Protocol #: 24-0230
Project Title: Management and outcomes of multisystem traumatic injury: A retrospective multicenter trial of combined traumatic brain injury, solid organ injury, and blunt cerebrovascular injury
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Version Date: 2/7/2025

I. Hypotheses and Specific Aims

A frequent challenge of polytrauma is the conflicting management of injuries to different organ systems.

This study aims to investigate outcomes in patients with multisystem traumatic injuries based on initial management of each injury.

Specific Aim #1: Compare outcomes of initial operative management versus NOM in trauma patients with combined blunt solid organ injury of the spleen, liver, or kidney and TBI on mortality, incidence of secondary brain injury as assessed by radiographic progression of TBI (change in intracranial hemorrhage, or cerebral edema), changes in neurologic status, or need for delayed neurosurgical intervention, and short-term functional outcomes including discharge Glascow Coma Scale (GCS), and discharge disposition.

Hypothesis #1: Early operative management of combined blunt solid organ injury and TBI in hemodynamically unstable patients will have no significant effect on in-hospital mortality, but will be associated with a lower incidence of secondary brain injury and improved short-term functional outcomes as compared with NOM.

Specific Aim #2: To evaluate the impact of the timing and modality of treatment of blunt cerebrovascular injury (BCVI) and TBI on in-hospital mortality and neurologic complications including incidence of ischemic stroke, progression of intracranial hemorrhage, and short-term functional outcomes.

Hypothesis #2: Early initiation of antithrombotic therapy (within 24 hours of admission) in trauma patients with combined BCVI and TBI will be associated with a lower incidence of ischemic stroke without a significant change in size of intracranial hemorrhage as compared with delayed initiation of therapy.

Specific Aim #3: To evaluate the impact different treatment strategies on outcomes in trauma patients with combined blunt solid organ injury and BCVI including failure of NOM (fNOM).

Hypothesis #3: Early initiation of antithrombotic therapy in trauma patients with combined blunt solid organ injury and BCVI will be associated with a lower incidence of ischemic stroke and similar or lower rates of bleeding complications, including total transfusion requirements and failure of NOM (fNOM) as compared with delayed initiation of antithrombotic therapy.

II. Background and Significance

Traumatic Brain Injury (TBI)

TBI is a major cause of morbidity and mortality, especially in young adults.[1] The primary goal in treatment of TBI is the prevention of secondary brain injury, by avoiding hypotension and hypoxia.[2] Local and systemic inflammation have been identified as an additional contributor to secondary brain injury where peripheral immune mechanisms lead to systemic release of proinflammatory mediators and entry of immune cells into the CNS.[3,4] Most patients do not require neurosurgical intervention and management of the TBI involves monitoring for progression of intracranial hemorrhage (ICH). Management of other concomitant injuries may include initiating and titrating antithrombotic therapy. This management can initiate conflicting priorities of care for the different injuries.

Blunt solid organ injury

The management of blunt solid organ injury has evolved overtime with a shift towards more conservative management, and emphasis on the preservation of organ function.[5] Most major trauma organization recommend nonoperative management (NOM) for blunt splenic, liver, and kidney injury in hemodynamically stable patients, without peritonitis irrespective of injury grade, patient age or presence of associated injuries.[5-9] NOM may include conservative observation with serial transfusions or angioembolization. This approach has been shown to be safe and effective in the majority of patients, but a small subset of patients will have complications including failure of NOM (fNOM) after blunt solid organ injury. fNOM is defined as the need for delayed operative intervention and is often associated with hypotension and worse outcomes overall, especially in patients with concomitant TBI.[10]

Blunt cerebrovascular injury (BCVI)

BCVI results from high-energy mechanism that cause shear injury to the carotid or vertebral arteries. Early initiation of antithrombotic therapy to prevent ischemic stroke, typically with aspirin or heparin, is the cornerstone of treatment. Rarely, open or endovascular interventions are required. The urgency or treatment must be balanced with the risk of hemorrhagic complications in trauma patients.

Combined injury

The management for each of these injuries in isolation is clear and well supported by literature. A frequent challenge of polytrauma is the conflicting management strategies of injuries to different organ systems with special challenges, where the management strategy for one injury may cause progression or complications for another injury. In these complex cases, the standard of care for an isolated injury may not be safe or appropriate with combination injury.

Combined TBI & blunt solid organ injury

For patients with combined TBI and blunt solid organ injury, NOM management of blunt solid organ injury may be associated with delayed hemorrhage and hypotension which could contribute to secondary brain injury. It has been proposed that in the setting of trauma, damaged immune organs like the spleen, may be a major contributor to peripheral immune response that can cause secondary brain injury. In animal models of TBI, early splenectomy downregulates certain inflammatory signaling pathways and improves cognitive outcomes.[11,12] Clinical

evaluation of these hypotheses have found mixed results. National trauma database studies show that NOM remains the predominant strategy, even in the presence of TBI.[13] Tariq et al. found no difference in outcomes between OM and NOM in these patients.[14] Looking specifically at blunt splenic injury and TBI, some studies have found that NOM is associated with better outcomes, while others have found no difference in outcomes between OM and NOM.[15,16] Given a clear mechanistic rational in favor of early OM in these patients, and conflicting clinical literature based on database studies which lack the necessary granularity, further investigation is needed to clarify management of these patients.

Combined TBI & BCVI

The management of combined TBI and BCVI presents an inherent conflict. Preventing hemorrhagic expansion is the priority in early TBI management, while BCVI necessitates prompt antithrombotic therapy to prevent ischemic stroke. Timing is the crux of the conflict: progression of traumatic ICH most often occurs within the first 24 hours of injury, whereas delaying BCVI treatment more than 24 hours from injury increases stroke rates.[17-19] Thus clinicians must carefully balance the risks of early versus delayed therapy. Existing literature suggests that early antithrombotic therapy can reduce the risk of ischemic stroke without significantly increasing the risk of intracranial hemorrhage progression, through optimal timing remains an area of ongoing investigation.[20-22]

Combined BCVI & blunt solid organ injury

For patients with concurrent BCVI and blunt solid organ injury, a similar challenge exists in balancing the risk of hemorrhage against the need for stroke prevention. Recent studies suggest that early antithrombotic therapy may be safe in this patient population, with no significant increase in bleeding complications or fNOM.[20,21] However, the optimal timing of antithrombotic therapy initiation remains controversial. While early therapy appears beneficial, particularly in reducing ischemic stroke risk, its impact on hemorrhagic complications in patients managed nonoperatively, requires further investigation.

To our knowledge, the majority of studies evaluating these complex multisystem injury patients have been limited to animal models, which have not been reproduced in human patients, or national trauma database studies, which lack the granularity to assess injury-specific complications and further examine outcomes. There is a significant gap in clinical guidance for these patients. Further research is needed to optimize management and improve outcomes in patients with combined TBI, BCVI, and blunt solid organ injury. Due to the relative infrequency of this disease process, additional robust, multi-institutional data which is sufficiently powered to test this question is needed.

III. Research Methods

A. Description of Population to be Studied

The population will include any trauma patients (>15 years) with combined blunt solid organ injury, TBI or BCVI admitted to a participating trauma center[1] between January 2017 and January 2024. Exclusion criteria include pregnant patients, and incarcerated patients who died < 4 hours after arrival. Additionally, we will exclude patients with a penetrating trauma mechanism. A traumatic brain injury will be defined as a head Abbreviated Injury Score (AIS)

[1] Designated by American College of Surgery Committee on Trauma.

greater than or equal to 1. A solid organ injury is defined as any American Association for the Surgery of Trauma-Organ Injury Scale (AAST-OIS) splenic, liver or kidney injury grade greater than or equal to 1. A blunt cerebrovascular injury is defined as any Biffl scale grade of the common carotid artery, internal carotid artery, or vertebral artery greater than or equal to 1.

B. Data/Sample Collection

Each participating institution will retrospectively identify patients who meet inclusion criteria for this protocol through relevant institutional trauma registries and patient EMR between January 2017 and January 2024. Variables to be collected include:

- Participating institution information
    - American College of Surgery Trauma Center Level
    - Annual trauma admissions and trauma activations
    - Existing institutional protocols or clinical practice guidelines for management of blunt organ injury, traumatic brain injury, or blunt cerebrovascular injury
- Patient identifiers (MRN, name)
- Demographic information
    - Age
    - Gender
    - Race
    - Ethnicity
- Pre-existing co-morbidities
    - COPD
    - CHF
    - Smoker
    - Chronic Renal Failure
    - Cirrhosis
    - Advanced Directives Limiting Care
- Admission diagnosis & related information
    - Mechanism of Injury
    - Cause of Injury
    - Injury Severity Score (ISS)
    - AIS by body region
        - Head/Neck
        - Face
        - Chest
        - Abdomen/Pelvis
        - Extremities
        - External
    - Arrival vital signs
        - heart rate
        - systolic blood pressure
        - diastolic blood pressure
        - shock index
- Hospital course
    - Hospital Length of Stay (LOS)
    - ICU LOS

    - Admitting Service
    - Venous thromboembolism (VTE) chemoprophylaxis[2] (regimen, date & time of initiation)
    - Therapeutic Anticoagulation (indication, regimen, and timing of initiation)
    - Withdrawal of life sustaining treatment (WLST)
    - Discharge Disposition
    - Mortality
    - Hospital Events
        - CPR
        - CAUTI
        - Deep Surgical Site Infection
        - CLABSI
        - DVT
        - Delirium
        - Myocardial Infarction
        - Organ Space SSI
        - Osteomyelitis
        - Pulmonary Embolism
        - Pressure Ulcer
        - Severe Sepsis
        - Stroke/CVA
        - SSI
        - Unplanned ICU Admission
        - Unplanned Intubation
        - Unplanned OR
        - VAP
        - ARDS
- Traumatic brain injury diagnosis & management
    - Arrival Glascow Coma Scale (GCS) and discharge GCS
    - Operative neurosurgery interventions performed (intervention type, date, time)
    - Radiographic progression of TBI[3]:
        - Intracranial hemorrhage (ICH)
        - Other[4]
    - Acute neurologic changes
    - Total number of brain imaging (i.e. noncontrast CT, CT arteriography, CT venography, MRI) performed during admission
- Blunt cerebrovascular injury (BCVI) diagnosis & management details
    - Biffl injury grade
    - Antithrombotic therapy (regimen, date & time of initiation)
    - Endovascular or surgical intervention performed (intervention type, date, time)

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[2] Type of VTE chemoprophylaxis with dose and frequency. Examples of chemoprophylaxis include low molecular weight heparin (LMWH), subcutaneous heparin (SQH), heparin infusion, aspirin, and direct oral anticoagulant (DOAC).

[3] Refers specifically to new or worsened findings on head imaging as compared to the initial imaging for admission

[4] New or worsened findings, excluding ICH, such as brain edema, midline shift, cerebral venous thrombosis, ischemia, etc.

    - CVA during admission (diagnostic modality, severity, date, time)
- Blunt solid organ injury diagnosis & management
    - AAST-OIS injury grade
    - Initial management of solid organ injury:
        - operative management[5] or non-operative management (NOM)
    - Other solid organ injury management:
        - Failure of non-operative management[6]
        - Indication for OM or fNOM[7]
        - Selective angioembolization of spleen, liver or kidney (angiography with or without embolization) during admission
        - Total number of blood transfusions[8] during admission

A Redcap database will be used to collect information from each institution. Participating institutions will identify patients who meet inclusion and exclusion criteria through an institutional trauma registry. Variables for each subject will be collected from the institutional trauma registry and abstracted from the electronic medical record. All data will be uploaded to the Redcap database. Each participating institution will assign subjects a unique study ID in their working dataset. A linking dataset will connect the unique study ID with any protected health information needed to identify the patient. This linking dataset will not be shared between institutions and each institution will be responsible for securing the linking dataset.

C. Study Design

This will be a multi-institution retrospective cohort study of patients admitted to a trauma service after traumatic injury between January 2017 and January 2024 with injury of at least 2 of the following: (A) blunt solid organ injury of the spleen, liver, and/or kidney, (B) TBI, or (C) BCVI. Patients with blunt solid organ injury who meet inclusion and exclusion criteria will be characterized according to initial management of solid organ injury with either (1) operative management (OM) or (2) NOM. OM includes patients who undergo exploratory laparotomy with repair (splenorrhaphy, hepatorrhaphy, or renorrhaphy) or removal (splenectomy, partial hepatectomy or nephrectomy) of the damaged organ within 4 hours of hospital arrival. NOM includes serial evaluation or selective angioembolization ~~of splenic bleeding~~. Patients with BCVI will be categorized according to the timing of initiation of antithrombotic therapy including aspirin or heparin infusion therapy with either (1) early initiation (2) delayed initiation or (3) no antithrombotic therapy. Early initiation is defined as initiation within 24 hours of admission, while delayed initiation is more than 24 hours from admission. Demographics, mechanism and severity of injury, treatment and outcome variables will be compared based on these groups.

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[5] Defined as open repair (splenorrhaphy, hepatorrhaphy, or renorrhaphy) or removal (splenectomy, partial hepatectomy or nephrectomy) of the damaged organ within 4 hours of hospital arrival.

[6] Delayed operative management for solid organ injury, defined as need for open repair or removal of damaged organ more than 4 hours after arrival to hospital.

[7] Primary indication for any operative management of solid organ injury (includes initial OM or delayed OM [i.e. fNOM]) as hemorrhagic shock, suspicion for blunt hollow viscous injury

[8] Including any units of whole blood (WB) or blood components: packed red blood cells (pRBC), fresh frozen plasma (FFP), platelets (PLT), cryoprecipitate (CRYO).

The primary outcome will be in-hospital mortality. Secondary outcomes will include ischemic stroke, radiographic progression of intracranial hemorrhage, total transfusion requirements during admission, need for delayed operative intervention, need for neurosurgery intervention, discharge GCS, total number of CT brain scans, discharge disposition, hospital and ICU length of stay, duration of mechanical ventilation unplanned admission to ICU, unplanned operation, and unplanned intubation.

D. Statistical Considerations

Descriptive statistical analysis will be performed for all variables with frequency scores for categorical data and mean/standard deviation for normally distributed continuous data. Outcomes will be compared using Chi-squared or Fisher's exact test for categorical variables, Wilcoxon rank sum test for nonparametric continuous variables and Student's t-test for parametric continuous variables. Multivariable logistic regression analysis will be performed to assess for development of secondary brain injury. P-values of <0.05 will be considered significant.

E. Potential Scientific Problems

The most likely scientific problem is that no association will be found between our independent and outcome variables which may limit the impact of our study. For this reason, we are starting with a retrospective study. An additional limitation is related to the retrospective nature of this study, in that patients will not be randomized to treatment options.

Current guidelines recommend NOM in patients who are hemodynamically stable regardless of age, solid organ injury severity or presence of other injuries including TBI, so presumably initial and pre-operative blood pressure and heart rate will differ significantly between groups. To nullify this effect, we will include these confounders as collected variables that can be included in the multivariable regression.

F. Summarize Knowledge to be Gained

There is limited available research comparing various treatment modalities for solid organ injury in the setting of TBI or BCVI. Any evidence which is available in humans is limited to national or large multi-institution trauma registry studies which often lack the granularity to evaluate preventable progression of disease (i.e. secondary brain injury or stroke). Available evidence in animal models suggests early operative management of solid organ injury may have a protective effect in TBI which has not been demonstrated in large trauma registry-based human studies. Additionally, the majority of available studies have been performed with national trauma database studies which lack the granularity to assess injury-specific complications or with single institution retrospective studies, which are limited by bias and lack generalizability. This study, by contrast, will represent a large population of diverse trauma patients, will be powered to detect small differences in the primary and secondary outcomes between groups, and will include the granularity to evaluate differences between treatment modalities.

G. Risks

The primary risk from secondary research is the potential loss of confidentiality. A Redcap database will be used to collect information from each institution. All data collected by participating institutions will be uploaded to the Redcap database. As previously described, each participating institution will assign subjects a unique study ID in their working dataset. A linking dataset will connect the unique study ID with any protected health information needed to identify

the patient. This linking dataset will not be shared between institutions and each institution will be responsible for securing the linking dataset.

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