Prospective, Randomized Trial Comparing Effect of General Anesthesia With and Without Neuromuscular Blockade on Postoperative Pulmonary Complications in Elective Cardiac Surgical Patients

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Introduction

Neuromuscular blockers (NMB) are medications commonly used by anesthesiologists during surgery to induce paralysis/muscle relaxation and facilitate the technical performance of surgery. However, the residual effect of neuromuscular blockade during the immediate postoperative period has been associated with an increased incidence of postoperative pulmonary complications. [1-6]. Residual neuromuscular blockade is a contributing factor to adverse events including delayed discharge from recovery, need for tracheal reintubation, impaired oxygenation and ventilation, aspiration, atelectasis and pneumonia. [3,6,7] These effects are likely mediated by decreased airway tone and impaired respiratory effort persisting during recovery from anesthesia.[8,9] Despite awareness of this problem for the last 35 years, residual neuromuscular blockade after anesthesia remains a common adverse event and has been the focus of initiatives by the Anesthesia Patient Safety Foundation as recently as February 2016.[10,11]

Despite widespread utilization of NMB during cardiac surgery, very little is known about residual neuromuscular blockade in patients following cardiac surgery. A recent large, retrospective study of a non-cardiac surgical database has linked intermediate-acting neuromuscular blockade and postoperative pulmonary complications in a dose-dependant manor. [6] Patients undergoing cardiac surgery are even more susceptible to the detrimental effects of residual neuromuscular blockade than in non-cardiac surgical patients, however no recent clinical studies have been directed at this population. The few studies that have examined NMB in cardiac surgical populations have served to shift routine practice away from older, long-acting NMB agents (e.g. pancuronium) toward the intermediate-acting agents (e.g. rocuronium or cisatracurium) commonly used during non-cardiac surgery.[12-16] Yet, cardiac surgical patients experience physiologic conditions not associated with non-cardiac surgery, such as exposure to hypothermic cardiopulmonary bypass which is known to decrease muscle strength substantially

even in the absence of NMB.[17,18] Additionally, the clinical effects of NMB may be intensified during hypothermia via complex pharmacokinetic and pharmacodynamic interactions not yet fully understood. [19-24] Cardiac surgical patients may also be more susceptible to the harmful effects of residual neuromuscular blockade due to significant comorbidities predisposing them to postoperative pulmonary complications.[25-28] Concern over detrimental effects of NMB have led some to call for minimizing or eliminating the continuous use of NMB during cardiac surgery, as acceptable surgical conditions may be achieved with adequate depth of anesthesia and blunting of the physiologic response to surgery.[29,30] Given the traditional role of neuromuscular blockade in the management of cardiac surgical patients, prospective data is needed to determine the effect of NMB in cardiac surgical patients as well as the surgical tolerability of protocols that minimize intraoperative paralysis.

The proposed prospective, randomized trial will assess the impact of neuromuscular blockade on early (≤72 hours post-ICU admission) postoperative respiratory complications. This clinical study will prospectively investigate two groups of patients undergoing elective cardiac surgery at the University of Chicago. In the experimental group, a very short-acting depolarizing NMB (succinylcholine) will be used for tracheal intubation and no other subsequent muscle relaxants throughout surgery. In the control group, an intermediate-acting non-depolarizing NMB (cisatracurium) will be used throughout the intraoperative period (our standard practice) and will be re-administered to maintain a moderate to deep level of muscle relaxation until the conclusion of surgery. Both groups will be monitored with peripheral nerve stimulators (ulnar and facial nerve) throughout the intraoperative period and immediate postoperative period. Residual neuromuscular blockade during the immediate postoperative period will be assessed in both groups objectively and subjectively.

Recent clinical studies support the use of intraoperative acceleromyography for titration of NMB based on the motor response of nerve stimulation.[31] Since during cardiac surgery, anesthesiologists have limited access to the patient's arms due to patient positioning, both the adductor pollicis and orbicularis oculi sites will be monitored with a TOF-Watch to provide for correlation as well as redundancy in the event of intraoperative disturbance of the adductor pollicis site due to surgeon positioning.

The primary outcome to be examined is the composite event of a postoperative pulmonary complication linked to residual NMB. Surgical tolerability (assessed via specifically designed cardiac surgeon rating scale and examination of undesired patient movement during anesthesia) and subjective/objective signs of postoperative weakness (patient questionnaire, neuromuscular blockade monitoring) are the secondary outcomes to be assessed.

Methods

A prospective, randomized protocol was designed to assess the impact of low/single dose NMB on the incidence of early respiratory complications in cardiac surgery. Reported incidence of respiratory complications after cardiac surgery ranges from 0.5-30% depending upon the particular complication and population subset being examined. The current study focuses on a pre-defined composite measure of respiratory complications that are potential sequelae of NMB-associated effects on respiratory muscle weakness. This primary outcome measure will include the following and will be determined through prospective observation for 72 hours following admission to the intensive care unit (ICU) postoperatively. (See "Data Collection: Respiratory Complications")

1. Failure to extubate within 24 hours of ICU admission time
    - Determined via documentation of extubation time

2. Need for tracheal re-intubation (≤72 hours post-ICU admission)
    - Determined via documentation of respiratory therapy/intubation events
3. Pneumonia
    - Defined by radiologist report or ICU attending assessment of new or progressive pulmonary infiltrate on chest x-ray *AND*
    - Clinical findings suggesting systemic infection (fever >38°C or <36°C *OR* WBC count >12,000/mm^3 or <4,000/mm^3) *OR* antibiotic therapy *OR* positive respiratory cultures/purulent sputum
4. Pulmonary aspiration
    - Diffuse infiltrates or consolidation of dependant lung segments on chest x-ray consistent with aspiration
    - AND clinical findings consistent with aspiration pneumonitis, including increasing oxygen requirements, suspected aspiration or increased work of breathing
5. Need for noninvasive respiratory support with CPAP or BiPAP therapy
    - Documented use required during first 72 hours post-ICU admission
    - Composite scoring of respiratory events does not include continuation of CPAP therapy as prescribed preoperatively for known obstructive sleep apnea (OSA)
    - Includes escalation of therapy (BiPAP treatment when previously CPAP only was needed)
6. ARDS (mild, moderate or severe) (≤72 hours post-ICU admission) based on Berlin definition:
    - Bilateral opacities on chest x-ray consistent with pulmonary edema
    - Arterial blood gas and ventilator setting evidence of PAO2/FiO2 ratio ≤300

- Not fully explained by cardiac failure or fluid overload

7. Mortality attributed to respiratory event (≤72 hours post-ICU admission)
    - Hypoxic or hypercarbic respiratory arrest

Secondary outcomes in the study will be:

1. Surgical Tolerability
    - Measured by a designed instrument that will be completed by the surgeon and anesthesia staff and will include reporting of the following (See "Data Collection: Surgical Tolerability")
        - Patient movement: Major (limb movement, coughing on ventilator), minor (diaphragm movement), none
        - Movement interfering with surgical progress: Yes, no
        - Surgical conditions: Excellent, good, poor
        - Total dose supplemental propofol required for suppression of movements
        - BIS recorded during patient movement
2. Weakness (See "Data Collection: Postoperative")
    - Blinded assessment of patient experience of weakness or respiratory difficulties on postoperative survey (See "Postoperative Survey")

Study Risk and Benefits

When continuous muscle relaxation is omitted, there is a risk of movement under anesthesia (e.g. coughing, limb muscle movement), which may interfere with surgery. Movement under anesthesia occurs occasionally even when muscle relaxation is provided continuously (during standard of care), but in the absence of muscle relaxation (non-standard of care), these movements may be more pronounced. Other anesthesia medications (i.e. anesthetic agents,

analgesic agents) are provided when muscle relaxation is not being administered to minimize these risks. In our study, midazolam and fentanyl (standard of care medications) will be administered in doses to avoid the potential for inadvertent movement. In the low dose muscle relaxant group, inadvertent patient movement will be treated with additional anesthesia with propofol, increasing the dose of volatile anesthetic, administering pain medication or if necessary for patient safety, administering muscle relaxants as required (i.e. reverting to standard of care). The risk of movement under anesthesia when low dose muscle relaxant is used is reasonable because providing anesthesia without muscle relaxation is an established technique used for other types of surgery (e.g. non cardiac).

As muscle relaxation has been associated with harmful effects (e.g. postoperative pulmonary complications), the use of low doses has some potential benefit. Results from this study may help future patients having cardiac surgery by providing guidance to the best way to conduct anesthesia to minimize respiratory complications.

Monitoring of Safety

There will be ongoing (case by case) review of adverse events and safety information between the principal investigator and co-investigators and any events will be addressed. Unanticipated problems requiring a revision to the protocol will be submitted to the IRB for review. A Data Safety Monitoring Board has been convened and will review the results early in the study as well as halfway through enrolment to address any safety concerns. A continuing review with examination of preliminary data will be conducted after 50 patients have been recruited.

Unanticipated problems (i.e. unexpected events that are related or possibly related to participation in the research that suggest that the research places subjects or others at risk of unknown harm or increased frequency of harm) will be reported to the IRB within 10 working

days of the investigator's knowledge of the event. In the event of a fatal or life-threatening unanticipated problem, enrolment will be halted and the IRB chair notified by phone immediately. A major deviation from the protocol will be reported within 10 working days via the "Unanticipated Problem" form. A minor deviation will be summarized at the time of continuing review on the "Continuing Review Form".

Power Calculation:

Previous studies of respiratory complications after cardiac surgery have suggested incidence rates ranging from 0.5-30%.[26,27,33-35] Many of these studies include atelectasis and pleural effusions in their composite calculation of respiratory complications, which are problematic because of diagnostic difficulty and less clear relationship to NMB use. The current study will focus solely on the respiratory complications previously defined. Assuming this composite has a potential incidence of 20% and that the effect size is 0.5, a total of 47 patients will be required in each arm to achieve a power of 80% with a p=0.05. A total of 100 patients will be recruited to account for crossover.

Inclusion Criteria

All patients >18 years old undergoing elective cardiac surgery (coronary artery bypass grafting [CABG], valve replacement or CABG + valve replacement) requiring cardiopulmonary bypass at the University of Chicago with one of two surgeons (Dr. Jeevanandam or Dr. Ota).

Exclusion criteria

Emergency surgery, extremes of age (<18 or >90 years), previous cardiac surgery, clinical contraindications to succinylcholine or cisatracurium, anticipated difficult tracheal intubation, preoperative mechanical ventilation, preoperative pharmacologic/mechanical hemodynamic support.

Study Protocol

Institutional Review Board approval will be obtained and the study will be registered with www.clinicaltrials.gov prior to commencement. All patients enrolled in the study will be randomized to either a standard protocol (Group CIS) or the single-dose NMB protocol (Group SUX) (See "Intraoperative Protocol"). All study and anesthetic drugs will be administered by the anesthesia care team. The neuromuscular blocking agents being studied will be dispensed by the operating room pharmacy, as is routine, and drawn up in the operating room for intravenous administration. ICU providers and surgeons will be blinded to the study group assignment, and intraoperative and postoperative care will otherwise be routine.

No compensation will be provided to study participants. Patients will be identified by review of operative room schedules and consent will occur prior to the standard preoperative interview. The data set created from study information will be maintained following study completion but all patient identifiers will be deleted. This will be maintained for a minimum of 6 years. Consent forms with patient identifying information will be held in a locked file in a locked office for a minimum of 6 years. Randomization will be performed by computer generation. Data analysis will be performed on an intention to treat basis.

Data Collection

The investigators will collect the following data points.

Patient Factors – See "Data Collection: Preoperative"

Intra-operative Factors – See "Data Collection: Intraoperative and Data Collection: Surgical Tolerability"

Post-operative factors – See "Data Collection: Postoperative, Data Collection: Respiratory Complications, Data Collection: Postoperative Survey"

Intraoperative Protocol

Patients are to receive the same standardized doses of medications as a total for the case. Induction/maintenance medications are to be administered with induction or prior to CPB, as hemodynamics allow. IV boluses of phenylephrine (100mcg), vasopressin (1 unit), ephedrine (10mg) or norepinephrine (8mcg) may be administered as required.

Induction/maintenance:

- Midazolam 0.1mg/kg
- Fentanyl 15 mcg/kg
- Isoflurane: titrated to maintain BIS <55 or prevent patient movement, minimum of 0.6% while on CPB
- Propofol bolus (0.2-0.5 mg/kg): as needed for patient movement
- Propofol infusion started (25-50 mcg/kg/min) at "drapes down", Isoflurane stopped
- Appropriate antibiotic administration according to hospital protocol

Mechanical Ventilation Parameters

- Tidal volume 6mL/kg of ideal body weight: male IBW = 50 + 2.3(height in inches – 60), female IBW = 45.5 + 2.3(height in inches – 60)
- RR appropriate to maintain pCO2 between 35-45 mmHg
- FiO2 100% intraoperatively
- PEEP 5

Neuromuscular Blockade

Group SUX	**Group CIS**
• Succinylcholine 1mg/kg • No additional muscle relaxants for case	• Cisatracurium 0.2mg/kg • Supplemental cisatracurium as dictated by peripheral nerve stimulator on the hand to maintain 1-2 twitches • Last dose given at sternum closure

TOF monitoring

- Place TOF-Watch monitor on left arm (ulnar nerve monitoring) and along facial nerve (orbicularis oculi monitoring)
- Left arm will be secured at the patient's side with the TOF-Watch hand stabilizer in place while allowing the hand/thumb free movement for measurement with TOF-Watch
- Assess TOF at times indicated on intraoperative data collection sheet
- Continue to monitor TOF ratio in group SUX even after initially returns to 100% and record changes during CPB/hypothermia

Data Collection: Preoperative

Group Assignment (circle one):	**Group SUX**	**Group CIS**
MRN: _____	Height _____cm Weight_____kg Ideal Body Weight_____kg	
Age: _____	Gender (circle one): M / F	
Preoperative creatinine:	_____mg/dL	
Surgical Date (mth/day/year)	_____/_____/_____	
Diagnosis:		
Proposed Surgery:		
Anesthesiologist (circle):	Chaney Gerlach Other:_____	
Surgeon (circle):	Jeevanandam Ota	

	YES	NO
Pulmonary disease (long-term bronchodilator/steroid use)		
• Obstructive sleep apnea diagnosis CPAP therapy: Yes_____cmH2O NO_____		
• Active smoker (current ppd:_____)		
• Smoking history (quit date:_____)		
Extracardiac Arteriopathy/PVD (claudication/carotid disease/vascular surgery, >50% stenosis)		
• HTN		
• Diabetes Mellitus		
• History of CVA		
Neurologic dysfunction (severely affecting ambulation or day-to-day function)		
• Preop functional status, partially dependant		
• Preop functional status, totally dependant		
Active endocarditis (still using antibiotics)		
Critical preoperative state (preop cardiac arrest or dialysis)		
Unstable angina (rest angina, IV nitrates, IABP)		
LV dysfunction (LVEF <30%)		

Recent MI (<90 days)		
Pulmonary hypertension (PA systolic >60mmHg)		
Isolated CABG		
Thoracic aortic surgery		
Post-infarct septal rupture		

Preop Meds		**YES**	**NO**
Cardiac	Beta-blocker		
	ACEi		
	ARB		
	Nitroglycerin		
	Diuretic		
	ASA		
	Plavix		
	Statin		
Pulmonary	Bronchodilators		
	Steroids		
Diabetes	Insulin		
	Oral hypoglycemics		
Other	Antibiotics		

Data Collection: Intraoperative

Time Point	TOF EYE	Bladder Temp (Celsius)	BIS measurement
Baseline (pre-muscle relaxant)			
Post-intubation			
Skin incision			
Sternotomy			
Heparin admin			
CPB 10 min			
CPB 30 min			
CPB 60 min			
CPB 90 min			
CPB 120 min			
CPB 180 min			
CPB 240 min			
CPB separation			
10 min post-Protamine			
Chest closure			
Drapes down			

	TIME		DATA
Induction		Initial ABG (FiO2 1.0)	
Incision		Post-Protamine ABG (FiO2 1.0)	
CPB on			
CPB off			
Chest closure			
Out of OR		Lowest CPB temp	
ICU arrival		Last OR patient temp	

Intraoperative Drug Totals	
Midazolam _____ mg	Phenylephrine _____ mcg
Fentanyl _____ mcg	Vasopressin _____ units
Cisatracurium _____ mg	Ephedrine _____ mg
Propofol _____ mg	Norepinephrine _____ mcg
	Epinephrine _____ mcg
Blood Product Units: RBC_____ FFP_____ Plt_____ Cryo_____	

Data Collection: Surgical Tolerability

Surgical Tolerability Assessment Tool (to be asked of primary surgeon at conclusion of surgery):

- Did you notice patient movement? **YES / NO**
    - If yes, how severe was the movement?

      MAJOR (limb movement, coughing on ventilator)

      MINOR (diaphragm movement)
    - Did movement interfere with surgical progress? **YES / NO**
- How were the surgical conditions, compared to expected? (1 being poor and 5 being excellent)

  1……2…….3……..4…….5
  (POOR … GOOD … EXCELLENT)

Patient Movement Record (to be completed by anesthesiologist)

	Clinical Scenario	BIS	Major movement (Y/N)	Interfere with Surgery (Y/N)
1				
2				
3				
4				
5				
6				

Data Collection: Postoperative

ICU arrival time:	_____:_____
ICU arrival hemodynamic support:	
ICU arrival spontaneous movement/resp effort*	YES / NO
TOF assessment at 20 min	TOF EYE_____

*Observed by investigator for 20min following ICU arrival – includes any gross movement of limbs or respiratory effort

Data Collection: Respiratory Complications

Composite incidence of respiratory complication:

Document presence of any of the following conditions during the first 72 hours postoperative (i.e. from the time of admission to the ICU)
See criteria defined in protocol

	YES	NO
Failure to extubate within 24h of ICU admission		
Need for re-intubation within 72h		
Pneumonia		
Aspiration		
Unanticipated need for noninvasive respiratory support (CPAP/BiPAP) during first 72h		
ARDS (PaO2/FiO2 ratio ≤300)		
Mortality attributed to respiratory arrest		

Outcomes:

ICU admission date/time:_____

Tracheal extubation date/time:_____

ICU discharge date/time:_____

Hospital discharge (or death) date/time:_____

Data Collection: Postoperative Interview

To be completed with patient on Post-op Day #7. Interviewer will be blinded to the patient group.

INTRAOPERATIVE AWARENESS? YES / NO

- Do you remember any events from during your surgery, from the time you "went to sleep" to the time you were brought to the intensive care unit?

IF YES: _____

PERI-EXTUBATION WEAKNESS? YES / NO

- At the time that you had the breathing tube removed, do you remember feeling weak, having a hard time breathing or coughing, or needing your breathing supported with a machine?

IF YES: _____

- If you had a hard time breathing, do you remember why this was (CHECK ALL THAT APPLY)?
    - **DUE TO PAIN**
    - **DUE TO MUSCLE WEAKNESS**
    - **DUE TO SLEEPINESS**
    - **DUE TO FATIGUE/BEING TIRED**
    - **DUE TO SORE THROAT/MOUTH SWELLING**

LEFT ARM PROBLEMS? YES / NO

- Are you or did you have any unusual symptoms in your left arm (such as pain, numbness, tingling) since your surgery?

IF YES: _____

POSTOPERATIVE PULMONARY COMPLICATIONS? YES / NO

- Do you believe you had a breathing complication after your surgery?

IF YES: _____

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