**Title: A Randomized Controlled Trial (RCT) comparing reversal effect of rocuronium with neostigmine or sugammadex towards cough response on emergence in patients undergoing general anesthesia**

**Evaluating the Cough Evoked Response on emergence in patients undergoing general anaesthesia trial (ECER TRIAL)**

**Introduction**

Emergence from general anesthesia can be associated with coughing, agitation, hypertension and tachycardia, which may cause various untowards events and side effects. (1,2,3,4) The incidence of cough is reported to be as high as 76 – 80%. (1). Coughing during emergence, may cause unfavorable side effects which include sore throat, nausea, bleeding from the surgical site, an increase in intracranial and intraocular pressures as well as cerebrospinal fluid rhinorrhea. (1,2,34)

Most patient cough during emergence from general anesthesia in the presence of a tracheal tube as during this time the patient is already in light plane of anesthesia or in the state of arousal and with presence of an endotracheal tube in situ is considered as an intense airway stimulant that can induce coughing. Studies show a number of factors that influence the incidence and severity of coughing on emergence which include smokers, chronic cough, hyperactive airway disease and drugs associated. Drug associated with coughing include usage of ACE inhibitors antihypertensive as well as the reversal agents. It is believed by fast reversal or returning of muscle strength with sugammadex, patient is able to react to the extensive stimulant of the airway by coughing. However no study so far to show association of muscle power after reversal of muscle relaxant with intensity and severity of cough during emergence.

A number of techniques have been used to prevent these adverse emergence phenomena, such as removing the tube while the patient is in a deep plane of anesthesia or the administration of local anesthetics or IV opioids. (1,2,4). Extensive studies have been done that shows the administration of IV opioids before emergence may be useful for preventing cough, agitation, and hemodynamic response but may cause delayed emergence and can be unpredictable. Recent studies show how superior and statistically significant remifentanyl form other opiods or lidocaine in obtundation of cough reflex on emergence. (1,2,3,4)

**Background**

 Muscle paralysis is mostly needed during maintainance phase of general anesthesia especially in operation that need full relaxation namely general abdominal surgery, neurosurgery and thoracic surgery. To achieve satisfactory muscle relaxation, non depolarizing muscle relaxant agents are used. These agents fall into two chemical grouping which is aminosteroid group; eg rocuronium and benzylisoquinolinium group; eg atracurium.

At the end of the surgery, reversal agents are needed to regain muscle power prior to extubation. Reversal agents that are commonly used to reverse the neuromuscular blockade include anticholinesterase agent; eg neostigmine and selective relaxant binding agent; eg sugammadex.

 Neostigmine is a quaternary amine anticholinesterase. As an anticholinesterase, neostigmine antagonizes the action of Acetylcholinesterase (AchE) enzyme by formation of carbamylated enzyme complex, therefore preventing degradation of Acetylcholine (Ach). More Ach is available at neuromuscular junction, competitively displace the relaxant agent and reverses the effect of muscle paralysis. However, the action of anticholinesterase is not specific to the neuromuscular junction but it also has effect at autonomic cholinergic receptors causing effects like bradycardia, increase salivation and intestinal motility. Anti muscarinic agents like atropine or glycopyrolate need to be co administered to opposed these effects.

 Sugammadex is categorized as a selective relaxant binding agent (SRBA) which is used for the reversal of neuromuscular blockade by aminosteroidal agents eg rocuronium. It is a modified gamma-cyclodextrin. Cyclodextrin are oligosaccharides that have a tube like structures. The core is lipophilic while the exterior is hydrophilic. Modification of the natural structure by adding few glucopyranose units increases the cavity size of the tube structure thus, allowing greater encapsulation of rocuronium within the cavity. Once sugammadex is administered, it will rapidly encapsulates rocuronium molecules within its lipophilic core making it unavailable to bind to the Ach receptor at neuromuscular junction. (5.6)

 The main advantage of sugammadex is the reversal of neuromuscular blockade is independent to inhibition of acetylcholinesterase. As a result, its administration does not cause side effects associated with unopposed inhibition of Acetylcholinesterase at muscarinic receptors. Secondly, it can be administered individually without co administration of anti muscarinic agent. Hence, reduces risk of drug errors. In addition, when fast onset and short duration of muscle relaxant is required, there is now an alternative option to suxamethonium, a depolarizing muscle relaxant. High doses of rocuronium can also provide rapid onset of muscle relaxant and with sugammadex available, the effect can be rapidly reversed. Neurophysiological monitoring using mMEPs confirmed that sugammadex provide a complete recovery profound and ‘deep’ residual rocuronium-induced neuromuscular blockade. (6,7)

However, sugammadex also has other undesirable effects or precautions. Rare effects; drug hypersensitivity reactions including anaphylaxis but noted to be dose dependant, some isolated cases noted to have profound bradycardia, commonly undesirable effect in light anesthesia including grimacing, coughing and movement of limbs, post operative recurrent residual neuromuscular blockade with suboptimal dose and short duration of prolongation of APTT and INR time.

During reversal phase of anesthesia, the induction agent that is commonly used, namely the volatile anesthesia or intravenous induction agent is turned off. Following that, reversal of muscle paralysis is achieved with administration of reversal agents either by using neostigmine or sugammadex. (5,6). Emergence from general anesthesia experienced by the patient sometimes can be associated with hazardous effects namely hypertension, tachycardias, arrhythmias, agitations, nausea, vomiting and most commonly cough. (1,2,3,4).

Fast reversal of muscle paralysis with sugammadex have been proved to be statistically significant compared to neostigmine, with mean recovery time but only slightly and transiently reduces PONV. Due to its fast recovery of muscle paralysis, sugammadex frequently causes cough on emergence, grimace and suckling of ETT tube.

The aim of this study is to compare the incidence of cough response during emergence in general anaesthesia with sugammadex or neostigmine as the reversal agent. We hope this study will help and guide clinicians to choose a safe and appropriate drug that can efficiently reverse the patient under general anesthesia with minimal risk of coughing on emergence and other adverse events.

**Hypothesis**

Reversal of neuromuscular blockade with either sugammadex or neostigmine at the end of neurosurgery will result in difference in the grade of cough response during emergence. Different dosage of sugammadex used for reversal may have different outcome in cough response.

**Objectives**

General : Comparing the clinical efficacy and safety of neostigmine and sugammadex as reversal for patients undergoing surgery under general anesthesia.

Specific :

Primary endpoint : to compare incident and severity of cough on emergence in patient undergoing general anesthesia receiving two types of reversal agents with different dosage.

 Secondary endpoint : 1) to compare reversal time taken by each drugs at different dosages

2) to document number of adverse event associated with sympatetic activation on emergence

( hypertension; sBP>160 or dBP >90, tachycardia; >100 ) in both groups in operation theatre and in recovery bay

3) incidence of unplanned ICU admission associated with the adverse events.

4) incidence of post operative residual paralysis and post operative respiratory complications

5) incidence of post operative nausea and vomiting

6) factors associated with severity of cough on emergence

**Methodology**

This is a prospective randomized controlled trial (RCT) study involving adult patients undergoing general relaxant anesthesia in operation theatre of University Malaya Medical Centre (UMMC).

Inclusion criteria:

1. Patients scheduled for elective or emergency operation under general relaxant anesthesia
2. ASA I - III according to American Society of Anaesthesiologist guidelines.
3. Patient’s age 15 - 70 years old.
4. Aim for extubation at the end of surgery
5. Procedure duration of 1 hour to 6 hours

Exclusion criteria:

1. Patient or relative refusal

2. Planned to remain intubated and ventilated

3. Patient on tracheostomy

4. Any contraindication to rocuronium, neostigmine or sugammadex such as

 allergy, severe renal or liver impairment, coagulopathy and on OCP.

5. Evidence of raised ICP or IOP

Sample Size:

Sample size calculation was performed using OpenEpi version 3.03 open source software. A total of 360 patients with n=120 per arms of the trial is required as sample size to achieve α=0.05 and power (1-β) >80%. Estimation was based on 15% reduction of main outcome in the intervention group.The three arms include sugammadex group 1 (1mg/kg for reversal and another 1mg/kg post extubation) , sugammadex group 2 (2mg/kg) and neostigmine/glycopyrrolate group (0.05mg/kg and 200mcg). After considering 5% drop out rate, total sample required is 420 (140 per group). The study is using a CHI SQUARE test with multivariate analysis to analyze the results.

Randomization:

A computer generated randomization method is used for this study. The patient will be randomly allocated to a study group to receive either sugammadex. The allocation of a patient to either group shall only be known to the initially randomizing person. This person is a research assistant. Both the patient and the research personnel, who are present during general anesthesia, will be blinded till completion of the study. The attending anesthesiologist will receive the sealed envelope containing patient randomized study drug at the end of surgery and need to prepare the allocated drug for the patient. Unblinding of the researcher only possible in case of medical emergency which requires knowledge of study drug identity ( eg in case of suspected anaphylaxis to the study drugs). Any adverse events likely resulting from study drugs participation will be reported to the UWA study centre as well as to the individual institutional review board (IRB) responsible for study approval at a teaching and research hospital.

**Steps**:

* 1. Once all inclusion criteria have been fulfilled and all exclusion criteria have been excluded, patients will be recruited from:

a) operating theatre: patients will be recruited from operation theatre by reviewing the elective list a day before or on day of operation and screening the emergency lists on daily basis.

b) pre anesthesia clinic.

* 1. Consent is taken from the patient and each of them will be given a patient information sheet.
	2. A dedicated research assistant will access the randomization website in order to randomize patient to either receive:

Group 1 : Sugammadex 2mg/kg (half dose given prior to extubation and another half exactly after extubation)

Group 2 : Sugammadex full dose of 2mg/kg prior to extubation

Group 3 : Neostigmine 0.05mg/kg + Glycopyrrolate 200 mcg

The attending anesthetist is unblinded and will prepare the reversal drugs required according to the randomized drug groups.

4. Theatre

 Patient will proceed with the planned surgery with the standardized

 common induction agents for induction:

 IV Fentanyl (1-2 mcg/kg)

 IV Propofol (1.5-2.5 mg/kg)

 IV Rocuronium ( 0.6mg/kg)

Maintenance phase :

Analgesia : opiods used may be fentanyl of 1mcg/kg, alfentanyl, remifentanil, morphine (0.1-0.2mg/kg) or non opiods based like parecoxib.

Muscle relaxant : rocuronium 5 - 20mg boluses to maintain TOF count of 1-2 twitces (if uses TOF count) until end of surgery.

Anesthesia : both total intravenous or volatile based anaesthetic techniques can be used.

TOF monitoring : Not compulsory. But if uses the TOF monitor in theatre, monitoring can be done quantitatively (TOF preferred). TOF is monitored during surgery every hour in order to maintain a TOF count of 1 - 2. 30 minutes prior to end of operation every patient should receive IV ondansetron 4mg as an antiemetic prophylaxis. At the end of the operation, ie the last few stitches by the surgeon, the volatile or intravenous anaesthethic agents should be discontinued. Emergence phase will be considered starting at the time of discontinuation of the volatile or intravenous anaesthetic agents until 5 minutes after tracheal extubation, during which the patient was intermittently stimulated at 1-2 minutes interval verbally or with gentle tactile stimulation. Once clinically suitable to reverse, the attending anesthetist will administer the study drug for reversal of muscle relaxant. The observer which is the investigator of the study will only be available during the emergence phase. The observer is blinded. During the emergence phase, the following variables were recorded every 3 min: mean arterial blood pressure (MAP), heart rate (HR), end-tidal (ET) CO2, MAC, Ramsay Sedation Scale, (1 = Anxious; agitated; 2 = Cooperative, oriented, and tranquil; 3 = Responds to commands only; 4 = Brisk response to a light glabelar tap; 5 = Sluggish response; 6 = No response), reversal time which is defined as time to response to verbal command or spontaneous eye opening, duration of time taken to tracheal extubation, the number and grade of coughing episodes (0: no cough; 1: mild; single cough; 2: moderate; more than 1: cough lasting for <5 s; 3: severe, sustained for more than 5 s), and the occurrence of nonpurposeful movement of the limbs. Tracheal extubation was performed when patients opened their eyes and responded to verbal command.

 After extubation, the patient is transferred to recovery area for observation and subsequently back to ward or direct to HDU with at least 6 litres oxygen is delivered via venturi mask.

During the first 1 h postoperatively (recovery phase), the severity of sore throat and pain were assessed using a Visual Analog Scale from 0 to 10, where 0 = no pain and 10 = the worst imaginable pain. The presence of PONV and the need for additional analgesics or antiemetics were recorded. Clinical management and the recording of the above-mentioned variables were done by attending anesthesiologist.

5. At the recovery bay:

 The patient will be monitored in the recovery after the operation. Vital signs are recorded every 15 minutes and sedation agitation score using a standard scale will be recorded every half an hour until ready for discharge. Any side effects or complications including hypertension, tachycardia, sorethroat or respiratory complications will again be managed accordingly and each treatment given will be documented.

1. The patient will be allowed for discharge to ward once discharge criteria are fulfilled:
	* 1. Return of pre operative baseline GCS
		2. Hemodynamically stable

All data will be collected and analyzed statistically using SPSS.

**APPENDIX**

**Ramsay Agitation Sedation Scale**

|  |  |
| --- | --- |
| **Clinical Score** | **Level of Sedation** |
| 1 | Anxious and agitated or restless or both |
| 2 | Cooperative, oriented and tranquil |
| 3 | Respond to command only |
| 4 | Exhibit brisk response to light glabellar (between the eyebrows) tap or loud auditory stimulus |
| 5 | Exhibit sluggish response to light glabellar tap or loud auditory stimulus |
| 6 | Exhibit no response to stimulus |

|  |  |
| --- | --- |
| **Clinical Score** | **Severity of cough** |
| 0 | no cough |
| 1 | mild; single cough |
| 2 | moderate; more than 1: cough lasting for <5 s; |
| 3 | Severe; sustained for more than 5 s |

**References:**

1. Syed Mohd Reza Gousheh, Hengameh Tayaranian Noorani et al, The Effect of Low-Dose Remifentanil on Responses to the Endotracheal Tube During Emergence from General Anesthesia, Journal of Anaesthesiology and Pain, December 2013
2. Diachun CAB, Tunink BP, Brock-Utne JG. Suppression of cough during emergence from general anaesthesia: laryngotracheal lidocaine through a modified endotracheal tube. J Clin Anesth 2001;13:447–51
3. J.H.Lee, B.N.Koo, Differential effects of lidocaine and remifentanil on response to the tracheal tube during emergence from general anaesthesthesia, BJA Oxford Journal Nov 2010
4. B lee, JR lee, S Na et al, Targeting smooth emergence: the effect site concentration of remifentanil for preventing cough during emergence during propofol–remifentanil anaesthesia for thyroid surgery, BJA.Oxford Journal.org, March 2009
5. Della Rocca G, et al, Reversal of rocuronium induced neuromuscular block with sugammadex or neostigmine : a large observational study, Acta Anesthesiology Scand, oct 2013
6. Dubois PE, et al A review of the interest of sugammadex for deep neuromuscular blockade management in Belgium, Acta Anesthesiol Belg, feb 2013
7. Pavoni V et al, Reversal of Profound and ‘deep’ residual rocuronium-induced neuromuscular blockade by sugammadex: a neurophysiological study. Minerva Anesthesiology. May 2012
8. Amir Qaseem, MD, PhD, MHA; Vincenza Snow, MD; Nick Fitterman, MD et al Risk Assessment for and Strategies To Reduce Perioperative Pulmonary Complications for Patients Undergoing Noncardiothoracic Surgery: A Guideline from the American College of Physicians, Annals of Internal Medicine 2006
9. Koyuncu O, Turhanoglu S et al Comparison of sugammadex and conventional reversal on postoperative nausea and vomiting : a randomized, blinded trial, J Clininc Anesth 2014 December 24th
10. Harald J. Sparr, Karel M. vermeyen et al. Early Reversal of Profound Rocuronium-induced Meeting Abstracts by Sugammadex in a Randomized Multicenter Study: Efficacy, Safety, and Pharmacokinetic, The Journal of the American Society of Anesthesiologists 5 2007, Vol.106, 935-943
11. Groudine, Scott B, Soto, Roy et al. A Randomized, Dose-Finding, Phase II Study of the Selective Relaxant Binding Drug, Sugammadex, Capable of Safely Reversing Profound Rocuronium-Induced Neuromuscular Block, Anesthesia & Analgesia, [March 2007 - Volume 104 - Issue 3 - pp 555-562](http://journals.lww.com/anesthesia-analgesia/toc/2007/03000)
12. Investigational product of sugammadex.
13. Stefan Josef Schaller et al. Sugammadex as a reversal agent for neuromuscular block: an evidence-based review