Section #1 - Protocol Identification	
Study Title:	A prospective, double-blind, randomized study to investigate the effect of sugammadex vs. neostigmine/glycopyrrolate on emergence delirium during sevoflurane-rocuronium anesthesia in pediatric patients
Institution Name	**Pusan National University Yangsan Hospital**
Investigator Contact Information:	**- Tae-Kyun Kim** **- Department of Anesthesiology and Pain Medicine,** **School of Medicine, Pusan National University,** **Geumo-ro 20, Meulgeumeup, Yangsan, Gyeongnam 626-770,** **South Korea** **- +82 55 3602129 / +82 10 35371971** **- +82 55 3602149** **- anesktk@pusan.ac.kr**
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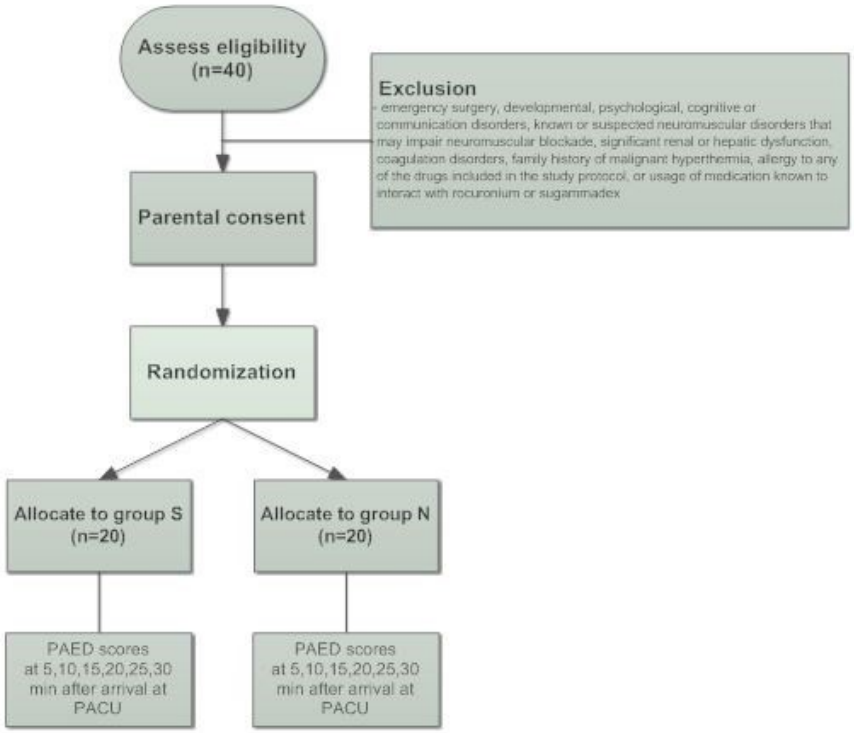
Section #2- Core Protocol	
Objectives & Hypotheses	Objectives. The aim of this study is to investigate the effect of sugammadex vs. a conventional acetylcholinesterase inhibitor, neostigmine on emergence delirium (ED) during sevoflurane-rocuronium anesthesia in pediatric patients Additionally, the efficacy features of sugammadex compared to neostigmine will be examined by measuring the time from start of administration of reversal agents to recovery of TOF ratio to 0.7, 0.8, and 0.9. Clinical hypotheses. Although the etiology of ED remains unclear, a sense of suffocation or breathing difficulty during emergence from anesthesia has been suggested as a possible cause (1). Thus, reversal of neuromuscular blockade with sugammadex in pediatric patients maintained with sevoflurane-rocuronium anesthesia may decrease ED due to its faster reversal of neuromuscular blockade and decreased possibility of residual blockade.
Background & Rationale, Significance of Selected Topic & Preliminary Data	ED is a postanesthetic phenomenon that develops in the early phase of general anesthesia recovery, (usually within the first 30 minutes,) and is defined as "a disturbance in a child's awareness of and attention to his/her environment with disorientation and perceptual alterations including hypersensitivity to stimuli and hyperactive motor behavior" (2). Children are often irritable, uncompromising, uncooperative, incoherent, and inconsolably crying, moaning, kicking, or thrashing (3,4). The incidence of ED varies from 2 to 80% (5-7), occurring more frequently in preschool boys (8,9). Risk factors also include the following: sevoflurane or desflurane anesthesia; ear, nose and throat surgery; preoperative anxiety (10). ED is known to increase physical, psychological, and financial burdens in the postanesthesia care unit, which emphasizes the importance of its prevention. Sugammadex has been studied in the pediatric population and has been

	shown to be useful when given in similar dosing regimens as that used in adults (11). It is licensed in children over 2 years for the routine reversal of neuromuscular blockade induced by rocuronium in UK (12). However, the Korea Food & Drug Administration (KFDA) has limited its use in the pediatric population to date.
Study Design	- A single-center, prospective, double-blind, randomized, clinical study - 40 children, ASA physical status I or II, preschool children aged 2-7 years, scheduled for an elective tonsillectomy with or without adenoidectomy will be included in the study. Patients will be excluded in cases of emergency surgery, developmental, psychological, cognitive or communication disorders, known or suspected neuromuscular disorders that may impair neuromuscular blockade, significant renal or hepatic dysfunction, coagulation disorders, family history of malignant hyperthermia, allergy to any of the drugs included in the study protocol, or usage of medication known to interact with rocuronium or sugammadex. - Patients will be randomly assigned to reversal of neuromuscular blockade with either sugammadex group (Group S) or neostigmine/glycopyrrolate group (Group N) by a computer-generated random number table.

Study Flowchart	
Study Procedures	Patients are admitted to the hospital the evening before surgery and are visited by the research anesthesiologist to conduct preoperative interviews. A 24G catheter is inserted into a peripheral vein the night before surgery or the morning of surgery. All patients will receive 0.005mg/kg glycopyrrolate as anticholinergic premedication ~40 minutes before induction of anesthesia. After arrival to the operation room, monitoring of; noninvasive arterial blood pressure, peripheral oxygen saturation, electrocardiograms and cutaneous temperature were applied. Neuromuscular conduction is assessed by TOF-Watch SX acceleromyograph device. The child's behavior during induction of GA is recorded using the Induction Compliance Checklist (ICC) consisting of 11 items (13). 1 mg/kg fentanyl and 2 mg/kg propofol is administrated to patients by intravenous (iv) route followed by an administration of 0.6 mg/kg rocuronium. Patients are intubated at the moment of TOF 0, and maintenance of anesthesia is provided by a combination of 50% O2-50% N2O and sevofluran (MAC 1.3-1.5). The cessation of electrocautery and removal of the mouth gag defined completion of surgery. At this time, sevoflurane and nitrous oxide are discontinued. At the end of surgery, inhaled agents are discontinued and the oxygen concentration is increased to 100%. No alterations are made to the ventilation settings, and no attempt is made to stimulate the patient. Time from the start of administration of reversal agents to recovery of the

	TOF ratio to 0.7, 0.8, and 0.9 would be recorded in both groups. Times from start of administration of rocuronium until reappearance of T2 will also be recorded. Return to T2 point (two contractions) on TOF device is replied by iv 2 mg/kg sugammadex administration to group S patients and 0.06 mg/kg neostigmine + 0.005 mg/kg glycopyrrolate administration to group N patients, both contained in a blinded syringe. With the return of the cough reflex, patients are allowed to breathe spontaneously. When patients demonstrate complete emergence from anesthesia by displaying a regular respiratory pattern, facial grimacing, gag reflex, and purposeful movement, patients are extubated and transferred to the PACU. Anesthetics and perioperative medications, the duration of anesthesia, time to regular breathing (i.e., time from administration of reversal agent to time of deep, regular breathing), time to awakening (i.e., time from administration of reversal agent to time of first cough, facial grimacing and gagging, purposeful movement, eye opening), and time to extubation (i.e., time from administration of reversal agent to time of tracheal extubation) were documented. All perioperative care will be at the discretion of the anesthesiologist or other care providers, blinded to the reversal agent, per routine practice and will not be influenced or intentionally altered as a result of participation in the study. One parent or carer meets the child on arrival in the recovery area and the child is allowed to regain consciousness undisturbed. During the postanesthesia recovery, trained and experienced postanesthesia care unit (PACU) nurses, also blinded to the administered agent, will document the presence or absence of ED based on Paediatric Anaesthesia Emergence Delirium (PAED) scale who are unaware as to which treatment group the child is allocated. The measurement time points of PAED scores are: on arrival to the PACU; every 5 minutes for the first 15 minutes; and every 15 minutes for the duration of the recovery room stay. PAED scale consists of five items: eye contact, purposeful actions, awareness of the surroundings, restlessness, and inconsolability, and a score of 10 or more considered a diagnosis of ED and a score ≥ 15 defined as severe ED (2). The first and and third item reflect disturbances in the child's consciousness, and the second item addresses changes in the child's cognition during an ED reaction. A delirium-specific score (ED I) is calculated from the first three items of the PAED score (eye contact, purposeful actions, awareness of the

surroundings), and defined as a total of nine points or higher. The sum of these items have demonstrated to be a superior indicator of ED (sensitivity 93%) and non-ED cases (specificity 94%), compared to that of other two items (ED II: restlessness, inconsolability) (14). The score is recorded at 5 min, 10 min, 15 min, 20 min, 25 min and 30 min after arrival at PACU. All pharmacologic and nonpharmacologic interventions, adverse events, clinical signs of residual paralysis, peripheral oxygen saturation, heart rate, and minutes of PACU stay will also be recorded.

Statistical Analysis and Sample Size Justification

The study data will be analyzed by the medical statistician at Pusan National University, Yangsan Hospital.

Variables/Time Points of Interest

- PAED scale at 5 min, 10 min, 15 min, 20 min, 25 min and 30 min after arrival at PACU (2). The maximum PAED after arrival in the PACU will serve as the primary outcome variable.

Makes eye contact with caregiver	4	3	2	1	0
Actions are purposeful	4	3	2	1	0
Aware of surroundings	4	3	2	1	0
Restless	0	1	2	3	4
Inconsolable	0	1	2	3	4

Secondary outcome variables are measured as following:

- Times from start of administration of rocuronium until reappearance of T2

- Time from the start of administration of reversal agents to recovery of the TOF ratio to 0.7, 0.8, and 0.9

- Time to regular breathing: time from administration of reversal agent to

	time of deep, regular breathing) - Time to awakening: time from administration of reversal agent to time of eye opening or child showing purposeful movements) - Time to extubation: time from administration of reversal agent to time of tracheal extubation) <u>Statistical Methods</u> Continuous data is reported as mean ± standard deviation and is analyzed using an independent sample t-test or analysis of variance for multiple comparisons with least significant difference test for post hoc analysis. Categorical data is reported as percentages and were analyzed using the Chi-square test or Fisher exact test as appropriate. Nonparametric data is reported as median and inter-quartile range and were analyzed using the Mann-Whitney U-test. A $P < 0.05$ will be considered statistically significant. <u>Power/Sample Size:</u> Based on the reference study, the predicted PAED score of control group is 17 (11-19) (median (range)). Applying a 40% difference in PAED score as the minimum clinically relevant difference and allowing significant level $\alpha = 0.05$ and β (1-power) = 0.2, consequently, 6 children per group should be required (15).
Adverse Experience Reporting	All drug-related adverse events will be reported to the IRB committee at Pusan National University, Yangsan Hospital.
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