The Effect of Precurarization with Rocuronium on the incidence and severity of Succinylcholine-Induced Fasciculations and Myalgias in a High Volume ERCP center

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1.0 Background

Since its clinical introduction in the early 1950s, succinylcholine, a short-acting depolarizing muscle relaxant, has become commonly used for rapid sequence intubation during general anesthesia[1,2]. In addition to its paralytic effects, succinylcholine administration in general anesthesia carries a multitude of risks, among which are muscle fasciculation and postoperative myalgia[3,4]. Currently, anesthesiologists are divided in whether rocuronium, a nondepolarizing muscle relaxant, effectively reduces both succinylcholine-induced fasciculations and postoperative myalgias in procedures under general anesthesia. There is sparse and inconsistent literature supporting the efficacy of rocuronium pretreatment for the prevention of succinylcholine-induced fasciculations and postoperative myalgias. .

Research into managing the side-effects of using succinylcholine first appeared in 1990 when Pace demonstrated, through a meta-analysis of 45 clinical trials, that nondepolarizing muscle relaxants reduced the frequency of postoperative myalgias by 30%[5]. Rocuronium, while not assessed in Pace's study, is now commonly used to prevent fasciculations and myalgias associated with succinylcholine. Motamed, (1998) demonstrated that pretreatment with rocuronium in elective general surgery reduced the incidence of succinylcholine-induced fasciculations[6]. In laparoscopic procedures in female patients under general anesthesia, Martin et. Al (1998), demonstrated that rocuronium prevented fasciculations but not postoperative myalgias[7]. Likewise, Joshi et. Al (1999) showed that rocuronium prevented succinylcholine-induced fasciculations but failed to prevent myalgias in patients undergoing elective ambulatory surgery with general anesthesia.[8].

In response to the growing literature pertinent to pretreatment of succinylcholine, Schreiber et. al(2005) performed a meta-analysis of 52 randomized trials between 1971 and 2003 to update the aforementioned meta-analysis performed by Pace. Schreiber concluded that doses of 10-30% of the effective dose of nondepolarizing muscle relaxants do significantly decrease the postoperative myalgias and fasciculations. Further, of the nondepolarizing muscle relaxants, rocuronium significantly demonstrated relative risks conferring both effectiveness in reduced fasciculations and 24 hours postoperative myalgia[9]. In 2009, Abbas et. al demonstrated that pretreatment of rocuronium in patients undergoing elective general surgical procedures under general anesthesia decreased the incidence of succinylcholine-induced fasciculations and myalgias[10]; however, in 2014, Kim in elective surgery with general anesthesia, demonstrated that pretreatment with rocuronium reduced fasciculations but did not significantly decrease the incidence of postoperative myalgias[11].

Previous studies looking at the efficacy of pretreatment with rocuronium to prevent succinylcholine fasciculations and / or myalgia were limited in many ways including, but not limited to, low numbers in the study groups, a lack of uniformity in the length of the case, and a lack of uniformity in the presence/absence or size of a surgical incision. Studies have demonstrated that patients with little surgical pain are more likely to complain of post-succinylcholine myalgias compared to patients who are preoccupied with terrible pain from surgical wounds. The length of the case also seems to impact the severity of post-surgical muscle pain independent of succinylcholine use. The actual etiology of post-succinylcholine myalgia has not been fully elucidated. It was originally thought that the induction of fasciculations by the acetylcholine-like action of succinylcholine at the neuromuscular junction caused muscle damage leading to myalgias, however, studies looking at the correlation between fasciculations and myalgias showed only a weak correlation. We hope to address some of these questions with this proposed study. Our group provides anesthesia to patients coming to Indiana University Hospital for ERCP (endoscopic retrograde pancreatography). ERCP cases are generally short (under 2 hours), are uniformly positioned, and do not result in a surgical wound. Because they are such short cases, yet still require general endotracheal anesthesia, succinylcholine is the drug of choice in our group as it results in rapid intubating conditions with a very short duration of action. As this is a high volume center, we have a unique opportunity to study the effect of pretreatment with a nondepolarizing neuromuscular blocker

(rocuronium) on succinylcholine induced myalgias while enjoying a mitigation of the confounding variables mentioned above.

Risks:
There is huge variability in the care of patients receiving succinylcholine in the anesthesia community at large and within our own group. Some people believe that succinylcholine should always be pretreated with a non-depolarizing neuromuscular blocker to prevent myalgias, while others believe that it should never be pretreated because, they believe, that the pretreatment doesn't work and is ineffective. This is a proposal to structure that variability into randomized groups and study the outcomes which will lead to a reduction of said variability going forward. There is no added risk to the patient as there is currently no standardization of the practice within our own group. Pretreating and not pretreating are both practiced daily.

2.0 Rationale and Specific Aims

Our hypothesis is that precurarization with rocuronium, followed by a 2 minute interval prior to administering succinylcholine will prevent, or ameliorate, succinylcholine induced myalgias compared to not pretreating, or pretreating with a shorter time interval prior to succinylcholine administration.

Primary endpoint: Does the patient have myalgias post succinylcholine administration with pretreatment with Rocuronium 2 minutes prior?

Secondary endpoint?

*Severity of myalgias
*Onset of myalgias postop relative to succinylcholine administration
*Correlation of myalgias with the presence of skeletal muscle fasciculation upon succinylcholine administration

3.0 Inclusion/Exclusion Criteria:

Inclusion Criteria:

- Undergoing elective Endoscopic Retrograde Cholangiopancreatography (ERCP) under general anesthesia
- Have been informed of the nature of the study and informed consent has been obtained
- ASA 1, 2 and 3

Exclusion Criteria:

- Patients will be excluded if they have chronic pain requiring daily opioid use greater than 30 mg PO morphine equivalent.
- Patients will also be excluded if their comorbid medical conditions require a true rapid sequence induction as precurarization with rocuronium increases the time to intubation which is undesirable in a patient who is at high risk for aspiration.
- Patients taking muscle relaxants at home for spasticity.
- Patients under the age of 18 years old.
- Any contraindication for using succinylcholine or rocuronium.
- Less than 50kg or greater than 120kg

4.0 Enrollment/Randomization

All Endoscopic Retrograde Cholangiopancreatography (ERCP) procedures scheduled at IU Health University Hospital on adult patients (18+ years old) will be identified. Subjects will be contacted face-to-face prior to surgery by one of the research team members. They will be informed about the study and all questions will be answered. The potential subjects will be given a copy of the informed consent form and

authorization form. The subjects will then be contacted face-to-face in POCU on the day of surgery and if participation is agreed upon, written consent will be taken. All patients will receive general endotracheal anesthesia consistent with acceptable standards of care.

A total of 300 subjects will be randomized by a/ computer program into 3 groups (100 in each group):

1. Group 1 (Control): 0 mg/kg of rocuronium pretreatment and 1 mg/kg (rounded up to the nearest 10 mg) succinylcholine
2. Group 2: 0.05 mg/kg (rounded up to the next mg) up to 5 mg of rocuronium pretreatment followed by 1.0 mg/kg (rounded up to the next 10mg) succinlycholine t = 1 min +/- 10 sec after pretreatment.
3. Group 3: 0.05 mg/kg (rounded up to the next mg) up to 5 mg of rocuronium pretreatment followed by 1.0 mg/kg (rounded up to the next 10 mg) succinlycholine t = 2 min +/- 10 sec after pretreatment.

Drug amount rounding takes into account the limitations to accurately measure drug doses in the clinical setting. Rocuronium is measured in a 1 ml tuberculin syringe with 1mg = 0.1ml. Rounding allows the provider to round to the next 0.1ml. Smaller increments cannot be accurately measured. Likewise, Succinylcholine is 20mg/ml and administered from a pre-labeled, calibrated 10 ml syringe. The above allowable rounding allows the provider to administer the drug to the next nearest 10mg=0.5ml for the same reason.

Randomization will be performed using Research Randomizer in blocks of 30. The primary investigator will inform the person doing the case as to what group the patients are randomized to. Both the patients and the research staff doing assessments will be blinded to the randomization.

5.0 Study Procedures

After IRB approval from Indiana University Hospital and with written and verbal informed consent from each patient, 300 ASA I, II and III outpatients scheduled for elective Endoscopic Retrograde Cholangiopancreatography (ERCP) under general anesthesia will be enrolled in this randomized-controlled study. The patients and the study personnel performing post-op assessments will be blinded. Anesthesiologists cannot be blinded during this study since they will be required to draw up the study drugs as well as managing the wait time between rocuronium and succinylcholine. Patients are assigned to one of three groups (n = 100 each group). Each patient will undergo a standard IV induction of anesthesia (Lidocaine 1mg/kg, propofol 1-2 mg/kg titrated to effect, and succinylcholine (administered as indicated by study group assignment). Study group details are as follows: Group 1 (Control) to receive no rocuronium and 1 mg/kg of succinylcholine (rounded up to the next 10mg). Groups 2 and 3 to receive 0.05 mg/kg (rounded up to the next 1mg) up to 5 mg of rocuronium; patients ranging from 50-120 kg. In Group 2, succinylcholine administration will occur at 1.0 mg/kg (rounded up to the next 10 mg) at t = 1 minute (+/-10 seconds) after pretreatment with rocuronium. In Group 3, succinylcholine 1mg/kg (rounded to the next 10 mg) will be administered at t = 2 minutes (+/- 10 seconds) after pretreatment. The Succinylcholine-induced fasciculations will be noted on study assessment sheet as either present or absent. . Myalgia assessment is to occur succinylcholine administration at t =3 hours and t = 24 hours and will be rated as described below.

Myalgia assessment:

Subjects will by queried at the above time points about muscle pain and scored based on their answers as follows.

0 – no pain /no muscle stiffness
1 – mild muscle pain and/or stiffness at 1 or more sites that does not limit daily activity
2 – Moderate muscle pain and/or stiffness at 1 or more sites that does not limit daily activity
3 – Moderate generalized muscle pain and/or stiffness limiting daily activity

4 – Severe muscle pain and/or stiffness at 1 or more sites limiting movement and preventing daily activity

6.0 Statistical Analysis

The statistical analysis will be conducted using SAS. Summary statistics will be calculated for the overall cohort, as well as by-treatment group. Categorical variables will be presented as frequencies and percentages, and groups will be compared with chi-square or Fisher's Exact tests. Distributions of the continuous variables will be assessed to determine if data transformations or non-parametric tests are needed. Continuous variables will be presented as mean and standard deviation and groups will be compared with ANOVA unless non-parametric tests are warranted, in which case, median and interquartile range will be calculated and Kruskal-Wallis tests will be used to compare groups. For variables with multiple measurements, these statistics will be given for each discrete time point. Myalgia will be assessed as both a categorical variable (any myalgia vs. none), and as an interval variable. A significance level of 5% will be used for all statistical comparisons.

To determine the effect of the treatments over time on the outcomes of interest, mixed models will be utilized, with fixed effects for treatment and time, as well as their interaction, and a random effect for subject. When necessary, additional variables may be added to adjust the models for other noted differences between the treatment groups.

Based on prior observation, the myalgia incident rate is 50%. With 100 patients in each of the three groups, will have 80% power to detect an odds ratio of 2.26 between any two groups, with two-sided tests and an alpha of 0.05 (5% significance level).

7.0 Reporting of Adverse Events or Unanticipated Problems Involving Risk to Participants or Others

Adverse events, other than those measured as end points, should be reported to the principal investigator, Dr. Leighan Bye at **317-902-5882.**

8.0 Study Withdrawal/Discontinuation

Participants may withdraw at any time.

9.0 Privacy/Confidentiality Issues

Participant privacy is an important goal of the researchers. Only members of the research team will have access to identifiable data. All study papers containing patient identifiers will be kept in each subjects confidential study file accessible to only the research team. All records will be kept in a locked room in a locked cabinet that only authorized staff enters. Collected data from each enrolled participant will be recorded on Redcap which is a secure web-based data collection tool. Quality assurance steps of testing Redcap will be completed by the study team prior to moving it into production mode. Quality control methods of randomly doing double checks of data entered for accuracy will be complete as well as extraction and cleaning of data for data analysis every 1 year. All electronic information and paperwork containing patient identifiers will be deleted or shredded when data analysis is completed and the paperwork is no longer needed, or for 7 years per Indiana law._

10.0 Follow-Up and Record Retention

Follow-up myalgia assessments will be performed at 3 hour and 24 hours after surgery.

The patient data related to the study will be entered into a secure REDCap database. Paper copies of study data will be kept in the locked anesthesiology offices. Following completion of the study, all copies of data collected will be stored for the required amount of time (min. 7 years) and then will be physically destroyed.

References:

1. Martyn J, Durieux ME. Succinylcholine. Anesthesiology. 2006Apr;104(4):633–4.

2. Ghatehorde NK, Regunath H. Intubation, Endotracheal Tube, Medications. [Updated 2017 Oct 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2018 Jan-.

3. Wong SF, Chung F. Succinylcholine-associated postoperative myalgia. Anaesthesia. 2000;55(2):144–52.

4. Hager HH, Burns B. Depolarizing Muscle Relaxants, Succinylcholine Chloride. [Updated 2018 Jun 13]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2018 Jan-.

5. Pace NL. Prevention of Succinylcholine Myalgias. Anesthesia & Analgesia. 1990;70(5)

6. Motamed, C., Choquette, R. & Donati, F. Can J Anaesth (1997) 44: 1262.

7. Martin R, Carrier J, Pirlet M, Claprood Y, Tetrault J-P. Rocuronium Is the Best Non-Depolarizing Relaxant to Prevent Succinylcholine Fasciculations and Myalgia. Survey of Anesthesiology. 1999;43(5):291–2.

8. Joshi G, Haile A, Thompson-Bell G, Cross S. Effects Of Pretreatment With Cisatracurium On Succinylcholine-Induced Fasciculations And Myalgia. Anesthesia & Analgesia. 1999;88(Supplement).

9. Schreiber J-U, Lysakowski C, Fuchs-Buder T, Tramer M. Prevention of Succinylcholine-induced Fasciculation and Myalgia: A Meta-analysis of Randomized Trials. Anesthesiology: The Journal of the American Society of Anesthesiologists, Inc . 2005Aug10;103:877–84.

10. Abbas N, Tariq S, Khan AW, Navi N, Khanzada A. To assess the effects of rocuronium pretreatment on succinylcholine induced fasciculations and postoperative myalgias. JPMA: The Journal of Pakistan Medical Association . 2009 Dec;59(12):847–50.

11. Kim KN, Kim KS, Choi HI, Jeong JS, Lee H-J. Optimal precurarizing dose of rocuronium to decrease fasciculation and myalgia following succinylcholine administration. Korean Journal of Anesthesiology. 2014;66(6):451.