EAST-SHIELD Trial (Study of Head Injury in Early Life due to firearm Damage)

An EAST Multicenter Trial Proposal

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Background and Significance

a. Burden of problem to be examined

In 2019, gunshot wound injuries became the leading preventable cause of death among children aged 1-19 years, surpassing motor vehicle collisions [1]. This disturbing trend persisted in subsequent years, with the pediatric mortality rate from firearms reaching 5.8 per 100,000 children in 2021 [2]. This increase correlates with a rise in shootings on U.S. K-12 school grounds [3]. Among these injuries, pediatric gunshot wounds to the head (GSWH) are a particularly devastating subgroup, with reported mortality rates ranging from 20% to 65% [4]. Interestingly, pediatric patients who suffer from GSWH have been observed to have lower mortality rates and better functional recovery compared to adults with similar injuries [5]. This suggests that unique factors govern outcomes in this population, yet current management guidelines are primarily based on adult recommendations, which may not be optimal for children [4, 6]. The lack of pediatric-specific guidelines for GSWH underscores the urgent need for updated, targeted recommendations to improve outcomes in this vulnerable population.

b. Review major published studies that exist on the topic

The existing literature on pediatric GSWH is limited to retrospective, single-center studies. Bandt et al. published the first major analysis of pediatric GSWH treated at their trauma center and identified clinical and radiographic findings which could be compiled into a scoring system (St. Louis Scale for Pediatric Gunshot Wounds to the Head; SLS) for prognostic evaluation [7]. The authors found that a score ≥ 5 was associated with a negative predictive value of 96.7% for mortality [7]. To date, the SLS is the only prognostic measure which has been validated for pediatric GSWH. DeCuypere and colleagues offer a larger sample size but show that the SLS lacks specificity for death, given that several survivors had SLS scores ≥ 5 [8]. They also evaluate a broader range of factors that influence mortality compared to Bandt et al., including coagulopathy and anemia at presentation [8]. In the largest retrospective study to date (96 patients), Arguello and authors also validate the SLS and, importantly, explore factors that influence functional outcome [9]. However, over two thirds (68.8%) of their included patients ranged from ages 16 to 21, which limits the applicability of their findings to younger patients [9-12].

Innovation and Impact

a. Outline how this idea is innovative and its anticipated impact

Preliminary data from our retrospective analysis of pediatric GSWH patients at ourinstitution (14 patients from 2010-2023; manuscript in preparation) shows that the Rotterdam CT Score [13] may be a better predictor of mortality in this population compared to the SLS. Moreover, we found that survivors had significantly lower serum glucose and lower INR at presentation than non-survivors. While our study and other published series are limited by small sample size, we are the first group to compare the SLS to other predictive models for pediatric GSWH and analyze the predictive accuracy of laboratory values such as serum glucose. Our proposed multicenter trial will be innovative in its investigation of comparable prognostic measures and laboratory deviations, improving non-invasive management. Additionally, it will be the largest study of pediatric GSWH patients ≤ 18 years old, which is critical given that the youngest patients in this group are understudied. Moreover, the inclusion of centers across the nation will allow the inclusion of various management protocols to yield a balanced standardization of practice. Finally, we will provide a detailed analysis of the role of neurosurgical intervention in pediatric GSWH patients, which has not been accomplished in previous studies, to develop evidence-based practices for surgical management of this population.

b. Describe what & how the proposed MCT will add to the existing body of knowledge and literature

Due to the (thankfully) low incidence of pediatric GSWH, the data on its management and prognosis are mostly limited to case studies, case series, and single-center studies. Large databases, such as the National Trauma Data Bank (NTDB), do not capture the granular data needed to determine which factors may contribute to in-hospital mortality or favorable functional outcome in our patient population, as they lack data regarding specific radiographic findings, management, and functional outcomes. We hypothesize that there are specific clinical variables (including presentation GCS, presentation vital signs, and severity of head injury based on existing metrics) that will predict mortality. A multicenter trial will help expand the sample size to evaluate factors that influence a relatively rare condition—pediatric GSWH—and to help identify or define prognostic tools such as the SLS that may help predict in-hospital mortality as a primary endpoint and functional outcome as a secondary endpoint. Additionally, data on medical and surgical management will be distinct from adults and specific to children with GSWH. On the other hand, the small number of patients per center will facilitate center participation; we anticipate the burden of chart review to be very low.

Specific aims/hypothesis

a. Primary aim

To identify the demographic characteristics, clinical presentations, laboratory values, radiographic changes, and surgical protocols which predict in-hospital mortality in pediatric GSWH patients.

b. Secondary aims

To identify the demographic characteristics, clinical presentations, laboratory values, radiographic changes, and surgical protocols which correlate with:

i. post-discharge mortality (based on last follow up identified)
ii. favorable functional outcome
iii. length of hospitalization
iv. surgical management, including everything from surgical debridement to ICP monitoring to decompressive hemicraniectomy
v. surgical or wound complications related to GSWH

c. Tertiary aims

To refine a risk score based on clinical and radiographic findings, similar to the SLS and potentially incorporate components of existing scores like the Rotterdam CT Score, Marshall CT Classification, Stockholm CT Score, and Helsinki CT Score, etc., for predicting mortality in the pediatric GSWH population, and to determine factors influencing complications and functional outcomes.

Methods

a. Design

Retrospective

b. Inclusion criteria

Patients will be included if they are ≤18 years old, presented to the hospital with a penetrating or perforating intracranial gunshot wound to the head and have an available head CT at the time of data extraction.

c. Exclusion criteria

Patients will be excluded if they present with cardiopulmonary arrest or are not sufficiently stable to undergo a head CT and if they do not have an available head CT at the time of data extraction. Transferred patients may be included if their first head CT is available for review.

d. Describe (completely but succinctly) how this project will be conducted

This study will be a retrospective, multicenter review of all pediatric patients who presented to the hospital with an intracranial gunshot wound between 01/01/2015-12/31/2024. Each participating center is responsible for obtaining individual IRB approval to access electronic medical records for patients who meet the inclusion criteria. Patients meeting the inclusion criteria will be identified by query of electronic medical records, and the exclusion criteria will be applied. A data collection tool will be provided, and each center will upload de-identified data to a centralized REDCap database supported by Rutgers New Jersey Medical School. Data use agreements (DUA) will be obtained should a participating institution require a DUA to share de-identified data. Data will then be analyzed.

Outcomes measures

a. Primary outcome

In-hospital mortality

b. Secondary outcome(s)

1. Extended mortality (3-month, 6-month, 1-year, 5-year, 10-year)

2. Extended Glasgow Outcome Scale (GOS-E) at latest available follow-up (favorable functional outcome defined as GOS-E ≥ 5)

3. Total length of hospitalization

4. In-hospital complication rate (pneumonia, meningitis or other CNS infection, wound infection at site of head injury, post-traumatic seizure confirmed by EEG monitoring, need for tracheostomy placement, need for PEG placement)

5. Compare the area under the curve (AUC) of receiver operating characteristic (ROC) curves for SLS, Rotterdam CT Score, Marshall CT Classification, Stockholm CT Score, and Helsinki CT Score.

Variables to be collected

a. Variables

Baseline participating institution information, demographics, baseline clinical characteristics, hospital course, treatments & interventions, outcomes of interest

b. Additional variables

See additional materials for detailed REDCap data collection forms.

Hospital characteristics: Trauma center level, pediatric trauma center status, state-verified status, number of beds, pediatric readiness score, hospital type (academic, teaching, community).

Demographics: Age, sex, race, ethnicity, BMI.

Clinical presentation: SBP, HR, RR, respiratory assistance, oxygen saturation, temperature, pupils (reactivity, dilated vs. pinpoint), ICP monitor placement (EVD or bolt), initial ICP, ED disposition.

Laboratory values: INR, sodium, potassium, glucose, base excess, hemoglobin, hematocrit, platelets, WBC, lactate, Cr, BUN.

Scoring: Admission GCS (eye-opening, verbal, and motor), ISS, AIS (General, Head & Neck, Chest, Abdomen, Extremities & Pelvis, External).

Radiology: Presence of visible intracranial pathology, involvement of deep nuclei and/or 3rd ventricle, mixed supra-/infratentorial involvement, number of lobes involved, trans-ventricular injury, bihemispheric injury, midline shift (size in mm), basal cisterns (visible, compressed, or effaced), high or mixed-density mass lesions (volume in cm^3; type: subdural hematoma, intracerebral hematoma, epidural hematoma; if subdural, single- or dual-sided), intraventricular blood, subarachnoid hemorrhage (location: convexities, basal cisterns), epidural hemorrhage, diffuse axonal injury (basal ganglia, splenium, or brain stem). These radiologic variables will be used to calculate SLS, Rotterdam CT Score, Marshall CT Classification, Stockholm CT score, and Helsinki CT score.

These scores are not routinely collected as standard of care in pediatric patients, but the criteria are all discernible from admission head CTs and routine presentation characteristics. Therefore, participating sites will be required to review imaging and collect the variables. The components of each score will be collected in order for us to calculate scores and assess if specific components of the score are more important for this population.

Surgery: Neurosurgical procedure, time to first procedure.

Discharge: Total hospital length of stay, days on ventilator, days in ICU, discharge disposition (home/rehab/nursing home/etc.), duration of latest follow-up, mortality (in-hospital, 3-month, 6-month, 1-year, 5-year, 10-year) GOS-E at latest available follow-up.

The purpose of collecting post-discharge data is to provide somewhat more robust outcomes when available. We understand that there is frequently poor follow up and that this additional outcome may have missing data. However, we will attempt to capture whatever follow up is available given that this will be the largest study of this patient population.

GOS-E is not routinely calculated in pediatric trauma patients with TBI. However, we intend to estimate this from functional outcome as documented from latest available follow up notes from physical therapy, occupational therapy, and other provider notes when available.

Data collection

a. Outline data collection plan/tool succinctly

Participating institutions will identify patients ≤ 18 years of age who have sustained a gunshot wound to the head from their trauma registries (AIS Head & Neck > 0, GSW as mechanism). Then, the patients' charts will be reviewed to determine if the injury was intracranial. If the patient meets inclusion criteria, data will be abstracted from the medical record. Deidentified data will be entered directly into REDCap. The REDCap database will be password protected and require dual authentication, and access will only be given to key personnel participating in the research project at each institution (up to two contributors per center). Once the data entry is complete, the PI and co-investigator at the primary institution will download the data for analysis.

b. Has IRB approval been obtained at the primary site?

IRB approved.

c. Is DUA required for participation in the study?

Participating institutions may require a DUA for their IRB. We will provide a template DUA for participating sites in additional study materials. Because there is no financial agreement and only deidentified data are being transferred, DUA may not be required from all centers.

d. Identify the individuals that will primarily be responsible for the data collection process

The contributing authors from each site will be responsible for data collection.

Statistical considerations & data analysis

a. Is there a primary statistician assigned to assist the PI with design & data analysis? If no, how was study design/power analysis determined? Who will handle analysis once complete?

While there is not currently a primary statistician assigned to assist the PI with design and data analysis, we have performed the below power analysis, and we anticipate that this will be a straightforward epidemiological study which will not require complex statistical analysis. Once data collection is complete, the co-PIs will conduct the statistical analysis and ensure the completion of the study.

b. Include detailed description of the data analysis plan

Descriptive statistics will be performed to describe frequency distribution for categorical data and central tendency for continuous data. Categorical data will be reported as percentages. Survival and mortality groups and favorable and poor functional outcome groups will be compared using chi-squared test for categorical variables and two-sample t-test for continuous variables, or Mann-Whitney U-test for non-normal data (Shapiro-Wilk test $p < 0.05$). A St. Louis Score ≥ 5 will initially be used as a cutoff to predict mortality, but the prognostic tool cutoffs with the best predictive ability will be assessed by generating ROC curves and calculating area under the curve (AUC). Youden's index (J) will be used to identify the optimal cutoff in the ROC analysis. Multivariate logistic regression will be used to identify independent predictors of survival or favorable functional outcome. Variables included in the regression will be selected based on both clinical and statistical significance with a plan to include demographics, presenting vital signs and GCS, CT findings of severity of injury, neurosurgical intervention, and injury severity. Optimal cutoff values for mortality prediction of various scores will be included in the regression model. Comparisons will be made between scores. All analysis will be conducted using R. Statistical significance will be set at $p < 0.05$ (2-tailed) and adjusted for multiple comparisons where appropriate. Bonferroni correction will be used to control for multiple comparisons.

c. Include power analysis

Based on our preliminary data, the mortality rate of pediatric GSWH patients is 65%.

To determine whether 20 independent variables (as listed above) are predictors of mortality, a multivariate logistic regression would require a sample size of at least 308 participants to achieve an alpha of 0.05 and 80% power. This calculation is based on the events per variable = 10 rule.

Enrollment procedure & need for informed consent

a. Please note what enrollment procedure for this study entails

Pediatric patients with intracranial gunshot wounds will be identified at each institution based on query of the trauma registry. Exclusion criteria will be applied once charts are reviewed for penetrating wounds. De-identified data will then be entered into a REDCap database. Since this is a retrospective chart review with de-identified patient information, no informed consent will be required. Patients will not be paid to participate, nor will there be any cost to the institution or patient for being a part of this study.

Our institution identified 14 patients who meet criteria for the study in the past 14 years. We anticipate that other institutions will have a similar rate of injury (approximately 1/year), so we estimate that each institution will contribute 10-20 patients, requiring anywhere between 15-30 institutions to participate. We estimate that data collection will be completed within 2 years. Due to the low number of patients expected from each institution, this study is highly feasible for participating sites.

b. Outline consent procedures here, if applicable

There are no consent procedures for this study due to its retrospective design and minimal risk to patients. A waiver of informed consent should be requested.

Primary site resources

a. Please indicate what resources are available at the primary study institution: presence of dedicated statistician, research personnel, availability of data collectors

Research personnel and availability of data collectors.

The primary site has access to REDCap which we will use for data collection. We have access to additional resources as needed through the Rutgers Clinical Research Unit.

References

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