



EAST MULTICENTER STUDY PROPOSAL

(Proposal forms must be completed in its entirety, incomplete forms will not be considered)

GENERAL INFORMATION

Study Title:

Reversal of pharmacologic platelet inhibition using platelet transfusion in patients with traumatic brain injury

Primary investigator / Senior researcher:

Babak Sarani, MD

Co-primary investigator:

BACKGROUND AND SIGNIFICANCE

Use this area to briefly (1-2 paragraphs only) outline the burden of the problem to be examined:

Aspirin and clopidogrel are very commonly prescribed medications in patients with vascular disease. Use of these medications is especially prevalent in the geriatric population who are also prone to falling. Persons over age 55 now account for up to 40% of non-concussion traumatic brain injury (TBI) annually. Pre-injury use of antiplatelet medications, especially clopidogrel, is independently associated with radiographic worsening of the brain injury as well as mortality following discharge in patients with TBI. Studies in TBI patients taking warfarin have consistently found that time to reversal of coagulopathy is directly associated with mortality, and it is logical to presume a similar relationship for patients on antiplatelet agents. Unfortunately, studies evaluating the efficacy of platelet transfusion to restore normal platelet function and/or impact on mortality in this patient cohort have yielded conflicting conclusions. All such studies have been limited by small sample size.

Although there are several commercially available assays to determine the presence of antiplatelet agents in the serum, there is only one FDA approved test that can quantify the degree of platelet dysfunction resulting from inhibition of the arachidonic acid (AA) and/or adenosine diphosphate (ADP) pathways, thrombelastography (TEG) platelet mapping. Aspirin functions by inhibiting the AA receptor on the platelet whereas clopidogrel inhibits the ADP receptor. In addition, the test can discern the difference in clot strength related to ideal platelet function (MA-CK) and actual platelet function in each pathway (MA-AA and MA-ADP). Thus, the test allows a reliable means to assess the degree receptor inhibition and actual platelet dysfunction in patients on antiplatelet agents as well as the degree of resolution of receptor inhibition and actual dysfunction following platelet transfusion. However, to date there are no trials correlating both the degree to which reversal of AA/ADP receptor inhibition as normalization of clot strength (MA) impacts on mortality in patients on aspirin or clopidogrel following TBI.

We hypothesize that platelet AA/ADP receptor inhibition is common in patients with TBI using antiplatelet medications and that TEG platelet mapping can be used to monitor reversal of this inhibition and normalization of clot strength. We further hypothesize that normalization of these parameters is associated with less progression of bleeding as noted on CT scan and improved patient-centered outcomes.

The specific aims of this multicenter study are:

Primary aim:

Primary aim should be succinctly stated here – single sentence ideal:

The primary aim of the study is to determine the efficacy of platelet transfusion for reversal of thrombocytopenia caused by use of pharmacologic antiplatelet agents in patients with TBI using TEG platelet mapping.

Secondary aims:

Any secondary aims should be stated here:

Secondary aims of the study include correlating the degree of reversal of thrombocytopenia with: 1. radiographic progression of TBI, 2. need for craniotomy or craniectomy following platelet transfusion 3. mortality, 4. hospital length of stay, and 5. discharge destination.

EXPERIMENTAL DESIGN/METHODS

Inclusion Criteria:

Inclusion criteria include: Age \geq 18 years old, isolated non-concussion TBI defined as subarachnoid hemorrhage, subdural hemorrhage, epidural hemorrhage, or intracerebral hemorrhage, preinjury use of either/both aspirin or clopidogrel, hospital which routinely performs TEG platelet mapping in the trauma patient

Exclusion Criteria:

Exclusion criteria include: Age $<$ 18 years old, multisystem injury, prisoner, pregnancy.

Therapeutic Interventions:

This is a prospective observational study only. Patients will be managed according to surgeon's discretion. Patients with TBI who are on antiplatelet agents will receive a platelet transfusion based solely on surgeon discretion. A platelet map TEG will be obtained on all patients and will be repeat following platelet transfusion in patients who receive this therapy. We will only measure platelet function and the impact of platelet transfusion once within the first 24 hours following arrival to the trauma center. In instances where a followup head CT scan is obtained, the change in the size of the hemorrhagic lesion will be assessed between the admission CT scan and the first followup scan.

If no specific interventions are required and this is only a retrospective or prospective observational study, include that language here. Such as: "Prospective observational study only. Patients will be managed according to surgeon's discretion."

Outcomes Measures:

Primary Outcome:

(List here)

The primary outcome of the study is the difference in percentage of AA or ADP receptor inhibition and the difference in the MA-AA or MA-ADP : MA-CK ratio before and after platelet transfusion.

Secondary Outcomes:

(List here)

The secondary outcome of the study involves correlating the degree of resolution of thrombocytopenia as defined above with radiographic progression of the brain injury, hospital length of stay, mortality, and destination for discharge.

Variables:

List the specific variables to be collected and analyzed here. For organization, it is useful to divide these into categories for consideration. Examples of categories might include: Demographics, Admission physiology, Management variables, Surgical variables, Outcomes

1. Demographics: Age, gender, injury severity score, mechanism of injury, head abbreviated injury score, use of aspirin, use of clopidogrel
2. Initial indices in the trauma bay: Systolic blood pressure, serum lactate (when available), arterial base deficit (when available), blood alcohol level (when available), hemoglobin, platelet count, INR, arterial pH (when available)
3. Interventions: Number of units of (single donor equivalent) platelets transfused
4. Outcome Measurements:
 - a. Platelet map TEG measurements (MA-CK, MA-AA, MA-ADP, percent inhibition AA, percent inhibition ADP) before and after platelet transfusion.
 - b. Platelet count after platelet transfusion
 - c. Change in the size of the hemorrhagic lesion as assessed by a radiologist using CT scan before and after platelet transfusion. All measurements will be recorded only during the first 24 hours following admission.
 - d. Need for craniotomy or craniectomy following platelet transfusion
 - e. Hospital length of stay
 - f. Discharge destination: Home, rehabilitation, skilled nursing facility, morgue

Data Collection and Statistical Analysis:

Outline the data collection plan and statistical analysis plan succinctly here

An example might include:

- *Standardized data will be collected for each patient (see data sheet, Appendix A). Risk factors for failure to achieve primary closure of the open abdomen will be assessed using univariate and multivariate analysis.*
- *Continuous variables will be compared using Student's t-test and the Mann Whitney U test. The Chi-squared tests or Fisher's exact test will be used to compare categorical variables. All variables with a p value <0.2 on univariate analysis will be entered into a multivariable logistic regression analysis to identify independent risk factors for failure to achieve primary fascial closure and development of complications. Data will be reported as adjusted odds ratios with 95 % confidence intervals. Statistical significance will be set at a $p < 0.05$.*

Standardized data will be collected for each patient as noted in the attached data sheet. Statistical analysis will be performed by a PhD biostatistician. Continuous variables will be compared using the students T-test or the Mann Whitney U test based on sample size and distribution of the data.

Categorical variables will be assessed using the chi-square test.

Because there are no previous studies upon which to base a power analysis, we intend to enroll 500 patient's as an arbitrary endpoint.

Consent Procedures:

Outline consent procedures here, if applicable. As an example for a prospective study where waiver of consent will be sought, verbiage might include:

"This is a prospective observational study, designed to prospectively record data on patients who are managed according to institutional patient management protocols. Thus, waiver of informed consent is requested. Data will be recorded on a data sheet and transferred to a secured database that is devoid of patient identifiers."

This is a prospective observational study, designed to prospectively record data on patients who are managed according to his additional patient management protocols and individual surgeon's discretion. Thus, waiver of informed consent is requested. Data will be recorded on a data sheet and transfer to a secure database that is devoid of patient identifiers.

Risk/ Benefit Analysis:

Succinctly outline a risk / benefit analysis. An example of this might include:

*"The incidence and natural history **DISEASE PROCCES TO BE STUDIED** is unknown. If the optimal timing for and type of intervention can be identified to optimize outcomes in these patients, then significant benefit will result."*

Because this is a prospective observational study that will not alter the care rendered, there is very little risk associated with the study.

Instructions for submitting data collection tools:

All data submissions should be entered through the EAST Multicenter Trial Taskforce website portal. Instructions can be found on the EAST website. The data collection sheet located under the Multicenter Trial Taskforce heading for this study can be utilized to record the data, and then the information transferred to the portal entry system. For any questions regarding this study, please contact the PI.

References:

Include a brief listing of key references here:

1. Bachelani AM, Bautz JT, Sperry JL, et al. Assessment of platelet transfusion for reversal of aspirin after traumatic brain injury. *Surgery* 2011;150:836-43.
2. Castellino FJ, Chapman MP, Donahue DL, et al. Traumatic brain injury causes platelet adenosine diphosphate and arachidonic acid receptor inhibition independent of hemorrhagic shock in humans and rats. *J Trauma Acute Care Surg* 2014;76:1169-76.
3. Davis PK, Musunuru H, Walsh M, et al. Platelet dysfunction is an early marker for traumatic brain injury-induced coagulopathy. *Neurocrit Care* 2013;18:201-8.
4. Downey DM, Monson B, Butler KL, et al. Does platelet administration affect mortality in elderly head-injured patients taking antiplatelet medications? *Am Surg* 2009;75:1100-3.
5. Joseph B, Pandit V, Aziz H, et al. Clinical outcomes in traumatic brain injury patients on preinjury clopidogrel: a prospective analysis. *J Trauma Acute Care Surg* 2014;76:817-20.
6. McCully SP, Schreiber MA. Traumatic brain injury and its effect on coagulopathy. *Semin Thromb Hemost* 2013;39:896-901.
7. Nekludov M, Bellander BM, Blomback M, Wallen HN. Platelet dysfunction in patients with severe traumatic brain injury. *J Neurotrauma* 2007;24:1699-706.
8. Nishijima DK, Shahlaie K, Sarkar K, Rudisill N, Holmes JF. Risk of unfavorable long-term outcome in older adults with traumatic intracranial hemorrhage and anticoagulant or antiplatelet use. *Am J Emerg Med* 2013;31:1244-7.
9. Sillesen M, Johansson PI, Rasmussen LS, et al. Platelet activation and dysfunction in a large-animal model of traumatic brain injury and hemorrhage. *J Trauma Acute Care Surg* 2013;74:1252-9.
10. Washington CW, Schuerer DJ, Grubb RL, Jr. Platelet transfusion: an unnecessary risk for mild traumatic brain injury patients on antiplatelet therapy. *J Trauma* 2011;71:358-63.



**EAST MULTICENTER STUDY
DATA COLLECTION TOOL**

Multicenter Study: _ Reversal of pharmacologic platelet inhibition using platelet transfusion in patients with traumatic brain injury

Enrolling Center: _____
Enrolling Co-investigator: _____

Demographics / Injury Variables:

Age: _____ Gender: _____

Mechanism of initial injury: Blunt Penetrating

ISS: _____ AIS Head: _____

Nature of TBI: EDH SDH SAH IPH DAI Skull fracture only

Admission Lab values:

Hemoglobin: _____ pH: _____ INR: _____ Lactate: _____ Base Deficit: _____

Platelet Count _____

TEG: %inhibition AA _____ %inhibition ADP _____ MA(CK) _____ MA(AA) _____ MA(ADP) _____

Size of intracranial hemorrhage _____ cm³

Management Variables:

Time from injury to platelet transfusion (in hours): _____

Number of units of platelets transfused (single donor equivalents) _____

Outcomes: (following platelet transfusion)

Platelet count _____

Hemoglobin: _____ pH: _____ INR: _____ Lactate: _____ Base Deficit: _____

TEG: %inhibition AA _____ %inhibition ADP _____ MA(CK) _____ MA(AA) _____ MA(ADP) _____

Repeat head CT: Size of intracranial hemorrhage _____ cm³

Time between initial and repeat CT of head (hours) _____

Did the patient undergo craniectomy/craniotomy within 12 hours of arrival Yes No

Did the patient undergo craniectomy/craniotomy more than 12 hours following arrival Yes No

Hospital LOS: _____ ICU LOS: _____

Mortality (circle one): YES NO

Discharge destination: Home SNF/Rehab Morgue