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Use of Anticoagulation Agents After Traumatic Intracranial Hemorrhage

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OBJECTIVE: **Anticoagulant therapy (ACT) after traumatic intracranial hemorrhage may lead to progression of hemorrhage, but in the presence of thromboembolic events, the clinician must decide if the benefits outweigh the risks. Currently, no data exist to guide therapy in the acute setting.**

METHODS: **We retrospectively identified all patients admitted to our institution with traumatic intracranial hemorrhage that received intravenous heparin, full-dose enoxaparin, or warfarin during their initial hospitalization over a 3-year period. We reviewed their demographics, hospital course, clinical indication and timing for initiation of ACT, and complications.**

RESULTS: **A total of 112 patients were identified. The median age and Glasgow Coma Scale score of these patients was 50.5 years and 9.5, respectively. Twenty-two patients required neurosurgical procedures for their presenting injury, including intracranial pressure monitors and/or open surgeries. Fifty-four patients had deep vein thrombosis or pulmonary embolism prior to initiation, and the remaining 20 patients had preexisting conditions or other indications for initiating ACT. The median time from injury to starting ACT was 8 days. Immediate complications occurred in 6 patients; however, none of these patients required a neurosurgical intervention. Delayed complications included progression of acute to chronic subdural hematoma that required intervention in 2 patients. One patient died from delayed hemorrhage.**

CONCLUSIONS: **For this patient population, the risk of immediate and delayed intracranial hemorrhages from initiating ACT therapy in intracranial injury must be weighed against the morbidity of delaying treatment. Although further studies are needed, our review provides the first rates of complications for this patient population.**

INTRODUCTION

Traumatic brain injury (TBI) has been demonstrated to be an independent risk factor for the development of venous thromboembolism (VTE).[1,2] The incidence of VTE in isolated head injury has been estimated at 25%, with the incidence in patients with major trauma approaching 60%.[1,3] Pulmonary embolism (PE) occurs in approximately 1.7% of patients with TBI and less than 1% of patients with major trauma, with a mortality rate estimated between 18% and 50%.[2,4] However, therapeutic anticoagulation use for the treatment of these conditions after TBI has not been examined.

Many studies have examined the safety and efficacy of prophylactic dosing of anticoagulants for the prevention of VTE and PE in the general neurosurgical and TBI patient populations. These studies have shown lower rates of deep vein thrombosis (DVT) and no increased incidence of hemorrhage when initiating prophylactic doses of subcutaneous heparin as early as 24 hours after stable imaging or postoperatively.[4,5]

Patients with preexisting conditions that require anticoagulation who suffer a TBI are another consideration. Per the National Hospital Ambulatory Medical Care Survey,[6] falls account for 40.5% of TBIs in all age groups, and this increases to 81.8% in older adults. Patients with falls who are older than 50 years of age are also twice as likely to have atrial fibrillation[7]; therefore, the reinitiation of their anticoagulation is another difficult decision facing clinicians.[8-10]

Key words
- Anticoagulation
- Intracranial hemorrhage
- Traumatic brain injury

Abbreviations and Acronyms
ACT: Anticoagulant therapy
DVT: Deep vein thrombosis
GCS: Glasgow Coma Scale
GOS: Glasgow Outcome Scale
IVC: Inferior vena cava
PE: Pulmonary embolism
TBI: Traumatic brain injury
tICH: Traumatic intracranial hemorrhage
UFH: Unfractionated heparin
VTE: Venous thromboembolism

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Few studies have examined the use of therapeutic anticoagulation for treating these thromboembolic events and preexisting conditions in the setting of traumatic intracranial hemorrhage (tICH). In this study, we examined a group of consecutive patients who presented with tICH who received anticoagulation during their hospital stay and the complications associated with starting anticoagulant therapy (ACT).

METHODS

A retrospective review was performed for all patients with TBI from 2010 to 2013 at Memorial Hermann Hospital Texas Medical Center, Houston, Texas, United States. The search criteria included *International Classification of Diseases* codes consistent with intracranial injury and claims demand management codes for pharmaceutical therapeutic ACT (intravenous heparin, enoxaparin, and warfarin). Patients whose presenting injury was not attributable to acute trauma were subsequently excluded. Those who did not have therapeutic ACT administered per the medication administration record were also excluded.

In our facility, all patients with trauma are started on DVT prophylactic dosing of either heparin or enoxaparin 24 hours after a stable head computed tomography scan. Patients with symptomatic DVT/PE or high-risk conditions are started on anticoagulation therapy 48 hours after stable cranial imaging, with repeat imaging obtained once the patient has reached therapeutic laboratory levels denoted as an international normalized ratio of 2–3 for warfarin or on enoxaparin at 1 mg/kg twice daily dosing. Patients with lower short-term risk conditions are restarted after 2 weeks with a similar imaging protocol.

For all included patients, demographics, including age, sex, race, mechanism of injury, Glasgow Coma Scale (GCS) score at presentation, medical history (prior anticoagulant or antiplatelet use), imaging findings, Injury Severity Score, ACT indication, type and dose of anticoagulation agent, surgical procedures, anticoagulation dosing information during hospitalization (time frame of ACT initiation) thromboembolic events prior to initiation, length of hospital stay with delineation for days spent in the intensive care unit, mortality, and Glasgow Outcome Scale (GOS) score on discharge, were reviewed. The intervals between primary injury, surgical intervention, stable radiographic findings, thrombotic event, and initiation were determined.

Complications by radiologic or clinical worsening after ACT initiation were noted. Radiologic studies were reviewed to determine if the worsening was a part of the natural history of the disease process or if it was an iatrogenic process ascribable to ACT. Immediate complications (less than 7 days), intermediate complications (7–14 days), and delayed complications (greater than 14 days) were differentially noted.

Descriptive statistics for doses of ACT, interval between primary injury to initiation, interval between neurosurgical procedure and initiation, and interval between stable radiographic examination and initiation were calculated.

RESULTS

Patient Identification

A total of 250 patients hospitalized with intracranial hemorrhage that received ACT were identified. Of those, 145 were excluded because their hemorrhage was nontraumatic. The remaining 105 patients were those who were admitted for tICH and received ACT during their hospitalization. Of these patients, 31 had concomitant antiplatelet therapy.

Demographics

The median age of these patients was 54 years (range, 16–87 years) and included 76% men (Table 1). The most common mechanism of injury was motor vehicle collision with 36% of patients represented followed by motor cycle crash (17%). The median Injury Severity Score for the available population was 24 (range, 8–50), and approximately 42% of patients had severe TBI (GCS score <9). Prior ACT or antiplatelet therapy was present in 32 patients (29%). A total of 29 patients (28%) required a neurosurgical procedure prior to initiation of ACT while in the hospital.

Indications for ACT

There were 82 thromboembolic events in our patient population. These events included 32 PEs, 44 deep vein thromboses, 4 myocardial infarctions, and 2 left ventricular thrombi. Of the DVTs, 23 were found in veins that fed into the superior vena cava, such as the axillary or internal jugular veins. There were 21 DVTs in veins feeding the inferior vena cava (IVC), such as the femoral or popliteal, and there were 4 mural thrombi in the IVC itself. Other indications for therapeutic ACT included extracorporeal mechanical oxygenation, atrial fibrillation, and restarting home medications. The median interval from primary injury to thrombotic event was 8 days (range, 1–31 days).

Type of ACT and Timing of Initiation

Heparin or enoxaparin with a transition to warfarin was the most frequent form of ACT, with 65 patients (62%) receiving this therapy. There were 33 patients (31%) who received only heparin or enoxaparin, and there were 7 patients (7%) who were only treated with warfarin. The median number of days from injury to initiation of ACT was 8 (range, 0–33). The median interval from stable computed tomography scan to initiation of ACT was 6 days (range, 0–32 days) (Figure 1 and Table 1). The median number of days that patients received ACT was 10 (range, 1–49).

Regarding patients with severe TBI (GCS score ≤8), ACT was started around relatively the same time as the combined population, with a median of 9 days (range, 2–24 days). For those that required intervention, the median time from neurosurgical procedure to initiation was 6 days (range, 2–23 days).

Complications and Outcomes

Three acute radiographic complications occurred in our patient population, but none required an operation. There were 3 clinical complications that also did not require surgery, including

Table 1. Baseline Characteristics and Treatment Data (N = 105)

Characteristic	Value
Demographics	
Males	80 (76)
Age (median) (years)	54
Mechanism of injury	
Autovehicle versus pedestrian accident	8 (8)
Fall from standing	16 (15)
Fall greater than standing	13 (12)
MVC	38 (36)
MCC	18 (17)
Other	10 (9)
Presenting condition	
GCS score severe (3–8)	44 (42)
GCS score mild/moderate (9–15)	61 (58)
ISS (median)	24*
Prior ACT/antiplatelet therapy	32 (29)
Required neurosurgical procedure	29 (28)
Condition at discharge	
Poor outcome (GOS score ≤3)	
Presenting GCS score ≤8	31 (70)
Presenting GCS score >8	33 (54)
Good outcome (GOS score >3)	
Presenting GCS score ≤8	13 (30)
Presenting GCS score >8	28 (46)
ACT data	
Heparin/enoxaparin	33 (31%)
Warfarin	7 (7)
Heparin/enoxaparin and warfarin	65 (62)
Days from injury to ACT (median)	8
Days from procedure to ACT (median)	6
Days from stable scan to ACT (median)	6
Days from injury to ACT with GCS score ≤8 (median)	9
Days of anticoagulation therapy (median)	10

Values are number of patients (%) or as otherwise indicated.
MVC, motor vehicle collision; MCC, motor cycle crash; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; GOS, Glasgow Outcome Scale; ACT, anticoagulant therapy.
*ISS for 68 patients (64%) of the total population.

epistaxis, a hematoma posterior to a tracheostomy site, and development of scalp hematoma. The median GOS score at hospital discharge was 3. Higher GOS score was seen with patients with higher presenting GCS score: 30% in the GCS score ≤8 group and 46% in the GCS score >8 group (Table 1).

The mortality rate was 8%, but no deaths were directly attributed to ACT therapy. There was one mortality secondary to hemothorax with uncontrollable output (1700 mL on initial placement with no response to blood transfusion), but intervention was limited because the patient was already in septic shock and the family did not want any further interventions. Also of note, mortality was lower in the GCS score ≤8 group (3 of the 8 deaths) and was primarily because of withdrawal of care by the family or complications of polytrauma.

There were 2 notable complications that presented in delayed fashion. One (2%) patient required surgery more than 2 weeks after injury because of a large chronic subdural hygroma (Table 2). Another patient presented after discharge and was found to have spontaneous intracranial hemorrhage concerning for aneurysmal rupture unrelated to the recent trauma.

DISCUSSION

Thromboembolic events complicate the clinical course of approximately 25% of patients with TBI.[1] In these patients, the decision to treat the thromboembolism involves balancing the risk of thromboembolism progression against worsening intracranial hemorrhage. Unlike chemical DVT prophylaxis, which has several studies examining its safety after tICH, there is little to guide clinicians in initiating therapeutic dosing of anticoagulation.[4,11]

Current guidelines on DVT and PE treatment recommend immediate ACT and continuation of that therapy for at least 3 months in the absence of contraindications.[12] The choices of anticoagulation include low-molecular weight heparin, fondaparinux, unfractionated heparin (UFH) or subcutaneous UFH.[13] UFH is also recommended in the treatment of acute myocardial infarction.[14]

Another frequently occurring complication (>10%) was atrial fibrillation and other arrhythmias warranting anticoagulation. Current data suggest that if patients have a CHA_2DS_2-VASc score >2 or a total yearly risk of ≥4%, it is an indication for starting anticoagulation.[9,13] There are some data in the perioperative population that suggest holding anticoagulation poses a risk of as high as 0.4% for a stroke or 1.6% for other thromboembolic events even with only 4 days of held anticoagulation.[15] Some reviews recommend holding anticoagulation for 2 weeks after intracranial hemorrhage, but there have been no definitive studies so far.[16,17]

Currently, our institution favors using intravenous UFH without an initial bolus, with a therapeutic target partial thromboplastin time of 60–80. We subsequently transition patients to an oral warfarin regimen with a goal of an international normalized ratio of 2–3. This practice is based on institutional experience and the reversible quality of these agents in the event of a new or worsening hemorrhage. IVC filters are used in select patients with lower extremity DVT that are at particularly high risk for hemorrhagic complications, have other systemic contraindications, or require surgical interventions at the time therapy is indicated.

We typically begin therapy as early as 48 hours from a stable cranial imaging when indicated. This allows for establishment and maturation of the clot to prevent uncontrolled bleeding after starting ACT. The short time frame also allows for timely therapy because recurrent thrombosis is detrimental to the mental and

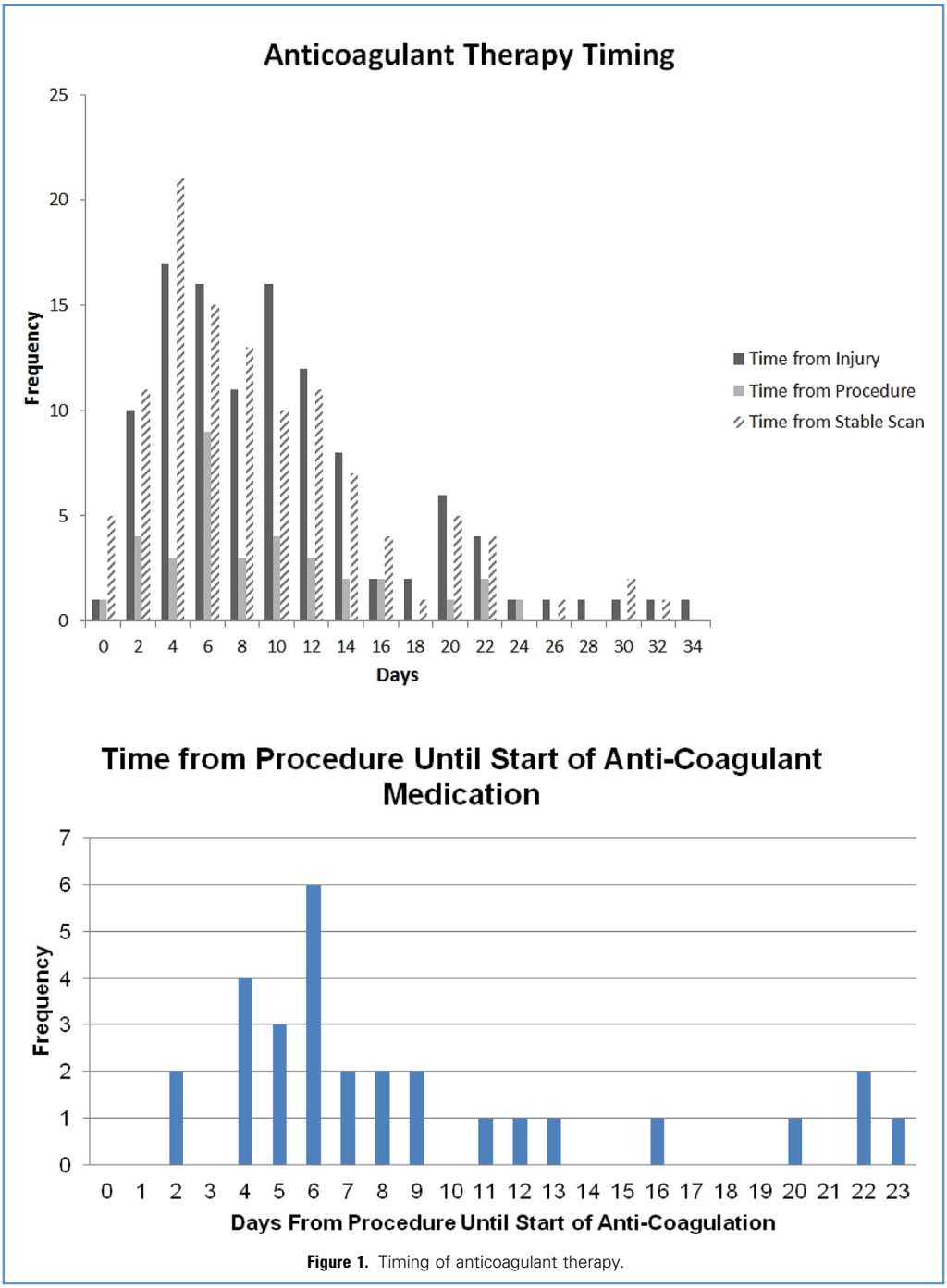

Figure 1. Timing of anticoagulant therapy.

physical health of the patient and potentially has an increase in mortality of up to 2 times in VTE.[12,18]

Much of the hesitance to ACT in the acute setting is the possibility of continued hemorrhage. Much of the data concerning this is from pretrauma ACT, which has shown dire outcomes with 80%–91% mortality in some series, and an absolute increase in mortality of 30% compared with matched control subjects.[19] However, the patients of these studies are anticoagulated before the traumatic event has taken place; therefore, the data do not truly apply to a postinjury population.

To our knowledge, there are currently only 2 studies available in the literature that have examined the effects of anticoagulation in patients with TBI. Byrnes et al.[20] prospectively studied anticoagulation in patients admitted to a trauma service with multisystem injury including TBI. Their results showed 1 patient (4%) with radiographic extension of the hematoma after ACT.[20]

Table 2. Treatment Conditions and Outcomes

Characteristic	Value
Thromboembolic events	
PE	32
DVT	44
Vein fed into SVC	23
In IVC	4
Vein fed into IVC	17
Myocardial infarction	4
Total events	82
Days from injury to event (median)	8
Therapy complications	
Acute radiographic complications	3 (3)
Acute clinical complications	0 (0)
Intermediate clinical complications	4 (4)
Long-term clinical complications*	2 (2)
Outcomes	
GOS score (median)	3
Mortality	10 (9)

Values are number of patients (%), number of patients, or as otherwise indicated.
PE, pulmonary embolism; DVT, deep vein thrombosis; SVC, superior vena cava; IVC, inferior vena cava; GOS, Glasgow Outcome Scale.
*Long-term follow-up rate for 83 patients (74%) of the total population.

This is similar to our study, which showed 3 patients (3%) with a radiographic change after initiation of ACT. However, no patients had an acute clinical complication that required surgery. There was 1 patient in our study (0.6%) with a long-term complication that required surgery. The patient developed a large subdural hygroma that required drainage during the same hospital stay.

Albrecht et al.[21] performed a retrospective review of delayed complications in a postinjury population (N = 10,782). They used Medicare coding to sample a database to find patients who were taking warfarin (defined as filling of a prescription in a 30-day period) after TBI. Their findings showed a decreased incidence of hemorrhagic stroke over the long term, but they did not have any direct patient data because their diagnoses were derived from billing codes.[21]

In our dataset, we also looked for delayed complications that were likely related to ACT therapy after TBI. We only had 1 patient (1%) with clinically significant subdural hematomas that required surgical drainage. There was also a single patient who required readmission for extraaxial intracranial bleeding, but his imaging was concerning for an aneurysmal source and considered unrelated to his previous injury.

The main limitation of this study is its retrospective nature and lack of a control arm. The lack of a control arm of the study is because of our belief that DVTs and VTEs should be adequately treated. This leaves very few patients in the retrospective population that do not have therapeutic intervention. There are some patients that receive alternative treatment modalities, such as IVC filter. However, in our population more than 60% would not benefit from IVC filter because the indication for anticoagulation was not lower extremity DVT (e.g., PE, atrial fibrillation, upper extremity DVT). We did not include patients who were anticoagulated after discharge from the hospital because this is a less acute setting with much lower risk of hemorrhagic complication.

CONCLUSIONS

In this retrospective review we examined 105 patients with thrombotic complications who were treated with ACT. Despite the limitations presented, we found few hemorrhagic complications. Previous studies on this matter have also been limited, either by sample size or method of data collection. However, our data support that ACT has a low risk of hemorrhagic complication after TBI, while allowing for adequate treatment of the acute thrombotic syndromes. Further studies are needed to better characterize this population's total risk of therapy and possible protocols for guiding how early ACT can be initiated.

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