A Trial of Adding Lung Protective Strategies to Existing Enhanced Recovery After Surgery (ERAS) Protocols and its Effect on Improving Post-Operative Lung Function

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PROTOCOL TITLE:

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PRINCIPAL INVESTIGATOR:

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1.0 Objectives / Specific Aims

- The objective of this study is to determine whether the addition of lung protective strategies to existing enhanced recovery after surgery (ERAS) protocols for colorectal surgeries and hepatobiliary surgeries will improve post-operative lung function.
- The hypothesis is that prospective subjects undergoing hepatobiliary and colorectal surgeries that have lung protective strategies added to their base ERAS protocols will have improved lung function as measured by post-operative PACU mean inspiratory capacity via incentive spirometry compared to the control group, who had the base ERAS protocols without lung protective strategies uniformly applied.

2.0 Background

Enhanced recovery after surgery (ERAS) protocols are evidence based care improvement processes for surgical subjects. Implementation of ERAS programs for perioperative management after surgery has resulted in major improvements in clinical outcomes and costs, making ERAS an important example of value-based care applied to surgery.[1]

Currently, MUSC has existing ERAS protocols in place for hepatobiliary and colorectal surgeries. These uniform ERAS protocols cover fluid intake, hydration, anti-emetics, pain control, and several other considerations. Ventilator management is not standardized in ERAS protocol and is left to the discretion of the anesthetic practitioner. Numerous studies have shown improvement in perioperative surgical outcomes with the use of lung protective [ventilator] strategies.[3] We are trying to prove that the addition of specific lung protective strategies to existing ERAS protocols can further improve subject post-operative lung function as measured by improved mean incentive spirometry inspiratory capacity readings compared to the controls.

3.0 Intervention to be studied (if applicable)

- A select number of researched lung protective interventions will be standardized and applied to existing and ongoing MUSC ERAS protocols for colorectal and hepatobiliary surgeries.
- The intervention arm of the study will be subjects undergoing colorectal and hepatobiliary surgeries who will have the standard ERAS protocol and lung protective strategies applied.
- The control arm of the study will be subjects going for colorectal and hepatobiliary surgeries who will have the standard ERAS protocols but will <u>not</u> have standardized lung protective strategies applied
- The Lung Protective Interventions to be added include:
    1. Pressure control ventilation-volume guaranteed (PCV-VG) ventilation at approximately 7cc/kg of predicted body weight (derived from combination of sex and height)
    2. Positive end-expiratory pressure (PEEP) 7cm $H2O^{5}$, PEEP will be titrated based on clincal needs of participants.

3. Immediately post intubation recruitment breath (30cm water for 30 seconds)
4. Every 1 hour recruitment breath (30cm water for 30 seconds)
5. 40% FIO2 initially – titrate up as necessary to maintain SPO2 >94%

4.0 Study Endpoints (if applicable)

- The end-point of the study will be completion of the 3rd incentive spirometry breath measurement at the 2 hour mark, whether it be in PACU or on the inpatient floor
- Study termination would include need for post-operative mechanical ventilation, need for post-op BIPAP/CPAP, admission to ICU, or inability to adhere to lung protective interventions due to subject intolerance.

5.0 Inclusion and Exclusion Criteria/ Study Population

Inclusion Criteria

- All subjects going for scheduled colorectal or hepatobiliary surgery at the MUSC ART hospital who would normally be utilizing the existing ERAS protocols
- English speaking
- Able to give informed consent
- Ages 18 years and older

Exclusion Criteria

- Emergency cases
- Pregnant subjects-confirmed by pre-operative urine pregnancy test
- Subjects with unique lung pathologies *including, but not limited to: advanced pulmonary fibrosis, lung transplantation recipients, end stage COPD, pulmonary Hypertension*
- Subjects on home O2

6.0 Number of Subjects

- This study will include 100 subjects in order to detect a 20% difference in the anticipated decrease in incentive spirometry inspiratory capacity breaths for the control and intervention groups.

7.0 Setting

- Ashley River Tower perioperative areas at MUSC.

8.0 Recruitment Methods

- Surgical schedules will be screened by research staff members to identify potential participants.

- An IRB approved, CITI trained, research team member that has been trained on the protocol will review the chart of potential participants to verify their eligibility.
- A study team member will approach the subject about the research study to discuss their willingness to participate in the holding room bay prior to their surgery.

9.0 Consent Process

- The consent process will take place in the subject's private bay in the pre-operative holding in Ashley River Tower of MUSC.
- Potential subjects will be invited to participate in the study prior to their surgery. They will be given time to ask questions and the study will be explained in detail to them. They will be given time to read the consent documents and ask any questions prior to signing consent.
- If they agree to participate in the study they will be asked to provide written consent AND sign the consent and HIPAA documents.

10.0 Study Design / Methods

- After obtaining informed consent, the subjects will be provided with an incentive spirometer. They will be educated in its use and will then proceed to take three separate maximum exertion inspiratory capacity breaths. All three measurements will be recorded and the subjects will then be randomized to the control or intervention group.
- They will proceed to the operating room where the existing baseline ERAS protocol for colorectal or hepatobiliary surgery will be implemented during their surgery. In addition to the existing protocols, the five lung protective strategies listed above will also be implemented throughout the course of the surgery for the intervention group.
- In the PACU, the subjects will be asked at the 30 minute, 1 hour, and 2 hour marks (time zero will be arrival to PACU) to once more take three separate maximum exertion inspiratory capacity breaths and all three measurements will be recorded.
- If the subjects are unable or unwilling to comply, this will be documented as well and re-attempted at the next scheduled study documentation milestone.
- The information that will be pulled from the subject's medical record will include age, gender, weight, height, BMI, O2 saturation, average intra-op tidal volume, and the absence or presence of supplemental O2 use.
- The data collected for the intervention subjects who will have the standardized lung protective strategies applied will then be compared to the control subjects who underwent the same surgeries and had the same colorectal and hepatobiliary protocols implemented, but without the use of standardized lung protective strategies.

11.0 Data Management

- The primary outcome of interest is the inspiratory capacity obtained in the PACU via the incentive spirometer.
- The secondary outcomes that will be observed are the numerical value for SPO2, SPO2 trend, and use or lack thereof of supplemental O2 in PACU in 15 minute intervals or up to two hours after arrival there.

- Our primary hypothesis is that subjects that will have lung protective strategies employed on them will have 20% superior mean inspiratory capacity breaths via incentive spirometry compared to the non-intervention controls.
- Only IRB approved study team members will have access to data. Each study subject will be given a study ID number that will be used to identify them throughout the study. All study staff will have their CITI certification and receive protocol training. All data will be kept on a password protected MUSC server and in a redcap database. All paper documents will be kept in a locked office, in a locked cabinet that only IRB study team members have access to.
- Our primary hypothesis is that use of lung protection protocol will result in smaller change in lung function, measured by Incentive Spirometry (IS).

H_0: change in $IS_I \neq$ change in IS_C
H_A: change in $IS_I <$ change in IS_C

The primary analysis will be a two-sided test of mean change in IS after surgery compared to pre-surgery IS.

Based on data from a study of 19 people undergoing lobectomy {Bastin, 1997 #14268}, we assume that the IS before surgery is 2642 mL (se=140; std=610). If the control group IS descreases by 40%, the mean change in the control group will be ~1000 mL (std dev=308). Assuming the intervention group IS decreases by 30%, the mean change in the intervention group will be ~800 mL. Assume shared std dev=350.

t tests - Means: Difference between two independent means (two groups)

Analysis:	A priori: Compute required sample size	
Input:	Tail(s)	= Two
	Effect size d	= 0.6666667
	α err prob	= 0.05
	Power (1-β err prob)	= 0.8
	Allocation ratio N2/N1	= 1
Output:	Noncentrality parameter δ	= 2.8674419
	Critical t	= 1.9934636
	Df	= 72
	Sample size group 1	= 37
	Sample size group 2	= 37

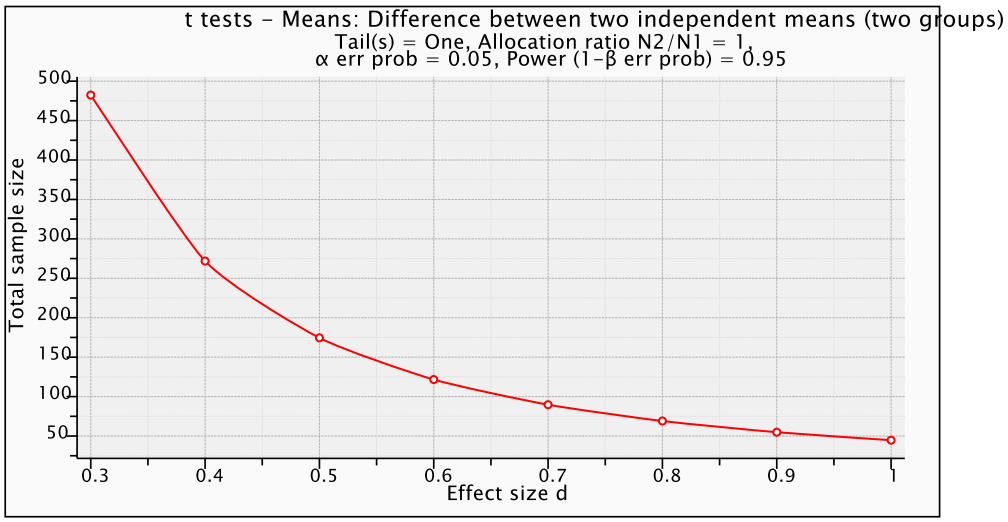
Sample size was determined using G*Power version 3.1.9.2 software. Using preliminary data, we estimate that we will need 37 subjects in each group (N=74) to have sufficient power (80%) at alpha=0.05 to test the hypothesis of a difference in mean change in IS for the two groups. To account for attrition due to withdrawals, we intend to enroll 50 patients per group. In the event that no withdrawals occur, enrolling 100 subjects (50 in each group) will give 91% power to distinguish between the two groups.

t tests - Means: Difference between two independent means (two groups)

Analysis:	Post hoc: Compute achieved power	
Input:	Tail(s)	= Two
	Effect size d	= 0.6666667

	α err prob	=	0.05
	Sample size group 1	=	50
	Sample size group 2	=	50
Output:	Noncentrality parameter δ	=	3.3333335
	Critical t	=	1.9844675
	Df	=	98
	Power (1-β err prob)	=	0.9099634

Baseline clinical and demographic factors for each group will be collected. Categorical data will be compared across the two groups with Chi-square tests of homogeneity and continuous data will be compared with t-tests for means. Covariables determined to be associated with IS measurement will be assessed for inclusion in a multivariate linear model.



12.0 Provisions to Monitor the Data to Ensure the Safety of Subjects (if applicable)

Data and safety monitoring will be performed by the research study committee in the Department of Anesthesia and Perioperative Medicine on an annual basis. The committee is comprised of several attending anesthesiologists, an emeritus dean of medicine and a biostatistician. Any adverse events will be reported to MUSC's IRB per protocol and will be evaluated by the committee.

14.0 Withdrawal of Subjects (if applicable)

- Participants will be withdrawn from the study if they expire intraoperatively, require post-op mechanical ventilation, require immediate ICU admission, require post-op BIPAP or CPAP use, or intra-operatively do not meet ventilation goals within the prescribed ventilator guidelines (likely due to intrinsic pathology).

15.0 Risks to Subjects

- Intervention group – the subjects may very temporarily desaturate while vent setting are being optimized as per protocol.
- There is a risk of loss of confidentiality.

16.0 Potential Benefits to Subjects or Others

- There is a potential to improve post operative lung function in future subjects if these additional lung protective procedures prove to be beneficial.

- There is a potential of improved post operative lung function as measured by a smaller reduction in inspiratory capacity in the intervention group compared to the controls.

17.0 Sharing of Results with Subjects

- Results will not be shared with participants or their families.

References

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2. Jabbari A, Alijanpour E, Amri Maleh P, Heidari B. "Lung protection strategy as an effective treatment in acute respiratory distress syndrome." *Caspian J Intern Med*. 2013;4(1):560–563.

3. Batchelor, T, Rasburn, N, Abdelnour-Berchtold, E, et al. "Guideline for enhanced recovery after lung surgery: recommendations of the Enhanced Recovery After Surgery (ERAS) Society and the European Society of Thoracic Surgeons (ESTS)." *European Journal of Cardio-Thoracic Surgery*. 2019;55(1):91-115

4. The Enhanced Recovery After Surgery (ERAS) Society. https://erassociety.org/

5. Futier, E, Constantin, J, Paugam-Burtz, C, et al. A Trial of Intraoperative Low-Tidal-Volume Ventilation in Abdominal Surgery. *The New England Journal of Medicine*. 2013; 369:428-437.