

EAST Multi-Center Trial Proposal

Title: Cerebrovascular injury Antithrombotic Therapy in Trauma

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Background & Significance:

Blunt cerebrovascular injury (BCVI) occurs in 2-3% of polytrauma patients and is associated with significant morbidity and mortality, primarily due to stroke [1,2,3,4]. Timely screening for BCVI, and the prevention of stroke have been key topics of investigation in the literature for the last several decades. Without pharmacological prophylaxis, patients with BCVI are at an inherently high risk for stroke, and this serious complication can occur early after injury. Studies of patients with BCVI-related stroke show more than half occur within 72 hours of admission (61%) [5]. Due to more liberal screening, more patients are diagnosed with BCVI than in the past, particularly those with low grade, clinically asymptomatic BCVI [1,3]. The evidence accumulated over the three decades unequivocally supports the use of prophylactic antithrombotic therapy in patients who have BCVI and no contraindications to anticoagulation, with reduction in stroke rates from 19-32% to 0.5-5% [6,7,8,4]. The majority (65%) of strokes in treatment eligible patients occur before initiation of antithrombotic therapy, further emphasizing the importance of early liberal screening and treatment [9]. As such, the current standard of care guidelines from the “Eastern Association for the Surgery of Trauma” and “Western Trauma Association” both include early initiation of antithrombotic therapy as cornerstones in management of patients with BCVI.

Despite much investigation on early liberal screening and the benefit of anti-thrombotic therapy if BCVI is identified, there are no definitive data on the ideal pharmacological regimen for stroke prophylaxis in BCVI. Numerous studies have shown no difference in the incidence of stroke between patients treated with systemic anticoagulation compared to those treated with antiplatelet therapy [6,10,11,2,3,12]. While some studies report lower incidence of stroke in patients treated with antiplatelet therapy [13,14], others have reported lower incidence of stroke in patients managed with systemic anticoagulation [15]. With the lack of substantive evidence supporting one regimen or the other, the existing literature shows clinical equipoise between antiplatelet therapy and systemic anticoagulation for the prevention of BCVI-related stroke. Although there is no definitive evidence showing clinical superiority of either regimen, there are reports of greater incidence of hemorrhagic complication and readmission in patients treated with systemic anticoagulation [14,11].

Innovation & Impact:

There has yet to be a large prospective trial comparing the efficacy of aspirin and systemic anticoagulation in patients with BCVI. Such a study is warranted to determine which therapy provides the best stroke prophylaxis while minimizing associated sequelae and cost. Due to liberal screening protocols and timely prophylaxis, the incidence of stroke in trauma patients with BCVI is rare. As such, a common limitation of studies of BCVI-related stroke are small sample sizes and retrospective designs. However, the diagnosis of BCVI is more frequently made today, making the clinical question of aspirin versus systemic anticoagulation common in the surgical ICU.

The study of BCVI related stroke is ideally suited for a prospective multi-center observational trial. Both treatments, aspirin and systemic anti-coagulation (typically IV Heparin), are considered to be standard of care treatment in injured patients with BCVI. Therefore, participation in this study requires no deviation from existing standard of care, presenting no more than minimal risk to research subjects. Conducting this study with the cooperation of multiple trauma centers is critical to achieving the required sample size necessary to determine clinical superiority in a low-incidence disease process such as BCVI related stroke.

A large prospective study has the potential to determine preferred stroke prophylaxis in patients with BCVI as well as to help minimize potential therapy related sequela. Additionally, the reduced use of IV systemic anticoagulation presents the opportunity to reduce hospital cost and nursing staff burden due to less expensive and time consuming therapy and monitoring.

Study Aims / Hypotheses:

Primary Aim:

To evaluate the efficacy of aspirin and systemic anticoagulation therapies for stroke prophylaxis in patients with traumatic BCVI. We hypothesize that antiplatelet therapy will be non-inferior to systemic anticoagulation in preventing strokes, as measured by incidence of stroke in each treatment group.

Secondary Aims:

To determine the incidence of progression and resolution of BCVI among antiplatelet and anticoagulation cohorts on follow up CT scan. We hypothesize that antiplatelet therapy will be non-inferior to systemic anticoagulation in time to resolution and will be associated with a decreased risk of progression, as measured by radiographic findings on CTA and recurrence of stroke symptoms respectively.

To evaluate the effect of aspirin and systemic anticoagulation therapies on mortality risk in patients with traumatic BCVI. We hypothesize that antiplatelet therapy will be associated with a reduced risk of mortality as compared to systemic anticoagulation, as measured by incidence of mortality in both groups.

To determine the incidence and significance of hemorrhagic complications associated with aspirin and systemic anticoagulation therapy for stroke prophylaxis in patients with traumatic BCVI. We hypothesize that the use of systemic anticoagulation will be associated with an increased incidence of hemorrhagic complications, and that such complications will be associated with increased morbidity.

To investigate time to stroke prophylaxis therapy initiation and time from therapy initiation to complication in patients with traumatic BCVI. We hypothesize that there will be a decreased time from injury to initiation of stroke prophylaxis in the antiplatelet group compared to the systemic anticoagulation group. We hypothesize that there will be a decreased time between initiation of stroke prophylaxis and hemorrhagic complication in the systemic anticoagulation group as compared to the antiplatelet group.

To evaluate management and outcomes for low grade traumatic BCVI. We hypothesize that antiplatelet therapy will be non-inferior to systemic anticoagulation in the prevention of strokes in patients with low grade traumatic BC VI, as measured by incidence of stroke.

To investigate the management and outcomes for patients with concomitant TBI and BCVI. We hypothesize that antiplatelet therapy will be associated with a reduced risk of hemorrhagic and will be non-inferior to systemic anticoagulation in the prevention of strokes, as measured by incidence of hemorrhagic complication and stroke.

Methods:

Design: Prospective multi-institutional observational study

Inclusion Criteria: All adult (>17 years of age) trauma victims with blunt mechanism of injury and CTA confirmed grade 1-4 cerebrovascular injury to one or more carotid or vertebral arteries who begin antithrombotic therapy within 36 hours of admission. Patients with traumatic brain injury will be included if they begin antithrombotic therapy within 36 hours of a stable CTA head.

Exclusion Criteria: Patients with stroke present on admitting CTA, patients with known pre-existing coagulopathy, children (<18 years of age), pregnant patients, patients with penetrating mechanism of injury, and patients with severe hemorrhage requiring massive transfusion protocol.

Description of project course:

Participating sites would enroll all admitted trauma patients in accordance with the above inclusion/exclusion criteria to the study prospectively over the course of 12 months. Patients will be identified as eligible and enrolled in the study on admission. Variables to be collected will be abstracted from the trauma registry at participating sites and will be entered in a de-identified manner to a secure REDCAP system organized by the University of Kentucky. All participating

sites will be required to complete and submit a data-use agreement with the University of Kentucky. All patient information will be managed in accordance with IRB procedures.

Outcomes:

Primary outcome: Incidence of stroke in patients diagnosed with BCVI.

Secondary Outcomes: Incidence and description of hemorrhagic complications in patients with BCVI. Time from admission to antithrombotic therapy initiation and to stroke.

Variables to be Collected:

See attached data collection file for complete list of included variables.

Methods of Data Collection:

Automated query and manual data abstraction from the trauma registry followed by manual data entry into REDCAP system.

Statistical Considerations & Data Analysis:

Statistical Methods:

Comparison of stroke incidence, incidence of hemorrhagic complications, mortality, and other discrete variables between antithrombotic therapy groups will be conducted with fisher's exact tests and chi-square analysis. Comparison of time to stroke, time to therapy initiation, and other continuous variables will be conducted with ANOVA or Mann-Whitney U test. Statistically ($p < 0.05$) and clinically significant variables will be included in multi-variate logistic regression to evaluate odds ratio of stroke in aspirin and systemic anticoagulation cohorts.

Enrollment & Informed Consent:

This proposed study is an observational study and requires no deviation from the existing standard of care. This study involves no patient allocation to treatment groups and does not include treatments that are not currently considered standard of care. As such, it presents no more than minimal risk to patients and we are requesting waiver of informed consent.

References:

1. Geddes AE, Burlew CC, Wagenaar AE, Biffi WL, Johnson JL, Pieracci FM, Campion EM, Moore EE. Expanded screening criteria for blunt cerebrovascular injury: a bigger impact than anticipated. *Am J Surg*. 2016 Dec;212(6):1167-1174. doi: 10.1016/j.amjsurg.2016.09.016. Epub 2016 Sep 29. PMID: 27751528.
2. Kim DY, Biffi W, Bokhari F, Brakenridge S, Chao E, Claridge JA, Fraser D, Jawa R, Kasotakis G, Kerwin A, Khan U, Kurek S, Plurad D, Robinson BRH, Stassen N, Tesoriero R, Yorkgitis B, Como JJ. Evaluation and management of blunt cerebrovascular

injury: A practice management guideline from the Eastern Association for the Surgery of Trauma. *J Trauma Acute Care Surg.* 2020 Jun;88(6):875-887. doi: 10.1097/TA.0000000000002668. Erratum in: *J Trauma Acute Care Surg.* 2020 Aug;89(2):420. PMID: 32176167.

3. Biffi WL, Cothren CC, Moore EE, Kozar R, Cocanour C, Davis JW, McIntyre RC Jr, West MA, Moore FA. Western Trauma Association critical decisions in trauma: screening for and treatment of blunt cerebrovascular injuries. *J Trauma.* 2009 Dec;67(6):1150-3. doi: 10.1097/TA.0b013e3181c1c1d6. PMID: 20009659.
4. Shahan CP, Croce MA, Fabian TC, Magnotti LJ. Impact of Continuous Evaluation of Technology and Therapy: 30 Years of Research Reduces Stroke and Mortality from Blunt Cerebrovascular Injury. *J Am Coll Surg.* 2017 Apr;224(4):595-599. doi: 10.1016/j.jamcollsurg.2016.12.008. Epub 2017 Jan 19. PMID: 28111193.
5. Burlew CC, et al. Time to stroke: A Western Trauma Association multicenter study of blunt cerebrovascular injuries. *J Trauma Acute Care Surg.* 2018 Nov;85(5):858-866. doi: 10.1097/TA.0000000000001989. PMID: 29847537.
6. Cothren CC, Biffi WL, Moore EE, Kashuk JL, Johnson JL. Treatment for blunt cerebrovascular injuries: equivalence of anticoagulation and antiplatelet agents. *Arch Surg.* 2009 Jul;144(7):685-90. doi: 10.1001/archsurg.2009.111. PMID: 19620551.
7. Lauerman MH, Feeney T, Sliker CW, Saksobhavit N, Bruns BR, Laser A, Tesoriero R, Brenner M, Scalea TM, Stein DM. Lethal now or lethal later: The natural history of Grade 4 blunt cerebrovascular injury. *J Trauma Acute Care Surg.* 2015 Jun;78(6):1071-4; discussion 1074-5. doi: 10.1097/TA.0000000000000654. PMID: 26151505.
8. Kelley W, Zreik K, Gergen A, Williams J, Jacobson LE, Nahmias J, Tatar A, Murry J, Grigorian A, Ong A, Stein DM, Scalea TM, Lauerman MH. Early Pharmacologic Therapy in Patients With Blunt Cerebrovascular Injury and TBI: Is it Safe and Effective? An EAST Multicenter Study. *Am Surg.* 2024 Jan 22:31348241230094. doi: 10.1177/00031348241230094. Epub ahead of print. PMID: 38253324.
9. Barrera D, Sercy E, Orlando A, Mains CW, Madayag R, Carrick MM, Tanner A 2nd, Lieser M, Acuna D, Yon J, Bar-Or D. Associations of Antithrombotic Timing and Regimen with Ischemic Stroke and Bleeding Complications in Blunt Cerebrovascular Injury. *J Stroke Cerebrovasc Dis.* 2020 Jun;29(6):104804. doi: 10.1016/j.jstrokecerebrovasdis.2020.104804. Epub 2020 Apr 16. PMID: 32305279.
10. Catapano JS, Israr S, Whiting AC, Hussain OM, Snyder LA, Albuquerque FC, Ducruet AF, Nakaji P, Lawton MT, Weinberg JA, Zabramski JM. Management of Extracranial Blunt Cerebrovascular Injuries: Experience with an Aspirin-Based Approach. *World Neurosurg.* 2020 Jan;133:e385-e390. doi:10.1016/j.wneu.2019.09.013. Epub 2019 Sep 12. PMID: 31521761.
11. Leverich M, Afifi AM, Rejent K, Ren G, Nazzal M, Osman MF. Mortality and morbidity following initiation of anticoagulant or antiplatelet treatment for blunt cerebrovascular

injury. *J Vasc Surg.* 2023 Sep;78(3):788-796.e6. doi: 10.1016/j.jvs.2023.05.031. Epub 2023 Jun 14. PMID: 37318429.

12. Biffi WL, Ray CE Jr, Moore EE, Franciose RJ, Aly S, Heyrosa MG, Johnson JL, Burch JM. Treatment-related outcomes from blunt cerebrovascular injuries: importance of routine follow-up arteriography. *Ann Surg.* 2002 May;235(5):699-706; discussion 706-7. doi: 10.1097/00000658-200205000-00012. PMID: 11981216; PMCID: PMC1422496.
13. Bonow RH, Witt CE, Mossa-Basha M, Cuschieri J, Arbabi S, Vavilala MS, Rivara FP, Chesnut RM. Aspirin versus anticoagulation for stroke prophylaxis in blunt cerebrovascular injury: a propensity-matched retrospective cohort study. *J Neurosurg.* 2021 Mar 26;135(5):1413-1420. doi: 10.3171/2020.10.JNS201836. PMID: 33770758.
14. Momic J, Yassin N, Kim MY, Walser E, Smith S, Ball I, Moffat B, Parry N, Vogt K. Antiplatelets versus anticoagulants in the treatment of blunt cerebrovascular injury (BCVI) - A systematic review and meta-analysis. *Injury.* 2024 Apr;55(4):111485. doi: 10.1016/j.injury.2024.111485. Epub 2024 Feb 27. PMID: 38452701.
15. Hanna K, Douglas M, Asmar S, Khurram M, Bible L, Castanon L, Ditillo M, Kulvatunyou N, Joseph B. Treatment of blunt cerebrovascular injuries: Anticoagulants or antiplatelet agents? *J Trauma Acute Care Surg.* 2020 Jul;89(1):74-79. doi: 10.1097/TA.0000000000002704. PMID: 32251264.