Study title: Safety of therapeutic anticoagulation in patients with traumatic brain injury: a multi-center prospective observational study

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Background & Significance:

Severely injured patients are at high risk for the development of venous thromboembolism (VTE). Despite aggressive mechanical and chemical prophylaxis, the incidence of VTE in trauma patients is reported to be as high as 40% in previous literature (1). Traumatic brain injury (TBI) is associated with an even higher incidence of VTE (2). Anticoagulation therapy (ACT) with different types of anticoagulants is considered as a primary treatment for the new onset VTE (3). ACT is also required if patients have other medical conditions including atrial fibrillation or mechanical heart valve (4, 5).

However, serious adverse events related to ACT, most importantly the progression of TBI, can be life-threatening. Care providers often face a dilemma between the risks of ACT versus thromboembolic complications in patients with TBI. Currently, a decision on initiating ACT is usually based on anecdotal experiences or expert opinions as there is scarce data regarding the safety of ACT following TBI (6). Our group conducted a single-center retrospective study which showed preliminary data regarding the safety of ACT in patients with TBI (This paper will be presented at the 29th EAST Annual Scientific Assembly) (7). We found that 8.3% of the study patients had progression of TBI on the repeat CT after ACT without neurological deterioration. Age ≥65 years was significantly associated with the progression of TBI after ACT. Hence, we sought to design a prospective study to validate our results.

Specific aim of multicenter study

Primary aim: To describe the current practice of ACT in TBI patients (indications, timing, type of anticoagulant) and their outcomes.

Secondary aim: To identify factors associated with the progression of TBI in patients who received ACT. To compare the outcomes including the progression of TBI and thromboembolic events in patients receiving ACT to a matched cohort of patients not receiving ACT

Experimental design/methods

Inclusion criteria:

- Patients ≥ 18 years of age
- Computed tomography-proven TBI
    - Subdural hematoma
    - Epidural hematoma
    - Intraparenchymal hemorrhage
    - Subarrachnoid hemorrhage

- Received anticoagulation therapy within 30 days of the initial injury
    - Unfractionated heparin
    - Low molecular weight heparin
    - Vitamin K antagonist
    - Direct thrombin inhibitor
    - Direct ani-Xa inhibitor
    - Other anticoagulants

Exclusion criteria:

- Patients of less than 18 years of age
- Pregnancy
- Patients transferred from outside institutions on therapeutic anticoagulation therepy
- Jail patients

Therapeutic interventions:
Prospective observational study only. Patients will be managed according to surgeon's discretion and/or institutional protocol.

Primary outcome: incidence of clinically significant progression of TBI following ACT

Secondary outcomes: incidence of the progression of hemorrhagic TBI on repeat CTs, major hemorrhagic complications, 30- and 60-day mortality, discharge functional status (Extended Glasgow Outcome Scale), discharge location (home, long-term acute care facility, rehabilitation facility, skilled nursing facility)

Variables:

- Patient baseline demographics
- Admission physiology
- Injury information
- Imaging (type of TBI, Rotterdam score)
- Management variables
- Indication for anticoagulation therapy
- Outcomes

Data collection and statistical analysis

Standard data will be collected for each patient enrolled in the study (below). Risk factors for the progression of TBI (clinical, radiographic) will be examined using univariate and multivariate analysis. We will report the mean values for parametric continuous variables and median values for non-parametric data. In univariable analyses, we will use Student-t test or Fisher's exact test for continuous variables and chi-square test or Mann-Whitney test for categorical variables as appropriate. Subsequently, multiple logistic regression models were created for each outcome adjusting for clinically significant potential confounders. We reported odds ratios (ORs) and 95% confidence intervals (CIs) for all variables.

1. Demographics
   Age
   Sex
   Race/Ethnicity: Caucasian/African American/Latino/Asian/Other
   Major comorbidities
   Charlson comorbidity index (Appendix 1)

   Height (cm)
   Weight (kg)
   BMI (calculated)
   Admission Vital signs
      SBP
      HR
      Glasgow Coma Scale (E: M: V:)
   Admission laboratory
      Na
      aPTT
      PT INR
      Hgb
      Platelets

2. Injury data

Mechanism of injury (GSW/SW/MVC/MCC/AVP/Assault/Fall/Other)
Injury severity score
Abbreviated injury scale (head region)
Type of TBI
SDH: max mm EDH: max mm SAH IPH/contusion DAI other:
Midline shift? mm
Rotterdam score on initial CT (Appendix 2)
Surgical procedures (y/n, list)
ICP monitoring (EVD/Bolt/Other)
Associated injuries

3. Data regarding ACT

Pre-/post-injury indication
Type of anticoagulant
Dosage
Timing of the initiation (post injury day #)
Monitoring laboratory values (aPTT, PT INR, anti-Xa level)

4. Outcome variables

Major complications related to ACT

a. Clinically significant neurological change (decrease in GCS <2, required higher level of care, neurosurgical interventions)
b. Progression of hemorrhagic TBI on the repeat CT scans (interpreted by attending radiologists at each participating site)
c. Clinically significant bleeding complications on ACT (required transfusion, surgical or IR intervention)

30- and 60-day mortality

Hospital length of stay
ICU length of stay
Mechanical ventilator days
Discharge functional outcome (extended Glasgow Outcome Scale: GOSE) (Appendix 3)
Discharge disposition

Consent procedures

This is a prospective observational study. Waiver of informed consent is requested. No intervention will be performed and no change in patient management will occur as a result of this study being conducted. All data will be collected by the research personnel, in a secure database with patient identifiers, but those identifiers will be coded with and kept in a secure locker or password-protected computers.

Risk/Benefit analysis

There is scarce data regarding the safety of anticoagulation therapy in patients with traumatic brain injury. If the risk factors for the progression of TBI following anticoagulation therapy can be identified to optimize outcomes in these patients, then significant benefit will result.

References

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Appendix 1. Charlson comorbidity index

Weight	Clinical condition
1	Myocardial infarct
	Congestive cardiac insufficiency
	Peripheral vascular disease
	Dementia
	Cerebrovascular disease
	Chronic pulmonary disease
	Conjunctive tissue disease
	Slight diabetes, without complications
	Ulcers
	Chronic diseases of the liver or cirrhosis
2	Hemiplegia
	Moderate or severe kidney disease
	Diabetes with complications
	Tumors
	Leukemia
	Lymphoma
3	Moderate or severe liver disease
6	Malignant tumor, metastasis
	Aids

Figure 1 - Charlson comorbidity index – weighting of the clinical conditions present among secondary diagnoses.

Appendix 2. Rotterdam score on initial head CT

TABLE 1. Rotterdam Computed Tomography Classification[a]

Predictor	Score
Basal cisterns	
Normal	0
Compressed	1
Absent	2
Midline shift	
No shift or shift ≤5 mm	0
Shift >5 mm	1
Epidural mass lesion	
Present	0
Absent	1
Intraventricular blood or subarachnoid hemorrhage	
Absent	0
Present	1
Sum score	+1

Appendix 3. Extended Glasgow Outcome Scale

Tabla 2. *Extended Glasgow Outcome Scale* (GOSE)[5]

1	Muerte
2	Estado vegetativo
3	Dependencia completa de otros
4	Dependencia de otros para algunas actividades
5	Incapacidad para volver al trabajo o participar en actividades sociales
6	Vuelta al trabajo con capacidad reducida, participación reducida en actividades sociales
7	Buena recuperación con déficit mental y social leve
8	Buena recuperación sin déficit

TAC in TBI study data collection sheet

Please fill out as completely as possible and indicate if data points are unknown or unavailable

Enrolling center:

Length of follow up: _____ days

Patient demographics and injury variables

Age:

Sex: Male Female

Race/Ethnicity: Caucasian African American Latino Asian Other

Charlson comorbidity index**:** _____ points
Please list positive conditions ( )

Weight (kg) / Height (cm): /

BMI

Physiological variables at arrival to emergency room: HR SBP GCS (E: M: V:)

Laboratory variables upon admission: (Na: aPTT: PT INR: Platelets: Hgb:)

Mechanism of injury: GSW SW MVC MCC AVP Assault Fall other:

Injury Severity Score:

AIS Head:

Type of TBI: SDH: max mm EDH: max mm SAH IPH/contusion DAI other:

Rotterdam score on initial CT:

Midline shift? _____ mm

Surgical interventions: Yes No (if yes, please specify:)

ICP monitoring: Yes No (if yes, EVD Bolt Other)

Associated injuries:

Transfer from another hospital? Yes No

TAC variables

Pre-injury indications: atrial fibrillation DVT PE mechanical heart valve other:

Post-injury indications: DVT PE atrial fibrillation other:

Timing of TAC: post-injury day #

Type of TAC: IV UFH infusion LMWH SC Coumadin Fondaparinux Argatroban Rivaroxaban other:

How many repeat CT obtained before TAC?

"Stable CT" before TAC? Yes No

Was patient in ICU when TAC initiated? Yes No

Monitoring laboratory values: PTT PT INR anti-Xa level other:

Was anticoagulation in therapeutic range >80% of time? Yes No

How many head CT obtained after TAC? Yes: __/__/__/__/__ hours after TAC No

Outcome variables

Neurological deterioration after TAC? Yes No

If Yes, how many hours after TAC initiated? _____ Hours

Any intervention required? Yes: _____ No

Was TAC discontinued? Yes No

Was TAC resumed? Yes: ____ days after No

Other bleeding complications related to TAC: Yes No

If yes, please specify:

Radiological progression of hemorrhagic TBI on repeat CT? Yes: _____ hours after TAC No

If Yes, was TAC discontinued? Yes No

Any intervention required? Yes: _____ No

Was TAC resumed? Yes: ____ days after No

Mortality: Yes: hospital day# _____ No

Major complications: Yes No

Hospital length of stay: _____ days

ICU length of stay: _____ days

Mechanical ventilation days: _____ days

Extended Glasgow Outcome Scale upon discharge:

Discharge location: Home LATC Rehab facility SNIF other: