EAST Multicenter prospective observational study of trauma patients on antiplatelet agents

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Research Strategy

Significance

With the introduction of more potent P2Y12 inhibitors comes a new challenge to trauma surgeons when faced with patients taking these medications. These agents possess more reliable pharmacologic antiplatelet properties than clopidogrel. Which is favorable since clopidogrel has been shown to have <25% inhibition of platelet activity in up to 30% of patients.[1] Along with increased platelet inhibition comes increased bleeding events.[2] With promising characteristics of decreased all-cause mortality and cardiovascular events, there has been an increase in these agents use compared to clopidogrel.[1] Little is known about the effect of these agents when a patients is injured.

Through examination of various antiplatelet agents, trauma surgeons will gain valuable knowledge when faced with patients taking these medications. Particular areas of information include; comparative bleeding events between agents, monitoring for progression of bleeding events and reversal strategy efficacy and risks. Successful completion of the study's aims will provide clinical evidence in the management of trauma patients taking antiplatelet agents.

Innovation

As innovation of newer antiplatelet agents occurs, trauma surgeons must gain clinical evidence in the approach to these medications. Through this multicenter, prospective trial, valuable information will assist clinicians in the management of trauma patients taking newer P2Y12 inhibitors. To date, there are no studies examining these newer agents in trauma patients.

Specific Aims

1. Discern any difference in bleeding severity of ticagrelor/prasugrel compared to clopidogrel with or without concomitant aspirin use (low dose vs. high dose).

2. Document effect of platelet transfusion on outcomes following injury in patients on antiplatelet agents including progression of traumatic brain injury, bleeding requiring surgery, angiography, or other intervention, re-bleeding following intervention, and death.

3. Document effect of Desmopressin (DDAVP) on outcomes following injury in patients on antiplatelet agents including progression of traumatic brain injury, bleeding requiring surgery, angiography, or other intervention, re-bleeding following intervention, and death.

4. Describe the variations between centers in the management and reversal strategies of antiplatelet agents in trauma patients along with monitoring of antiplatelet activity

5. Comparison of bleeding events of patients on antiplatelet agents to other oral anticoagulants will be performed.

Approach

We seek to ascertain information on the optimal management of trauma patients on newer antiplatelet agents through a multicenter, prospective trial. This will allow data analysis of various approaches to their trauma management as well as provide information on the bleeding significance when agents are compared.

Study design

Prospective, multi-center, observational study of patients on antiplatelet agents or oral anticoagulants evaluated at Level 1, 2 or 3 Trauma Centers. Data and outcomes will be observational and involve no prescribed therapeutic interventions or alterations from standard patient care. Institutions and providers will conduct normal diagnosis and management procedures without interference from this study.

Inclusion Criteria: The following criteria must be met for patients to be eligible for this study:

1) All patients consulted on or admitted by the trauma service, including inter-facility transfers will be eligible for inclusion.
2) Currently on aspirin, clopidogrel, prasugrel, ticagrelor OR
3) Currently on anticoagulants (warfarin, dabigatran, edoxaban, rivaroxaban, apixaban, betrixaban

Exclusion Criteria

1) Prisoners or inmate status
2) Patients <18 years of age
4) Pregnancy

Data collected will include:

1) Demographics such as age, gender, race*
2) Injuries and injury severity*
3) Initial assessment and management such as laboratory values of coagulation including TEG, CT findings, need for surgery/angiography, transfusion of blood products*
4) Outcomes such as bleeding, re-bleeding and death*

*See data collection sheet

Enrollment need not be limited to centers with TEG/ROTEM or platelet function analysis capabilities, but if they are in use as part of the centers routine trauma protocols, we would appreciate the collection of this additional information. We will plan to specifically invite centers

who do use TEG/ROTEM or platelet function analysis as part of their trauma protocols. Our goal is to have 50% of centers utilizing TEG/ROTEM or platelet function analysis.

Patient consent and Risk
This is an observational study that will not alter institutional management protocols or patient care, as such enrollment in this study will pose no additional medical risk to participants. Thus, waiver of informed consent is requested. Data will be recorded on a data sheet via a secured database that is devoid of patient identifiers thus posing minimal risk of breach of confidentiality.

Data collection
The study will be carried out though a secure, deidentified web-based data entry system, REDCap. Each center will be able to enter their data in a secure data collection instrument; allowing study staff to monitor subjects. Communication via secure email, telephone and monitoring the data collection instrument will provide exchange of information and questions. The University of Florida College of Medicine- Jacksonville (UFCOM-J) Department of Surgery has an experienced research coordinator and research assistants to assist with this trial.

Timeline
This study will be completed over a 30 month period

1) Recruitment of centers and IRB approval 4 months
2) Enrollment of patients 12-24 months
3) Data analysis and manuscript preparation 2 months

Analysis
After review of contemporary studies addressing antiplatelet agents in trauma patients, one study found 7.9% of trauma patients were taking antiplatelet agents.[3]It is estimated that 1,500 to 2,000 patients would need to be enrolled. With total centers enrolled needing to be approximately 15. This is based off Kobayashi et al's study looking at novel oral anticoagulants, as they also looked at aspirin and clopidogrel.[4]

Comparisons will be made on bleeding severity using transfusion requirements and AIS grades for patient on different agents. Additionally, reversal strategies and outcomes will be measured, if given; comparing those that receive attempts at reversal versus not. The endpoints listed above will then be compared between the different groups. The statistics performed will be t-tests and/or Mann-Whitney U and chi-square. Logistic regressions will also be used to evaluate for any end-data point with $p<0.2$ associated with increased severity or reversal.

IRB
The UFCOM-J will be the studies primary IRB (Approved, IRB 201702366). Each institution participating will be asked obtain institutional approval and adhere to their institutions' IRB protocol's regarding multicenter trials. This is an observational study that will not alter institutional management protocols or patient care, as such enrollment in this study will pose no additional medical risk to participants. Thus, waiver of informed consent is requested. Data will

be recorded on a web-based data sheet and transferred to a secured database that is devoid of patient identifiers. Thus, posing minimal risk of breach of confidentiality.

Impact

The results of this study will inform clinicians about the possible risks of increased bleeding events in trauma patient taking the newer P2Y12 compared to other antiplatelet agents and compare with other anticoagulants. Additionally, data collected in this study will assist clinicians with management strategies to mitigate progression of bleeding events, should modalities show efficacy.

References

1. Ferro A. Newer antiplatelet agents in acute coronary syndrome. Br med J. 2016;352:h7025.
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3. Bonville DJ, Ata A, Jahraus CM, et al. Impact of preinjury warfarin and antiplatelet agents on outcomes of trauma patients. Surgery. 2011;150(4):861-868.
4. Kobayashi L, Barmparas G, Borsage P, et al. Novel oral anticoagulatns and trauma: The results of a prospective American Association for the Surgery of Trauma Multi-Institutional Trial. J Trauma Acute Care Surg. 2017;82(5):827-835.