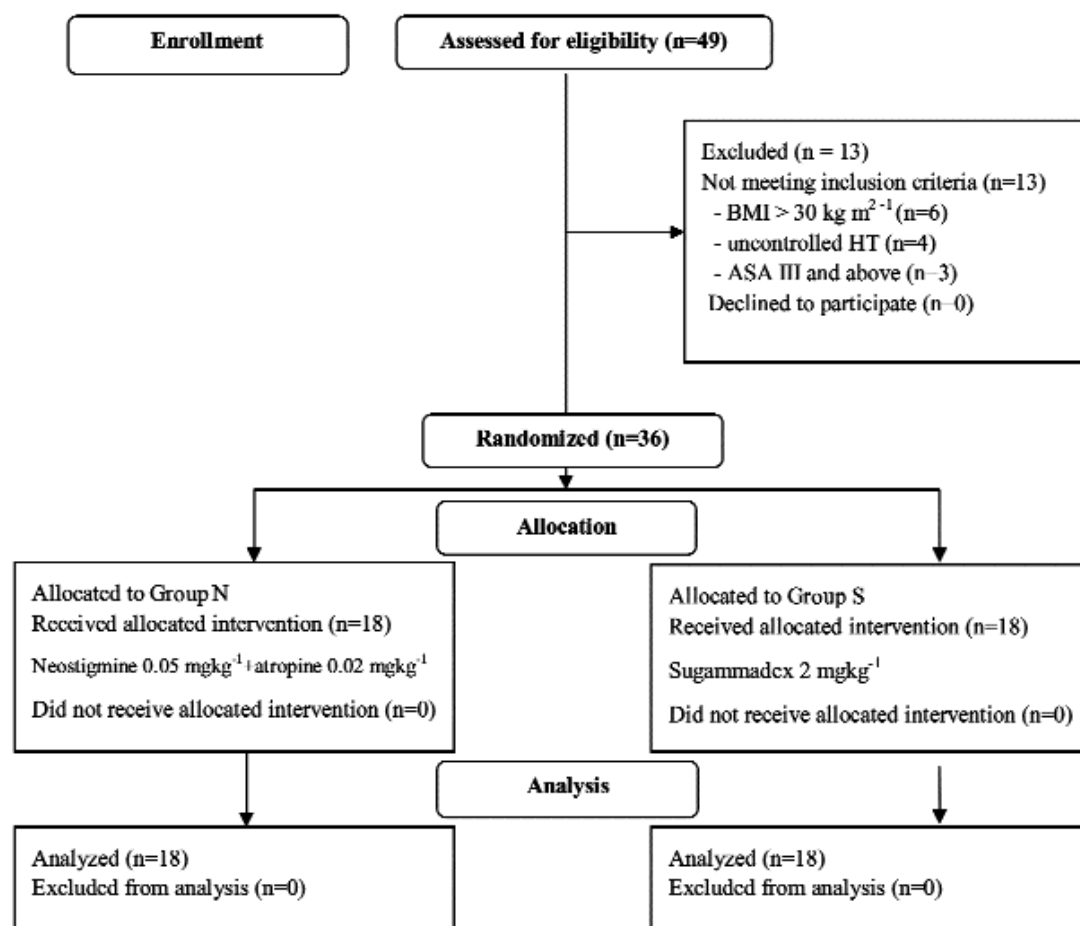


Figure: CONSORT flow diagram of the randomised trial.¹⁷

significantly higher at all measurement intervals compared to the baseline value ($p < 0.05$). There was no statistically significant difference in IOP at T2 interval compared to the baseline value, but it was significantly higher at all other measurement intervals in Group S ($p < 0.05$).

Intergroup comparisons yielded statistically significant difference in HR at T2 and T3 intervals which was higher in Group N ($p < 0.001$ at T2; $p < 0.05$ at T3). MAP was significantly higher at T2 interval in Group N ($p < 0.01$). Although IOP values were significantly higher at T2 and T3 intervals in Group N than in Group S ($p < 0.01$), but there was no significant difference between the groups at the rest of measurement intervals.

No significant difference was found between the groups regarding consumption of rocuronium and remifentanyl, duration of surgery and quality of extubation (Table-3). Median extubation times were measured as 7 min

(range: 4-20) and 2 min (range: 1-8), in Group N and Group S ($p < 0.001$). There was no significant difference between the groups regarding adverse reactions ($p > 0.05$).

Discussion

Results of current study demonstrated that neostigmine/atropine combination leads to significantly higher levels of IOP in the measurements after administration of the reversal agent and one minute after the extubation when compared to sugammadex for the antagonism of neuromuscular blockade with rocuronium.

Neuromuscular blockers are utilised in general anaesthesia practice for amelioration of surgical conditions and to facilitate intubation. The recovery of the effects of nondepolarising neuromuscular blockers is accomplished through the acetylcholinesterase inhibitors such as neostigmine. The mechanism of action

of these drugs is by the way of increasing acetylcholine concentration in the synaptic cleft. In order to antagonise the muscarinic effects of acetylcholinesterase inhibitors such as bradycardia, prolongation of QT interval, bronchoconstriction, hypersalivation, they are used in conjunction with an anticholinergic agent such as atropine or glycopyrrolate.¹¹ Sugammadex is a contemporary alternative to conventional decurarisation of cholinesterase inhibitors. Sugammadex, effective on steroidal nondepolarising neuromuscular blockers binds rocuronium or vecuronium molecules and, thereby, causes a decrease in the plasma concentrations of these molecules. This results with rapid decurarisation. Muscarinic side effects are not expected in decurarisation of this mechanism.

Anticholinergic and parasympatholytic drugs inhibit the cholinergic and parasympathetic innervation on the ciliary body and iris muscles. Blockade of parasympathetic innervation may result in increased resistance to humour aqueous drainage causing increase in IOP. Systemic administration of these drugs may cause undesirable or hazardous complications due to pupillary dilatation and paralysis of accommodation.¹² Orally or parenterally used atropine may cause similar effects with direct ocular exposure. However, systemic administration is expected to cause relatively less effect since the amount of drug that reaches the eye is relatively small. Unless a predisposing factor exists, systemic anticholinergic drugs may not cause serious situations.¹²

Despite a single dose systemic atropine may not cause a major effect on IOP in patients with open angle glaucoma, and it may result in IOP increase up to 44%. This effect would be more pronounced in patients with closed angle glaucoma, and therefore miotic eye drops are recommended in these patients simultaneously with systemic atropine.¹² In conditions like tracheal intubation and extubation, where IOP rise is expected, these increases may be more prominent and may cause potentially hazardous complications, especially in patients with borderline optic disc perfusion.

Like, intubation, endotracheal extubation may cause sympathetic system activation by stimulating the upper airways. Depending upon the sympathetic stimulation during laryngoscopy, intubation and extubation, plasma concentrations of noradrenaline and adrenaline increase causing an increase in heart rate and blood pressure.¹³ Tracheal extubation, aspiration, cough and gag raise intracranial and IOP. Therefore, it is stated that these

effects may proceed with undesirable consequences, especially in patients with increased intracranial pressure or penetrating ocular injury.^{14,15} Not only the increase in arterial pressure is responsible for acute rise in IOP, but also the vasoconstriction and increase in the central venous pressure due to increased sympathetic activity and adrenergic stimulation are also closely related to rising IOP.¹⁶ Additionally, adrenergic stimulation may cause an acute IOP rise through increased resistance against humour aqueous flow in the trabecular meshwork between anterior camera and Schlemm's canal.¹⁷

One study¹⁸ compared the effects of propofol and urapidil on haemodynamics and IOP administered immediately before extubation in ophthalmic surgery patients. Propofol used in the extubation period inhibited the cardiovascular stress response and IOP rise effectively. Especially when compared with the pre-induction period, IOP increased up to 75% (from 16.8 to 29.4mmHg) at the extubation period in the urapidil group. IOP was reported to return to pre-induction values 10 minutes after the extubation. In our study, compared to pre-induction values IOP increased up to 60% and 100% higher values after the extubations in Group S and Group N, respectively.

One study¹⁹ compared the effects of intubation and extubation in ophthalmic surgery on haemodynamic parameters and IOP over glaucomatous and normal children. It detected significant IOP rise after the intubation in both groups which was more pronounced in the glaucoma group. Moreover, it established IOP rise in both groups after extubation (from 15.5 to 22.9 mmHg in the normal group and from 31.5 to 38.7 mmHg in the glaucoma group). There was no statistically significant difference between the groups. Both groups showed significant increases in heart rate, systolic and diastolic blood pressure after the intubation and extubation.

Another study²⁰ compared the IOP changes in insertion and extraction of laryngeal mask airway and endotracheal tube (ETT). It determined an IOP increase of 49% (from 12.0 to 17.9mmHg) after the intubation compared to pre-intubation in the ETT group. After extraction of ETT, this rise was detected as 50% compared to pre-extraction (from 11.3 to 17.1mmHg). These hikes were found to be highly significant ($p < 0.001$). In both group of patients, IOP returned to basal values in 10 minutes at the latest. IOP changes were found to be consistent with the cardiovascular response.

Compared with baseline measurements, HR, MAP and

IOP values raised significantly after the administration of reversal agent in neostigmine/atropine combination group in this study. Whereas there was no significant difference in the sugammadex group after the administration of reversal agent. In the period after extubation, the follow-up parameters were significantly higher in both groups than the baseline measurements.

Sugammadex effect over IOP was assessed in a single case report²¹ in literature. Eighty-six-year-old female with narrow angle glaucoma was operated for femur fracture under general anaesthesia. Propofol and rocuronium were applied for induction of anaesthesia; propofol and remifentanyl were applied for maintenance of anaesthesia. Tracheal tube was extracted and laryngeal mask was placed at the conclusion of surgery. TOF value of 80% was reached via sugammadex in the dose of 2mgkg⁻¹, while subsequently an additional dose of 1mgkg⁻¹ enabled full reversal of neuromuscular blockade with a TOF ratio of 100%. IOP was reported to be under 20mmHg in this period. Mean IOP value was above 20mmHg (21.5mmHg) after extubation at T3 measurement interval in Group S in our study. IOP raised above 20mmHg in Group N at T2, T3, T4 measurement intervals. In that single case in literature,²² IOP increase could be prevented by tracheal extubation before administration of reversal agent and follow-up by laryngeal mask in the arousal period.

Since it was reported that IOP would be affected by the depth of anaesthesia,¹⁹ pre-induction IOP value was determined as baseline value instead of pre-extubation value, in the present study. Profound anaesthesia was reported to decrease IOP more than 15mmHg.²² Extubation may be carried out under profound anaesthesia in patients where IOP rise is not desired, but this kind of extubation may lead to obstruction in the upper respiratory tract, laryngospasm and pulmonary aspiration.¹⁹

It is known that coughing, straining and vomiting may cause temporary, but significant rises in IOP.²³ Coughing may result in IOP values as much as 50mmHg.²⁴ Therefore, it must be especially avoided in patients where this rise would be detrimental such as glaucoma or penetrating ocular trauma. No significant difference was shown between the groups respecting the extubation quality and cough incidence in the present study. Furthermore, tracheal extubation with sugammadex as a reversal agent is expected to be uneventful in comparison with neostigmine-atropine combination.

The major limitation of this study is the possibility of being unable to standardise the factors affecting IOP completely. Even though the patients were excluded in the presence of conditions known to affect the IOP, such as laparoscopic surgery, prone position, use of drugs affecting IOP and ocular surgery, more optimal results may be obtained if personal factors, such as preoperative anxiety, were controlled and the patients undergoing single type of surgery were included.

Conclusion

Lower end-extubation IOP values were obtained in patients who received sugammadex for the reversal of neuromuscular blockade. Sugammadex may be a better option for the reversal of neuromuscular blockade in conditions when IOP increase is not desired such as glaucoma and penetrating eye injury.

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