
Primary investigator: Kazuhide Matsushima, MD

Email: kazuhide.matsushima@med.usc.edu

Co-Primary investigator: Stefan Leichtle, MD

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

Exclusion criteria:

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

Appendix 1. Charlson comorbidity index

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

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

Appendix 2. Rotterdam score on initial head CT

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal cisterns</td>
<td>0</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Compressed</td>
<td>1</td>
</tr>
<tr>
<td>Absent</td>
<td>2</td>
</tr>
<tr>
<td>Midline shift</td>
<td></td>
</tr>
<tr>
<td>No shift or shift ≤ 5 mm</td>
<td>0</td>
</tr>
<tr>
<td>Shift &gt; 5 mm</td>
<td>1</td>
</tr>
<tr>
<td>Epidural mass lesion</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>0</td>
</tr>
<tr>
<td>Absent</td>
<td>1</td>
</tr>
<tr>
<td>Intraventricular blood or subarachnoid hemorrhage</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
</tr>
<tr>
<td>Sum score</td>
<td>+1</td>
</tr>
</tbody>
</table>
Appendix 3. Extended Glasgow Outcome Scale

Tabla 2. Extended Glasgow Outcome Scale (GOSE)\textsuperscript{5}

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Muerte</td>
</tr>
<tr>
<td>2</td>
<td>Estado vegetativo</td>
</tr>
<tr>
<td>3</td>
<td>Dependencia completa de otros</td>
</tr>
<tr>
<td>4</td>
<td>Dependencia de otros para algunas actividades</td>
</tr>
<tr>
<td>5</td>
<td>Incapacidad para volver al trabajo o participar en actividades sociales</td>
</tr>
<tr>
<td>6</td>
<td>Vuelta al trabajo con capacidad reducida, participación reducida en actividades sociales</td>
</tr>
<tr>
<td>7</td>
<td>Buena recuperación con déficit mental y social leve</td>
</tr>
<tr>
<td>8</td>
<td>Buena recuperación sin déficit</td>
</tr>
</tbody>
</table>
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: