Study Title: Brain vs. Bone: Does fracture fixation technique influence outcomes in patients with traumatic brain injury (TBI)?

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Background and significance:

Traumatic brain injury (TBI) is a major health-care related problem in the United states and while progress has been made in understanding of the pathophysiology of this injury this has not yet led to substantial improvements in outcomes.[1] In 2010, the Centers for Disease Control and Prevention (CDC) estimated that TBIs accounted for approximately 2.5 million emergency department (ED) visits, hospitalizations, and deaths in the United States either as an isolated injury or in combination with other injuries. Of these persons, approximately 11% (283,630) were hospitalized and discharged and approximately 2% (52,844) died.[2] TBI frequently occurs in the setting of polytrauma and this remains a major obstacle in improving outcomes given that mortality in up to one third of the patients with multiple injuries is attributed to the TBI.[3,4] One of the most common concomitant injuries that accompanies TBI is long bone fractures.[5] In the last decade, the optimal method and timing of long bone fracture fixation has remained a topic of debate [6-8]and even less is known about optimal fracture management in the setting of TBI.

While some groups advocate immediate definitive fixation with intramedullary nailing (IMN) or open reduction and internal fixation (ORIF), others support the concept of "damage control orthopedics" (DCO) with temporary stabilization with external fixation. Although IMN has become the gold standard for femur fractures as it allows stable fixation and faster time to fracture union, it is associated with devascularization of the cortex, increased intramedullary pressure, and marrow embolization that is thought to potentiate neurological injury. [9-11] IMN has been shown, in the absence of intracranial hemorrhage, to be associated with long term cognitive impairment secondary to marrow embolization.[12] On the other hand, ORIF may be associated with hypoperfusion, soft tissue injury and subsequently a decrease in cerebral perfusion.[13]Therefore, the main focus of the perioperative management remains to prevent secondary brain insult and worsening cognitive outcomes.

Early stabilization is thought to be associated with more favorable outcomes and fewer complications, shorter hospital length of stay, and decreased pulmonary complications.[14] Opponents suggest that early definitive stabilization is detrimental in the severely injured patients especially in the setting of concomitant head, chest and abdominal injury due to increased blood loss, surgical stress, pulmonary complications and an increased mortality.[15-19] Several other researchers have suggested a lack of benefit to early stabilization and the strength of the evidence supporting early stabilization is considered low.[14]

More recently, it has been shown in animal models, that long bone fractures in the setting of a TBI worsen early neurologic recovery and subsequent learning and memory. [20] Given the risk of adverse neurologic sequela in the setting of concomitant long bone fractures, and in

moving toward identifying treatment strategies in the TBI patient with polytrauma that improves outcome, it seems essential to better characterize the progression of a TBI based on fracture fixation type as this may influence the future management of TBI patients with long bone fractures.

Specific Aims:

Primary Aim: Determine whether the type of lower extremity fracture fixation technique (external fixation vs. intra medullary nailing vs. open reduction internal fixation) influences cognitive outcomes in patients with TBI utilizing the Ranchos Los Amigos Score (RLAS) at discharge.

Secondary Aims:

1. Determine whether the type of lower extremity fracture fixation technique (external fixation vs. intra medullary nailing vs. open reduction internal fixation) influences Glasgow Coma Scale (GCS) and specifically the motor score at time of discharge when compared to admit GCS.
2. Determine whether timing of fracture fixation influences outcomes in patients with TBI.

Experimental design/Methods:

Design: This is a prospective observational study

Eligibility Criteria:

a. **Inclusion Criteria:** 18years of age and older, Motor Glasgow Coma Score (GCS) < 6 within approximately 24 hours of admission, Head Abbreviated Injury Score (AIS) > 2, and operative lower extremity long bone fracture (femur or tibia).
b. **Exclusion Criteria:** Determination of non-survivability on admission, prisoners, parole or probation, pregnant patients. Patients managed at a transferring facility for greater than 24 hours.

Therapeutic intervention: This is a prospective observational study and patient management will be in accordance with the specific institutional patient management protocols.

Outcome measures:

Primary outcome: To determine whether the method of fracture fixation influences cognitive outcomes in patient with mild to severe TBI utilizing the Ranchos Los Amigos Score (RLAS) at time of discharge.

Secondary outcomes: To determine whether the method of fracture fixation influences the motor GCS at discharge. Determine the timing to operative intervention and stabilization of lower extremity long bone fractures in the setting of traumatic brain injury.

Clinical evaluations:

a. **Baseline facility information**
b. **Baseline information and Medical History:** baseline demographic, medical history, and Injury-specific data (AIS head, AIS per body region, and mechanism of injury)
c. **Initial evaluation:** Vital signs (VS) and Glasgow Coma Scale (GCS) score and motor score on admission, transfusion requirement first 24 hours, fracture type/grade.

d. **Hospital course:** GCS/motor score, VS and intracranial pressure (if available) on day of, 6 hours and 24 hours post fracture fixation, fracture fixation technique, time to operation from admission,
e. **Operative course:** Length of procedure, estimated blood loss, intraoperative transfusions, and intraoperative hypotension or hypoxia
f. **Outcomes:** Overall length of stay (LOS), ICU LOS, ventilator days, other procedures performed. Ranchos Los Amigos score (RLAS), GCS and motor score at discharge, disposition, and mortality

Data collection and statistical analysis:

Data collection tool: The monetary reward associated with this research award will be used to purchase the AAST data collection tool that is shared with EAST.

Statistical considerations and data analysis:

The goal of this prospective observational study is to determine if there is a difference in outcomes in TBI patients whose lower extremity fractures are managed with one of three surgical methods: external fixation, IMN, or ORIF.

Bivariate analysis will be conducted to determine the unadjusted relationship between the 3-way treatment group and descriptive variables with the primary outcome measure, the Rancho Los Amigos Scale (RLAS) score at discharge. The outcome measure will be dichotomized as (1-4, poor cognitive function) versus (5-8, improved cognitive function). Descriptive variables to be analyzed will include demographic and clinicopathologic variables. Continuous data will be compared using the Student's t test for normally distributed variables and the Wilcoxon rank-sum test for non-normal data; categorical variables will be compared using Pearson's chi-square, Fisher's exact test, and the Mantel-Haenszel chi-square (to detect linear trends). Variables that are statistically significant and clinically important will be entered into a logistic regression model as possible confounders for the 3-way treatment variable and its effect on poor cognitive function, as measured by the dichotomous RLAS. Adjusted odds ratios (OR) and their 95% confidence intervals (CI) will be presented. P-values below 0.05 will be considered statistically significant (corresponding to a 95% CI for the OR that does not include 1.00). Multiple two-way comparisons between treatment groups will be conducted at the 0.01 alpha level.

Following analysis of the primary outcome measure, similar bivariate analyses will be presented for secondary outcome measures such as mortality, ICU length of stay and hospital length of stay. Because of the non-normal nature of the length of stay data, these two outcome measures will be analyzed in terms of categories.

It is anticipated that there will be approximately 200 patients in each of the three fracture fixation arms of the study. At the 0.01 alpha level, taking into account multiple comparisons, these sample sizes will be sufficient to determine a difference between any two proportions of patients with severe cognitive impairment at discharge of 10% and 25% (i.e., a 15% difference) with 92% power. For proportions of 10% and 30% (20% difference), power will increase to 96%. As the proportions of patients having impairment increase, power will decrease slightly for parallel comparisons. Proportions of 20% versus 35% will yield power of 79% and proportions of 20% versus 40% will yield 97% power.

Enrollment procedures/ Informed Consent: This is a prospective observational study, designed to prospectively record data on patients who are managed according to institutional patient management protocols. Thus, informed consent is waived.

Risk/Benefit analysis: Institutional Review Board approval will be obtained at all institution. This is a prospective observational study designed to record data on patients managed according to institutional patient management protocols. There is no intervention conducted in this trial therefore the greatest risk involved in participating is a breach of confidentiality. This risk will be minimized by de-identification of all patient information and storing all study data on a secure password protected server (AAST data tool) that is only accessible by authorized study personnel.

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