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ORIGINAL ARTICLE

Evaluation of a protocol for early detection of delayed brain hemorrhage in head injured patients on warfarin

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Abstract

Purpose In 2007, Essentia Health St. Mary's Medical Center (SMMC), a Level II trauma center in northeastern Minnesota, implemented a protocol for patients who presented with blunt head trauma and were receiving warfarin for anticoagulation. The purpose of this study was to determine the incidence and risk factors of early delayed, warfarin-associated intracranial hemorrhage (ICH).

Methods Adult patients with signs and symptoms of head injury on warfarin who were admitted by protocol to SMMC between March 2007 and June 2015 were included. Patients were observed for neurologic change and received a follow-up head CT scan within 24 h after an initial negative scan.

Results Among the 232 episodes of care studied, there were 204 patients. The average age was 71; 51% of patients were female. Most patients presented with Glasgow Coma Scale score of 15 and had signs of head trauma. The majority of patients (63%) had a therapeutic International Normalized Ratio (INR) for their indicated condition, but 19% of patients had a supratherapeutic INR and 19% had a subtherapeutic INR. The incidence of early delayed ICH was 1.7%; none of these cases required operative intervention or were fatal.

Conclusions For patients who were anticoagulated with warfarin and had sustained minor traumatic brain injury, implementation of our protocol showed low incidence of early delayed ICH in the first 24 h. We believe withholding warfarin for several days and careful follow-up regarding its resumption is warranted, especially in the setting of supratherapeutic INR.

Keywords Traumatic brain injury · Warfarin · Delayed hemorrhage

Background

Traumatic brain injury (TBI) is a major health concern. In the United States alone, nearly 1.5 million people are treated in emergency departments (ED), 275,000 people are hospitalized, and 51,000 people die annually from TBI [1]. Recent trends in ED visits for TBI reveal significant increases for all age groups, but most significantly in people aged 65+ due to

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falls [2, 3]. Studies suggest that anticoagulated patients are at an increased risk of intracranial hemorrhage (ICH) after head trauma [4, 5]. However, these patients have improved outcomes when their injury is quickly recognized and care is expedited [6].

Warfarin, a vitamin K antagonist, has been the most common oral anticoagulant in the United States since its FDA approval in 1954 [7]. Although it is an effective treatment for reducing thromboembolic events, warfarin has several disadvantages, including a risk of bleeding and costly monitoring requirements [8]. The risk of lethal spontaneous brain hemorrhage from dicoumarol derivatives was known years before warfarin was introduced [9].

The development, improvement, and widespread utilization of head computed tomogram (CT) scans helped to raise the issue of delayed ICH as a clinical concern. In 1992, Stein et al. brought attention to new or progressive brain lesions in traumatized patients with coagulopathy on sequential head CT scans in a series of 253 patients [10]. Among them were 38 patients with negative initial head CT scans that were not further discussed. Coagulopathy was present in 127 patients who were five times more likely to have a progressive brain lesion than those without coagulopathy. In this paper, a brain lesion did not necessarily mean brain hemorrhage and pharmacologic anticoagulation was not mentioned. All coagulopathies were thought to be secondary to intrinsic mechanisms initiated following brain injury. In 2006, Cohen et al. and Itshayek et al. both described patients on anticoagulant or antiplatelet medications with initial negative head CT scans following minor head trauma who subsequently deteriorated clinically with major intracranial hemorrhage on follow-up head CT [5, 11]. The majority of these patients had received warfarin.

Delayed ICH in patients on warfarin is a concern after minor head trauma and a negative initial CT of the head [5, 11–15]. Although these patients can deteriorate rapidly, optimal management for early detection of delayed traumatic ICH remains unclear [12–17]. In 2007, Essentia Health St. Mary's Medical Center (SMMC), a Level II trauma center in northeastern Minnesota, implemented a protocol for all patients who presented with blunt head trauma and were receiving warfarin for anticoagulation. We hypothesized that signs and symptoms of head trauma can identify patients on warfarin who have increased risk of early delayed ICH after an initially negative head CT. Our study was intended to assess the rate of early delayed ICH and identify specific risk factors of warfarin-associated head injury that would predict those at highest risk for early delayed ICH.

Methods

This study was reviewed and approved by the Institutional Review Board at SMMC. We retrospectively reviewed the records of 299 consecutive episodes of care for patients who received warfarin, had signs and/or symptoms of minor head injury, and were admitted by protocol to SMMC between March 2007 and June 2015. Other inclusion criteria were patients > 18 years of age, an International Normalized Ratio (INR) > 1.2, blunt mechanism of trauma, admission Glasgow Coma Scale (GCS) 13–15, and an initially negative head CT. Episodes of care where patients had an injury > 12 h prior to admission, INR ≤ 1.2, GCS < 13, or did not receive a follow-up head CT scan were excluded from the study ($n = 67$) (Fig. 1). Of the remaining 232 episodes, there were 204 individual patients. None of the excluded episodes of care with a follow-up head CT scan had a delayed ICH.

In accordance with hospital protocol, arriving patients receiving warfarin who had suffered signs or symptoms of head trauma were triaged immediately to an ED room for

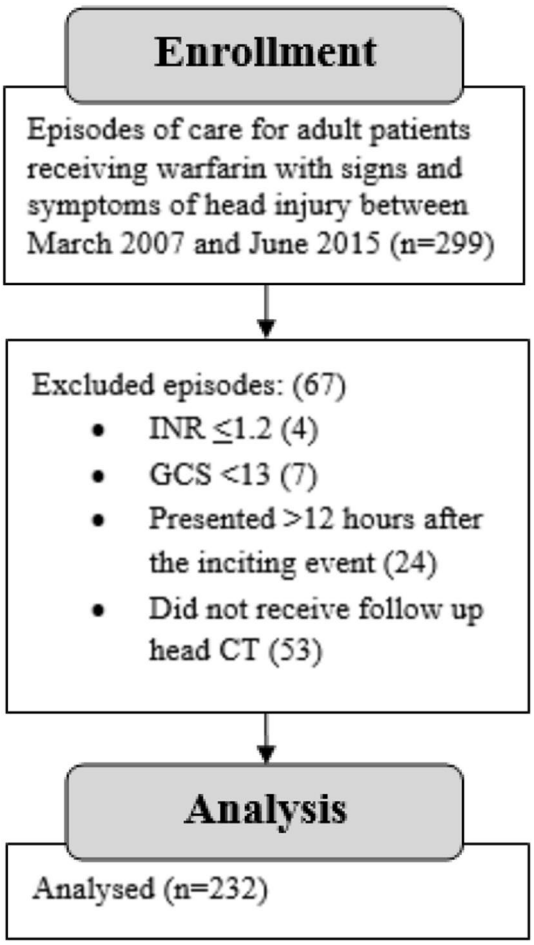

Fig. 1 Study process

evaluation, diagnosis, and treatment. These patients were promptly seen by the ED physician and had their lab work drawn, including an immediate INR. Non-contrast head CT scans for these patients were given highest priority by our radiology department, both in its acquisition and attending staff interpretation. Positive results for intracranial hemorrhage were called immediately to the ordering ED physician. Patients with an initial negative head CT were admitted primarily to the hospitalist service for neurological observation and a follow-up head CT was obtained within 24 h of admission.

From the medical record of each episode of care, the following information was abstracted: age, gender, mechanism of injury, admission GCS score, signs and/or symptoms of head trauma, any associated injuries, initial INR, results and times of the initial and follow-up head CT, the management of anticoagulation during observation, indication for anticoagulation, neurological change during observation, neurosurgical interventions, and disposition upon discharge.

Follow-up head CT results were categorized as negative or positive for a new ICH. A positive result was defined by the presence of subarachnoid hemorrhage, intraparenchymal hemorrhage, subdural hematoma, epidural hematoma, or intraventricular hemorrhage, as described in the radiographic report in the medical records. Consultation with neurosurgery was obtained for all patients with a positive follow-up head CT.

Data were entered in an Excel© spreadsheet and analyzed with SPSS©, version 23.0. Frequencies were calculated for demographics, characteristics of head trauma, and response to intervention. The therapeutic INR range for the indications of atrial fibrillation and hypercoagulable state was 2.0–3.0, and 2.5–3.5 for a replaced mechanical heart valve. An INR above or below these ranges was considered supratherapeutic or subtherapeutic, respectively. Therapeutic range for INR was calculated separately for patients with replaced heart valves.

Table 1 Characteristics and clinical presentation of care episodes with a negative initial CT scan ($n=232$)

Age (years), mean (SD), range	71 (1.9), 29–96
Gender, *n* (%)	
Male	114 (49)
Female	118 (51)
Mechanism of injury, *n* (%)	
Ground level falls	187 (81)
Fall from height	28 (12)
Vehicle involved	9 (4)
Other	8 (3)
Glasgow Coma Scale, *n* (%)	
15	218 (94)
14	12 (5)
13	2 (1)
Associated injuries, *n* (%)	50 (22)
Signs of head trauma present, *n* (%)	216 (93)
Symptoms of head trauma present, *n* (%)[a]	96 (41)
Headache	43
Loss of consciousness	23
Other	30
Reason for warfarin	
Atrial fibrillation	126 (54)
Replaced heart valve	21 (9)
Hypercoagulable state	73 (31)
INR, mean (SD), range[b]	2.6 (0.8), 1.4–6.9
Subtherapeutic	43 (18.5)
Therapeutic	146 (62.9)
Supratherapeutic	43 (18.5)
Initial head CT performed within 1 h of admission	191 (87)
Hours between Head CT, mean (SD), range	21 (11.1) 3–142

INR international normalized ratio, *SD* standard deviation

[a]Patients may have had multiple symptoms

[b]The therapeutic range for the indications of atrial fibrillation and hypercoagulable state was 2.0–3.0. The therapeutic range for replaced heart valve was 2.5–3.5

Results

Between March 2007 and June 2015, 299 consecutive episodes of care in patients receiving warfarin were eligible for the study protocol. After exclusions, 204 patients with negative initial head CT scans remained in the study accounting for 232 episodes of care. Table 1 shows the baseline characteristics for these patients. The average age was 71 and 51% of patients were female. The majority of the patients (81%) had ground level falls as the mechanism of injury. Most patients presented with GCS of 15 (94%) and had physical signs (93%) and/or symptoms (41%) of head trauma. The most common concussive symptoms were headache and loss of consciousness. The mean admission INR was 2.6 ± 0.8. The most common indication for warfarin therapy was atrial fibrillation (54%), followed by hypercoagulable state (31%), and mechanical heart valves (9%). Therapeutic INR was found in the majority of patients (63%), but 19% of patients had a supratherapeutic INR and another 19% had a subtherapeutic INR. Warfarin was reversed with either vitamin K or fresh frozen plasma in 23 cases (10%) at the discretion of the admitting service. In 6 episodes, reversals were in patients with supratheraputic INRs. In no case was the reversal urgent for patient care. Most patients (87%) received their initial head CT within 1 h of admission. The average time between head CT's was 21 ± 11 h. The incidence of delayed ICH was 1.7%.

Of the four patients who presented with a positive second head CT, one had continuation of anticoagulation. All four

of these patients sustained ground level falls and were prescribed warfarin for atrial fibrillation (Table 2). While the average age of these patients was higher compared to the entire cohort (77 versus 71), the small number of patients in this group precluded secondary analysis of associated factors for early delayed intracranial bleeding. Neurosurgery consultation was obtained for all these patients. The brain hemorrhages were considered trivial and none of the cases required operative intervention.

Discussion

In this study, we present one of the largest available analyses of patients on warfarin anticoagulation with mild head injury and initial negative head CT scan. Among the 232 episodes of care included, the incidence of early delayed ICH within 24 h was 1.7%. None were considered significant. The practice of admission for observation and follow-up head CT scan is unwarranted in most patients. This is especially important when considering patients with recidivism. In this study, 17 patients had more than one admission; 13 had one additional admission; 3 patients had 3 additional admissions; and one patient had 6 additional admissions (14 negative head CT scans). This patient was younger than most of our patients with a history of recurrent thromboses and frequent falls. The multiple same site CT scans in this patient pose a real risk for radiation-induced carcinogenesis. This patient once recognized, was a critical influence for us to review our data.

The current literature supports this position. In four studies of similar design and patient characteristics consisting of a total of 586 patients, the incidence of delayed intracranial hemorrhage within 6–24 h of injury was 1.9% [12–15]. Only 1 patient (0.2%) had a significant early delayed ICH [12]. This patient required craniotomy and evacuation of a subdural hematoma. With the addition of our 232 episodes, the cumulative risk of significant early delayed ICH in patients on warfarin with minor head trauma and initial negative head scans remains rare (0.1%). The low incidence of delayed traumatic ICH found in two recent studies suggest that discharging anticoagulated patients from the ED after a normal head CT scan is reasonable as long as they receive clear patient instructions and close follow-up [16, 17].

Over the past 20 years, guidelines for the management of patients on anticoagulation with mild TBI have evolved. The first guidelines were developed by the Italian Society for Neurosurgery in 1996 and were similar to the 2002 guidelines from the European Federation of Neurologic Societies updated without changes regarding anticoagulation in 2012 [18, 19]. Both of these guidelines recommended a head CT scan followed by clinical observation for those patients with intracranial lesions. Additional recommendations included 24-h observation in patients with a negative initial CT scan with risk factors and follow-up head CT scan for those patients on anticoagulation prior to discharge. Originally published in 2007, the National Institute for Health and Care Excellence (NICE) criteria from the United Kingdom made significant changes in their 2014 update [20]. At the time of presentation, these guidelines also recommend patients obtain an initial head CT scan and a provisional radiology report within one hour of the scan. However, if imaging is negative, GCS is 15 and no other factors warrant hospital admission, the patient may be discharged. Similarly, the 2013 New South Wales guidelines recommended that if a patient on anticoagulants had an initial negative head CT scan and was clinically improving or had GCS of 15, the patient could be discharged home for observation with extra caution, or be admitted to the hospital [21]. We are aware of no US guidelines for management of mild head injury in patients on oral anticoagulants and a negative head CT scan.

In conjunction with similar current publications, our study supports the NICE and New South Wales minor head injury guidelines for patients on warfarin. Neurologically normal patients with a negative head CT scan may be discharged to home with observation and explicit instructions on recognizing delayed ICH including the actions to take should it occur.

Nowhere in the literature or guidelines are there recommendations about management of the patient's warfarin following minor head injury. Nishijima, et al. recommends against actively reversing the anticoagulation with blood products, but does not discuss continuing warfarin after ED discharge in patients with negative head CT scans [16]. Our results show that the risk of an early (< 24 h) delayed ICH is 1.7%. If these patients continue their warfarin daily dosing, they may have a larger unmonitored hemorrhage. In these patients, it may be prudent to hold the warfarin.

There is risk and benefit to both continuing and withholding anticoagulation. Hemorrhage can occur if it is not held in the initial days following head trauma, while thrombosis may occur if it is held. Both outcomes have been seen in our practice. The risk of aggravating early delayed intracranial hemorrhage (1.7%) by not withholding anticoagulation exceeds the daily risk of thromboembolism if anticoagulation is withheld (less than 0.05%/day), irrespective of the indication for anticoagulation [22–25]. Because of this, we recommend discharging patients who do not otherwise have a reason for admission (no support at home or other injuries requiring admission) and withholding anticoagulation 3–5 days until the patient can follow-up with their primary provider, as a therapeutic INR will decline towards normal over several days [26]. On the other hand, supratherapeutic INRs require greater vigilance (consider admission) and INR monitoring. Understanding the imprecision of this data, the individual physician must make their own best decision.

Table 2 Population of positive follow-up head CT ($n=4$)

Age/sex	GCS	Mechanism of injury	Signs and symptoms of head trauma	INR	Reason for warfarin	Initial warfarin management	Follow-up head CT and exam	Disposition
91M	15	Ground level fall	Contusion at the left lateral orbit with laceration	2.8	AF	Warfarin held, not reversed	Small subarachnoid hemorrhage at right basal cistern. Asymptomatic	Neurosurgery consulted. INR reversed. 2nd follow-up head CT stable. Discharged to home. Warfarin held for 2 weeks
66M	15	Ground level fall	Strike on head	2.8	AF, ICD	Warfarin continued	Punctate intraparenchymal hemorrhage of the right frontal lobe Asymptomatic	Neurosurgery consulted. INR reversed. 2nd follow-up head CT stable. Discharge to home. Warfarin held for 2 weeks
68M	15	Ground level fall	Large abrasion to left face	2.5	AF	Warfarin held. Oral vitamin K given	Tiny subarachnoid hemorrhage Asymptomatic	Neurosurgery consulted. Discharged to home. Warfarin held for 1 week
83F	15	Ground level fall	Scalp hematoma. Contusion to the left temporoparietal area	2.7	AF	Warfarin held, not reversed	Interhemispheric hemorrhage New nausea and mild headache	Neurosurgery consulted. INR reversed. Developed new bilateral PE and placed back on therapeutic anticoagulation. Discharged to skilled nursing facility with warfarin

M male, *F* female, *GCS* Glascow Coma Scale score, *INR* international normalized ratio, *AF* atrial fibrillation, *ICD* implantable cardioverter defibrillator, *PE* pulmonary embolism

Withholding anticoagulation in the CT negative patient beyond 2 weeks is ill advised [27–29]. Changing to an oral anti-Xa or thrombin inhibitor should also be considered, particularly in the patient with recurrent falls, as they had significantly lower risk of ICH in the large atrial fibrillation trials versus warfarin [30–33]. Discharge instructions should include the signs, symptoms, and actions plans for acute thromboembolism as well as for delayed ICH if the patient is discharged from the ED with anticoagulation withheld. For safety, patients discharged from the ED should be observed and not discharged home alone.

This study is limited by the use of retrospective data from a single institution. The small number of positive follow-up head CTs did not allow us to identify risk factors for early (< 24 h) delayed ICH following minor head trauma in patients on warfarin. The strengths of this study are the large number of patients included in the study, consecutive enrollment of patients into the protocol and the presence or absence of early delayed ICH determined by follow-up head CT. Assessed in conjunction with like studies, our study strengthens the recommendation for ED discharge of most patients with a minor traumatic brain injury who are also anticoagulated. The follow-up head CT scan will be positive in few patients, but a clinically significant result is rare. Routine follow-up head CTs for all anticoagulated patients with mild TBI are a wasteful use of resources and incur unnecessary expense. Prospective randomized trials and cost-effectiveness analyses will be necessary to further guide clinicians toward standardized guidelines for patients who sustained minor head trauma on warfarin and an initial negative head CT.

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Author contributions JLH assisted with data collection, data analysis, and manuscript preparation. TAW assisted with literature search and manuscript preparation. PC assisted with the data analysis, interpretation, and manuscript preparation. CAM acquired funding, supervised staff, and assisted with manuscript preparation. MME assisted with data collection. SDE conceived the study, assisted with data collection and interpretation, and manuscript preparation. All authors reviewed and approved the final manuscript.

Compliance with ethical standards

Conflict of interest No conflicts of interests to declare: this research was funded in part by a Grant from Essentia Health Duluth Clinic Foundation.

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