SLEEP-TIME (Sedation Level after Emergent Exlap without Primary Fascial Closure—TIME to Closure)

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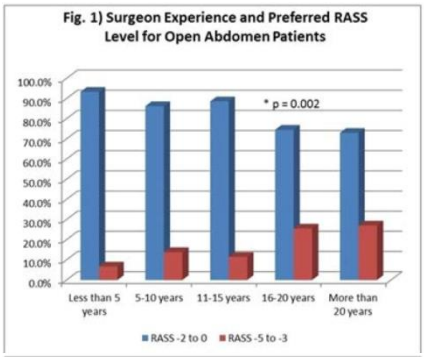
I. Specific Aims and Impact

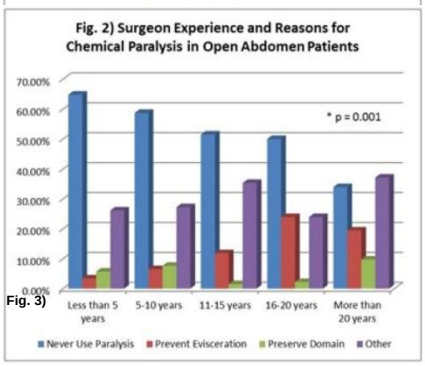
a. Impact

Damage control laparotomy (DCL) has become the standard of care for a number of emergent surgical conditions, including trauma, general surgical emergencies, and other conditions in which certain commonalities exist; patients arrive to the point of care with markers of critical illness or poor outcome (hemorrhage, sepsis, shock, respiratory failure, or compartment syndrome) or these conditions develop during the course of preoperative or intraoperative care. DCL is initiated in an attempt to prevent organ dysfunction and the "lethal triad" of acidosis, coagulopathy, and hypothermia that results from continued operative management in the setting of progressive physiologic derangement(1).

After DCL, re-establishing primary fascial closure (PFC) is of paramount importance. Data from a review of 344 patients after trauma DCL revealed a 25% incidence of wound complications after primary fascial closure, but more startling was the high rate of fistula in patients for whom PFC could not be achieved. This incidence increased dramatically after 8 days with the abdomen open(2). Thus, interventions that promote PFC were encouraged, and it was believed that such interventions included deep sedation or even chemical paralysis(3).

With advances in critical care, the utilization of deep sedation and chemical paralysis has been implicated in the high incidence of delirium in critically ill patients(4), and this in turn has been associated with increases in the odds of mortality(5). However, the specific impact on the critically ill and injured patient population with an open abdomen has not been well studied. Recently, the group from Vanderbilt indicated that chemical paralysis did not affect the time to the achievement of primary fascial closure in patients after trauma damage control laparotomy(6), although the effect on delirium and other complications such as critical illness polyneuropathy was not mentioned. Although the AAST Open Abdomen Study Group yielded a great deal of data and mortality and complications associated with damage control laparotomy, this work also did not study delirium or other ICU complications(7-9). No work has as of yet been published on the impact of sedation in this critically ill and injured population.





We surveyed the active and senior EAST membership last year on the attitudes among practicing surgeons regarding aspects of open abdomen management. We identified surgeon experience (defined as the length of time since the completion of fellowship or residency) as a key factor in the attitude toward sedation and paralysis. Surgeon experience was associated with deep sedation (RASS≤-3, p=0.002, Fig 1) and chemical paralysis (p=0.003). Experienced surgeons were less concerned about delirium and more concerned about evisceration as the reason for choice of sedation level (p=0.043) and more concerned about evisceration as the reason for use of paralysis (p=0.001, Fig 2). Using multivariate logistic regression, surgeon experience was associated with deep sedation (OR 3.6 [95%CI 1.3, 10.4], p=0.017 for ≥20 years; OR 3.5 [95%CI 1.1, 10.4], p=0.025 for 15-20 years). Trauma center level was also significant (OR 7.2 for RASS≤-3 [95%CI 1.7, 31.0], p=0.008 for level III/IV vs level I/II). In short, the significant evidence linking sedation with harm to critically ill patients has not affected the care that we deliver to patients after trauma and emergency surgery.

We subsequently performed a 5 year retrospective single-center analysis of 66 patients after trauma DCL that served as pilot data for this proposal. In this patient cohort with mean ISS of 27.0±14.1, mean ICU stay of 13.3±13.0 days, and mean ventilator dependence of 9.0±9.9 days, we noted that PFC was achieved in 69.8±68.3 hours in 59/66 patients. Median length of exposure to sedative infusions (including propofol, dexmetetomidine, and benzodiazepines) was 2.1 days. Shorter sedation exposure was not associated with prolonged time to PFC (HR 0.604 [95%CI 0.350-1.041,p=0.070], Fig 3). After adjusting for age, ISS, bowel discontinuity, and abdominal vascular injury, longer than median sedation exposure was associated with a 12.7% decrease in the proportion of coma-free delirium-free ICU days [95%CI 0.8%, 24.6%, p = 0.037].

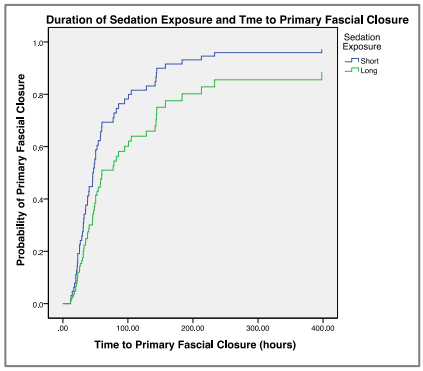


Fig. 3)

With the impending completion of this single center project, we sought to take the next step in attempting to prove our hypotheses concerning the effects of prolonged sedation exposure in critically ill and injured surgical patients.

b. Specific Aims

i. We will enroll a multicenter retrospective cohort of patients with an open abdomen after trauma or emergency general surgery to determine the effect of sedation level on time to primary fascial closure, adjusting for confounders.

ii. Using the above cohort, we will determine the confounder adjusted effect of sedation level on secondary outcomes, including surgical complications (unplanned return to OR, dehiscence/evisceration, fistula, abdominal sepsis), delirium-free coma-free days, and ventilator-free days.

II. Research Strategy

a. Significance

The precise number of patients managed with DCL is unknown(7); however DuBose and colleagues enrolled 572 patients in 2 years among 14 ACS-verified Level I trauma centers when conducting a project on trauma DCL. Thus it can be speculated that the number of patients undergoing DCL for traumatic and non-traumatic causes in the United States in a year might number in the tens of thousands at least. This is an extremely ill group of patients with high rates of complications and mortality, as well-characterized in multiple studies on the subject(2, 8, 9). However, although a great deal is written about various aspects of management of the open abdomen including feeding(10, 11) and fluid management and diuretics(12), little if any literature is available concerning the optimum management of sedation in these patients(13). Thus, the management of sedation in critically ill patients after DCL remains a largely unexplored research area in a highly ill and relatively large population. Given the significant gains that have been documented with maneuvers to reduce delirium through pain management prior to sedation, daily sedation interruption, and daily spontaneous breathing trials(14), it stands to reason that an improvement in sedation management for patients after DCL could reduce delirium, and thereby improve mortality in this critically ill subset of patients.

b. Innovation

As mentioned above, there is little literature to offer the practitioner guidance in this particular area of open abdomen management. Our group is the first to conduct work in this are, and our data indicates that our management as regards sedation and chemical paralysis in patients after DCL is largely affected by our personal training experiences rather than specific literature or clinical practice guidelines. Although our work has not been published, we have a wealth of preliminary data that is outlined in this proposal to offer a sound scientific basis for further investigation. It is our hope that the results from a multicenter trial sponsored by the Eastern Association for the Surgery of Trauma could offer significant innovation in the field and result in significant changes in management.

c. Approach

i. Study Design

This trial is intended as a multicenter retrospective trial.

ii. Study Population

This study will potentially include any patient with temporary abdominal closure after laparotomy, provided they satisfy the inclusion and exclusion criteria below:

1. Inclusion Criteria
    a. Adult patients
    b. Open abdomen with any form of temporary abdominal closure after exploratory laparotomy
    c. Richmond Agitation Sedation Score (RASS) recorded at least daily.
    d. Confusion Assessment Method-ICU (CAM-ICU assessment for delirium) recorded at least daily.
    e. Date of admission after January 1, 2017 to ensure that recent advances in critical care and trauma/emergency surgery are maximally implemented.
2. Exclusion Criteria
    a. Children under the age of 18
    b. Prisoners
    c. Pregnant women
    d. Prior abdominal operation
    e. Current open abdomen not related to traumatic or incisional hernia
3. Data Collection: Specific variables to be collected and analyzed
    a. Age (years, all patients with age > 90 yrs to be recorded as 90)

b. Sex (0 = female, 1 = male)

c. Charlson Comorbidity Index (see Appendix 1 or https://www.mdcalc.com/charlson-comorbidity-index-cci)

d. Injury Severity Score (ISS) for trauma patients (see Appendix 2 or https://www.mdcalc.com/injury-severity-score-iss)

e. Anatomic Injury Severity Score—Head (AIS-Head) for trauma patients (see Appendix 2 or https://www.mdcalc.com/injury-severity-score-iss)

f. Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score for non-trauma patients (see Appendix 3 or https://reference.medscape.com/calculator/apache-ii-scoring-system)

g. Emergency surgery (1 = yes, 0 = no)

h. Primary service (1 = trauma, 2 = emergency general surgery, 3 = surgical oncology, 4 = general surgery, 5 = transplant surgery, 6 = vascular surgery, 7 = thoracic surgery, 9 = other service)

i. ARDS (0 = no, 1 = P/F ratio < 200, 2 = P/F ratio < 150, 3 = P/F ratio < 100)

j. Dialysis (0 = no, 1 = yes)

k. Surgical variables

    i. Primary fascial closure achieved (0 = no, 1 = yes)

    ii. Type of temporary abdominal closure (1 = Commercial device, 2 = Barker-style (home-made wound-vac), 3 = towel clip skin closure, 4 = Wittman patch, 5 = other)

    iii. Small bowel resection performed at first or subsequent operation (0 = no, 1 = yes)

    iv. Colon resection performed at first or subsequent operation (0 = no, 1 = yes)

    v. Presence of bowel discontinuity (0 = no, 1 = yes)

    vi. Abdominal vascular procedure performed at first or subsequent operation (0 = no, 1 = yes)

    vii. Packs retained at first or subsequent operation (0 = no, 1 = yes)

    viii. Time to first and subsequent takeback (hours)

    ix. Time to restoration of bowel continuity (hours)

l. Duration of exposure (hours) to paralytic infusion

m. Duration of exposure (hours) to sedative and analgesic infusions

    i. Dexmetetomidine

    ii. Propofol

    iii. Midazolam

    iv. Lorazepam

    v. Fentanyl

    vi. Morphine

    vii. Dilaudid

n. Daily fluid status (will be entered up to 30 days in ICU or until primary fascial closure or adjunct fascial closure achieved. Includes daily urine output, daily blood product transfusion (mL of RBC, mL of FFP, mL of platelets, mL of cryoprecipitate), IV fluid in CC (including maintenance fluid and piggyback medications), enteral/parenteral nutrition in cc)

o. Outcomes

i. Time to primary fascial closure if achieved (hours)

ii. Surgical complications

1. Unplanned return to OR (0 = no, 1 = yes)
2. Dehiscence (0 = no, 1 = yes)
3. Evisceration (0 = no, 1 = yes)
4. Fistula (0 = no, 1 = yes)
5. Abdominal Sepsis (0 = no, 1 = yes)

iii. Daily RASS score (in morning or consistent time preferred, record for up to 30 ICU days)

iv. Daily CAM-ICU score (in morning or consistent time preferred, record for up to 30 ICU days)

v. Delirium-free coma-free days (defined as number of days in ICU with RASS -2 or higher and CAM-ICU negative)

vi. Ventilator days

vii. ICU days

viii. Pneumonia

ix. Mortality

4. Data Collection Software: RedCap

5. Data Analysis

This will be a non-inferiority trial based on the premise that light sedation (RASS 0 to -2) is not inferior to deep sedation (RASS -3 to -5) with respect to the primary outcome of days to primary fascial closure and delirium-free coma-free days as determined by RASS and CAM-ICU assessment. The RedCap database will be ported to SPSS 22.0. The primary outcome of days to primary fascial closure will be analyzed by standard hypothesis testing between groups in an unadjusted fashion and then after adjustment for demographic, management, and surgical variables listed above with a p value < 0.20 between groups using linear regression analysis. The same technique will be applied to delirium-free coma-free days.

6. Sample Size & Power Estimates

Using calculations for continuous outcome non-inferiority trials, with the presumption that 1 day earlier fascial closure is clinically significant (Miller RS *et. al.*, J Trauma. 2005 Dec;59(6):1365-71) and that the standard deviation of the days to fascial closure is 3 days (approximated from data available in available references (Smith SE *et. al*., Am J Surg. 2018 Apr 18. pii: S0002-9610(18)30332-5, Dubose JJ *et. al*., J Trauma Acute Care Surg. 2013 Jan;74(1):113-20), this study would have 90% power to meet the non-inferiority threshold at a $p < 0.05$ with 155 patients in each group (310 patients total).

7. Potential Limitations:

a. Variances in practice between institutions could result in bias. We seek to understand the extent of this variation by including many different institutions, with expert management provided by EAST membership to make adherence to current practice more likely.

b. We do not have a priori knowledge of which patients might benefit from deep sedation or light sedation. As a result, we have sought to minimize bias by having broad inclusion criteria.

8. Study Portability

Based on the above power analysis it would be estimated that 310 patients would be sufficient to achieve 90% power for the non-inferiority threshold, but a sample size of at least 400 patients would be preferable to ensure that concerns such as imbalance in number between groups (light versus deep sedation) and missing data do not adversely

affect the statistical power of the study. As mentioned above, we seek to ensure that management of patients in the study reflects the current standard of care; for this reason only patients admitted January 1, 2017, or later will be included. A single center review at our center including only trauma patients with temporary abdominal closure over a five-year period accrued 66 patients. It would therefore be anticipated that a moderate- to large-sized hospital (>500 beds) might accrue 1-3 patients on a monthly basis that satisfy inclusion criteria when both trauma and non-trauma patients are included. Thus over the approximately two-year period of acceptable accrual, we would expect similarly sized hospitals to accrue 40 patients; thus we would anticipate recruiting ten centers. In addition to the primary site, we have tentative approval from one other site already. Due to the significant effect of the SCCM-endorsed ABCDEF bundle on the data collection and outcomes of this study, we will also obtain data from each participating site concerning if that site has active implementation of the ABCDEF bundle elements (Pain/Agitation/Delirium, spontaneous awakening and breathing trials, avoidance of benzodiazepine sedation, regular monitoring of delirium, early mobility, and family engagement), any charting of bundle compliance, and any followup of outcomes. This information will be added to the database for each center.

9. Communication between Participating and Primary Sites

   Once sites are recruited, each site would identify a local principal investigator (PI) who would assume ultimate responsibility for the execution of the study at that location. A model IRB would be created and submitted for approval at the primary site and this would be forwarded to all site PI's to submit as needed to the IRB's at the individual sites. Should the primary IRB or research office believe that a shared data use agreement is necessary, this would be submitted to each site PI. As this is a retrospective study, it is anticipated that informed consent will be waived. Questions or concerns would be forwarded from the site PI to the primary PI. If necessary, conference calls will be utilized to address multi-site issues. The need for face-to-face meetings is not anticipated.

10. Anticipated Results

    We are currently in the process of completing a single-center retrospective analysis of trauma patients requiring damage control laparotomy. This study of 66 patients with mean ISS of 27.0±14.1, mean ICU stay of 13.3±13.0 days, mean ventilator dependence of 9.0±9.9 days, and mean hospital stay of 20.9±16.9 days indicated that shorter length of exposure to sedative infusions resulted in an increase in the proportion of ICU days that were coma- and delirium-free. Shorter length of exposure to sedative exposure was not associated with prolonged time to PFC in a multivariate analysis including generation of a complex propensity score. We would anticipate that multicenter data would validate our single-center results. Should this in fact occur, we would expect an overall trend toward decreased use of sedative infusions for critically ill patients after damage control laparotomy, including an increase in coma-free delirium-free ICU days, potentially a decrease in length of mechanical ventilation, and perhaps even a decrease in mortality.

11. Plans for Presentation and Publication

    Once data analysis is complete, we plan to submit an abstract to a future EAST meeting along with a manuscript directed toward the *Journal of Trauma and Acute Care Surgery*. We then would hope to perform a multicenter prospective observational trial or RCT to validate the results. We would seek to maintained continued investigation of sedation level and delirium in this critically ill surgical population.

12. Long-Term Investigator Plans

    With our interest in critically ill post-trauma and post-surgical patients, particularly those with an open abdomen, we seek to perform additional investigations to assist with optimization of their management. This may include alternative means of resuscitation such as hypertonic saline administration or direct peritoneal resuscitation. Finally, we will seek to find additional modalities with which to minimize the risk of delirium and cognitive decline among this population.

III. Summary

Damage control laparotomy revolutionized the field of trauma surgery; Hirshberg and Mattox comment on how damage control surgery “can no longer be confined to a single chapter” in a textbook on trauma surgery (15). Yet, as with any significant advance in care, we now are required to face the consequences of damage control laparotomy. Although many patients now survive who previously would have died from a lethal triad of coagulopathy, acidosis, and hypothermia, these patients are now subject to numerous complications that impair their future survival and their quality of life. These include surgical complications such as fistula and sepsis, certainly. But just as in other fields of critical care, we have come to realize that survivors of critical illness and injury have to face the effects of delirium and critical illness polyneuropathy. If there is a way to minimize these risks and, in so doing, improve the quality of life for survivors of trauma and critical illness, it is incumbent upon us to do so. The proposal contained herein has the potential to alter the care of tens of thousands of trauma patients and offer significant improvements in function, quality of life, and perhaps even mortality. It is our hope that the Committee will choose to sponsor this multicenter trial on the management of sedation after damage control laparotomy.

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Appendix 1. Calculating Charlson Comorbidity Index

https://www.mdcalc.com/charlson-comorbidity-index-cci

Parameter	Classification	Score
Age (yrs)	< 50 50-59 60-69 70-79 ≥80	0 +1 +2 +3 +4
Diabetes mellitus	None Uncomplicated End-organ damage	0 +1 +2
Liver disease	None Mild (e.g. Childs' A) Moderate/Severe (e.g. Childs' B-C)	0 +1 +3
Malignancy	None Leukemia, lymphoma, localized solid tumor Metastatic solid tumor	0 +2 +6
AIDS	No Yes	0 +6
Moderate to severe CKD	No Yes	0 +2
CHF	No Yes	0 +1
MI	No Yes	0 +1
COPD	No Yes	0 +1
PVD	No Yes	0 +1
CVA/TIA	No Yes	0 +1
Dementia	No Yes	0 +1
Hemiplegia	No Yes	0 +2
Connective Tissue Disease	No Yes	0 +1
Peptic Ulcer Disease	No Yes	0 +1
Sum		

Appendix 2. ISS Scores

https://www.mdcalc.com/injury-severity-score-iss

Worst injury in each body area	Classification	Score
Head/neck	No Injury	0
	Minor	1
	Moderate	2
	Serious	3
	Severe	4
	Critical	5
	Unsurvivable	6
Face	No Injury	0
	Minor	1
	Moderate	2
	Serious	3
	Severe	4
	Critical	5
	Unsurvivable	6
Chest	No Injury	0
	Minor	1
	Moderate	2
	Serious	3
	Severe	4
	Critical	5
	Unsurvivable	6
Abdomen	No Injury	0
	Minor	1
	Moderate	2
	Serious	3
	Severe	4
	Critical	5
	Unsurvivable	6
Extremity/pelvis	No Injury	0
	Minor	1
	Moderate	2
	Serious	3
	Severe	4
	Critical	5
	Unsurvivable	6
External	No Injury	0
	Minor	1
	Moderate	2
	Serious	3
	Severe	4
	Critical	5
	Unsurvivable	6
Sum of squares of 3 most severely injured body areas (75 is selected if 6 selected for any area)		

Appendix 3. APACHE II Scores

https://reference.medscape.com/calculator/apache-ii-scoring-system

Parameter	Classification	Score
Temperature (degrees C)	≥41	+4
	39.0-40.9	+3
	38.5-38.9	+1
	36.0-38.4	0
	34.0-35.9	+1
	32.0-33.9	+2
	30.0-31.9	+3
	≤30.0	+4
MAP (mmHg)	≥160	+4
	130-159	+3
	110-129	+2
	70-109	0
	50-69	+2
	≤49	+4
Respiratory Rate (BPM)	≥50	+4
	35-49	+3
	25-34	+1
	12-24	0
	10-11	+1
	6-9	+2
	≤5	+4
A-a PO2 (for FiO2 > 50%) or PaO2 (for FiO2 < 50%	≥500	+4
	350-499	+3
	200-349	+2
	<200 or PaO2 > 70	0
	PaO2 61-70	+1
	PaO2 55-60	+3
	PaO2 <55	+4
Arterial pH or HCO3	≥7.7 or ≥52	+4
	7.6-7.69 or 41-51.9	+3
	7.5-7.59 or 32-40.9	+1
	7.33-7.49 or 23-31.9	0
	7.25-7.32 or 18-22.9	+2
	7.15-7.24 or 15-17.9	+3
	<7.15 or <15	+4
Serum Sodium (mEq/L)	≥180	+4
	160-179	+3
	155-159	+2
	150-154	+1
	130-149	0
	120-129	+2
	111-119	+3
	≤110	+4
Serum Potassium (mEq/L)	≥7.0	+4
	6.0-6.9	+3
	5.5-5.9	+1
	3.5-5.4	0
	3.0-3.4	+1

	2.5-2.9 <2.5	+2 +4
Serum Creatinine	>3.5 >3.5 in Acute Renal Failure 2-3.4 2-3.4 in Acute Renal Failure 1.5-1.9 1.5-1.9 in Acute Renal Failure 0.6-1.4 <0.6	+4 +8 +3 +6 +2 +4 0 +2
Hematocrit	≥60 50-59.9 46-49.9 30-45.9 20-29.9 <20	+4 +2 +1 0 +2 +4
WBC	≥40 20-39.9 15-19.9 3-14.9 1-2.9 <1	+4 +2 +1 0 +2 +4
GCS	3-15	(15-GCS)
Age	≥75 65-74 55-64 45-54 ≤44	+6 +5 +3 +2 0