RESEARCH

The Effect of Time to International Normalized Ratio Reversal on Intracranial Hemorrhage Evolution in Patients With Traumatic Brain Injury

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ABSTRACT

The incidence of geriatric traumatic brain injury (TBI) is increasing throughout the United States, with many of these patients taking anticoagulation (AC) medication. The purpose of this investigation was to determine the effect of time to international normalized ratio (INR) reversal on intracranial hemorrhage evolution in TBI patients taking prehospital AC medication. We hypothesized that rapid reversal of INR improves outcomes of head-injured patients taking AC medication. Admissions to a Level II trauma center between February 2011 and December 2013 were reviewed. Patients presenting with an initial INR of 2.0 or more, computed tomographic scan positive for intracranial hemorrhage, and INR reversal to less than 1.5 in hospital were included. Patients with nontraumatic intracranial hemorrhage were excluded. Reversal of INR was achieved using some combination of fresh frozen plasma, prothrombin complex concentrate, and vitamin K. A binary logistic regression model assessed the adjusted impact of rapid INR reversal on intracranial hemorrhage evolution. Significance was defined as $p < .05$. One hundred subjects were included. Four patients with nontraumatic intracranial hemorrhage were excluded, resulting in a final study population of 96 patients. The most common intracranial hemorrhage in the study population was subarachnoid hemorrhage (71.9%), followed by subdural hemorrhage (35.4%). Reversal of INR of less than 5 hr was not associated with intracranial hemorrhage evolution; however, reversal of less than 10 hr was found to be associated with a decreased odds ratio for intracranial hemorrhage evolution ($p = .043$). Rapid reversal of elevated INR levels (<10 hr) may decrease intracranial hemorrhage evolution in TBI patients taking prehospital AC medication.

Key Words

Anticoagulation reversal, International normalized ratio, Intracranial hemorrhage evolution, Traumatic brain injury

BACKGROUND/SIGNIFICANCE

Between 1992 and 2009, the incidence of elderly traumatic brain injuries (TBIs) in Pennsylvania has nearly doubled (Ramanathan, McWilliams, Schatz, & Hillary, 2012). This trend will only increase as the geriatric population in the United States is predicted to more than double by 2030 (U.S. Department of Health and Human Services, 2012). Consequently, many emergency departments (EDs) and trauma centers are, and increasingly will be, flooded with elderly TBI patients. Many of these patients take prehospital anticoagulants to combat the sequelae of chronic illnesses. Lavoie et al. (2004) found that as many as 9% of elderly TBI patients were taking the anticoagulant warfarin before their trauma.

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These TBI patients taking prehospital anticoagulation (AC) medication, such as warfarin, are commonly at a higher risk for intracranial hemorrhage expansion and unfavorable outcomes (McMillian & Rogers, 2009). A recent study by Peck et al. (2014) found a significant relationship between prehospital anticoagulants/antiplatelets and mortality in TBI patients. The study also found that patients taking AC medication had a greater risk for intracranial hemorrhage evolution. Another study found that patients taking prehospital Coumadin (warfarin), aspirin, or Plavix (clopidogrel bisulfate) have a threefold increase in the rate of worsening repeat head computed tomographic (CT) scans (Joseph et al., 2014). Franko, Kish, O'Connell, Subramanian, and Yuschak (2006) also showed increased intracranial hemorrhage, increased length of stay, and increased mortality for patients taking AC medication compared with the control. Because of this increasing level of evidence in the literature, rapid reversal of the international normalized ratio (INR) by factor replacement therapy or platelet addition is recommended by the American Heart Association and the American Stroke Association to reduce intracranial hemorrhage expansion (Hemphill et al., 2015).

To follow these guidelines, many EDs throughout the country have adopted novel diagnostic workup protocols to expedite the treatment of TBI patients taking

prehospital AC medication to improve outcomes. Most treatment protocols include a rapid INR reversal to minimize the risk of intracranial hemorrhage evolution. In some cases, the rapid INR reversal has shown an increase in favorable outcomes (Ivascu et al., 2005). Conversely, other studies show that early reversal of AC was not associated with improved neurological outcome and may not be sufficient alone in treating these TBI patients (Dowlatshahi et al., 2012; Goldstein et al., 2006). As there is currently little consensus on the impact of rapid INR reversal on TBI outcomes, further research is needed. In this retrospective study, we sought to add to the literature on this understudied issue by determining the effect of time to INR reversal on intracranial hemorrhage evolution in TBI patients taking prehospital AC medication. We hypothesized that rapid INR reversal of prehospital AC medication would significantly reduce intracranial hemorrhage evolution.

METHODS

Approval for this study was granted by the institutional review board. A retrospective analysis of data from February 2011 to December 2013 was conducted using the trauma registry at our suburban Level II trauma center. Included were all patients with intracranial hemorrhage taking prehospital AC medication (INR > 2) whose INR was reversed (<1.5) during their hospital stay. Patients with nontraumatic intracranial hemorrhages were excluded. Age, race, gender, date of admission, admission Glasgow Coma Scale (GCS) score, Abbreviated Injury Scale (AIS) head score, Injury Severity Score (ISS), and type of hemorrhage were queried. Initial INR, time of INR reversal, initial and subsequent CT results, presence of an intracranial hemorrhage, and presence of intracranial hemorrhage evolution were extracted from patient charts. Interrater reliability was tested, and extracted data maintained greater than 95% agreement between investigators. The time from ED presentation to an INR of less than 1.5 was calculated to determine the time to INR reversal. Reversal of INR was achieved by using some combination of fresh frozen plasma, prothrombin complex concentrate (PCC), and vitamin K. The suggested dosage and time of administration were determined by the anticoagulant reversal management guideline described by Edavettal, Rogers, Rogers, Horst, and Leng (2014).

The INR reversal time was categorized into two groups—a reversal in less than 5 hr and a reversal in less than 10 hr. Subsequently, the study population was separated into two groups: those with no evidence of intracranial hemorrhage evolution, and those with positive intracranial hemorrhage evolution on repeat CT scans. Stepwise regression analysis was used to calculate adjusted odds ratios (AORs) of intracranial hemorrhage evolution for patients with an INR reversal under 5 hr and under 10 hr. In this analysis, the odds ratios were adjusted for age, GCS score, ISS, and AIS head score. As a measure of model performance, the area under the receiver operating characteristic (ROC) curve was determined.

RESULTS

A total of 100 patients with intracranial hemorrhage taking prehospital AC medication were identified. Of this, four patients were excluded from the analysis as they presented with nontraumatic intracranial hemorrhages, resulting in a final study population of 96 patients. Demographic characteristics of the 96 patients are included in Table 1. Patients were predominantly composed of severely injured (mean ISS = 18.2 ± 7.5), geriatric trauma patients with a median age of 83.0 years (range = 76.3–87.8 years). Patients 65 years or older accounted for 92.7% of the study group (n = 89), and trauma by fall was the predominant mechanism of injury (n = 87; 90.6% of study group). In terms of TBI demographics, the study population, on average, presented with severe head injuries (mean AIS head score = 3.91 ± 1.0). The most common type of intracranial hemorrhage was a subarachnoid hemorrhage (71.9%), followed by a subdural hemorrhage (35.4%).

Upon admission, the mean initial INR of the study population was 3.40 ± 1.51 and, on average, took 13.3 ± 10.5 hr to reverse to a level below 1.5. Within

TABLE 1 Population Demographics

Median age in years (IQR)	83 (76–88)
Gender	
Male	49%
Female	51%
Admission GCS score	
15	64.9%
14	23.4%
≤13	11.7%
AIS head score	
2–3	36.5%
4	27.1%
5	36.5%
Average time to INR reversal (hr)	13.3 ± 10.5
Mean presenting INR	3.40 ± 1.51
Mortality (n)	12.5% (12)
Intracranial hemorrhage evolution (n)	35.4% (34)

Note. AIS = Abbreviated Injury Scale; ED = emergency department; GCS = Glasgow Coma Scale; IQR = interquartile range; INR = international normalized ratio.

the designated time-to-reversal groupings, 14 patients achieved reversal in less than 5 hr (14.6%) and 49 patients achieved reversal in less than 10 hr (51.0%). The mean reversed INR for the study population was 1.25 ± 0.11.

A total of 34 patients were found to have intracranial hemorrhage evolution based on follow-up head CT scans (35.4%). In adjusted analysis, INR reversal in less than 5 hr was not associated with intracranial hemorrhage evolution (AOR = 0.35; 95% CI [0.04, 3.14]; $p = .348$); however, reversal in less than 10 hr was found to be associated with a decreased odds ratio for intracranial hemorrhage evolution (AOR = 0.38; 95% CI [0.14, 0.98]; $p = .043$). Overall, these models were found to have acceptable discrimination, with area under the ROC curve of 0.79 for the less than 5 hr model and 0.74 for the less than 10 hr model (Table 2).

DISCUSSION

The results of this investigation suggest that reversal of elevated INR levels in less than 10 hr significantly decreases the likelihood of intracranial hemorrhage evolution in TBII patients taking prehospital AC medication. This finding allows us to reject the null hypothesis.

To our knowledge, this is the first article in the literature to express a time to INR reversal that alone optimizes intracranial hemorrhage evolution. A previous study has shown an association with decreased intracranial hemorrhage evolution and expedited INR reversal but was demonstrated within rapid response protocols to identify TBI patients on preinjury warfarin (Ivascu et al., 2005). As part of the protocol, patients had less time from presentation to physician evaluation and less time required to obtain imaging. Therefore, these patients likely had faster times to neurosurgical intervention if needed. Our study was not an evaluation of protocol implementation. Therefore, early identification and early surgical intervention were not significant confounding factors, increasing the likelihood of association between early INR reversal time and decreased intracranial hemorrhage evolution.

Our findings are similar to other investigators who reported positive outcomes with timely INR reversal (Goldstein et al., 2006; Ivascu et al., 2005) and directly contradict the study showing no association between INR reversal and positive outcomes (Dowlatshahi et al., 2012). We consequently recommend rapid and aggressive reversal of INR in TBI patients taking prehospital AC medication, ideally under 10 hr, in an attempt to decrease intracranial hemorrhage evolution.

LIMITATIONS

Our study has several limitations. First is the strikingly long mean time to INR reversal of 13.3 hr. Our institution has previously implemented a reversal protocol including PCC, which has been shown to more rapidly reverse INR (Edavettal et al., 2014). Even after this implementation, time to INR reversal is much longer then desired. Many factors may contribute to this delay including wait times in triage, time to intracranial hemorrhage diagnosis, time to initial INR, and time to administration of reversal agent. Prompt INR reversal is challenging to achieve, even with a protocol in place. Swift collaboration between care teams is necessary for the treatment of TBI patients taking AC medication to expedite the INR reversal process and minimize intracranial hemorrhage evolution.

Other limitations are as follows: First, as the nature of this investigation was retrospective, this work suffers from the inherent threats to validity present in any retrospective analysis. Second, the treatment algorithms were not standardized, increasing the variability of care between physicians. Third, these results represent only the findings of a single institution, as evident by our relatively small sample size, and may not be generalizable

TABLE 2 Adjusted Odds Ratios for Intracranial Hemorrhage Evolution in Patients With Traumatic Brain Injury With INR Reversed in Less Than 5 hr and Less Than 10 hr

	Reversal Time <5 hr		Reversal Time <10 hr	
Variable ($N = 96$)	Adjusted Odds Ratio [95% CI]	p	Adjusted Odds Ratio [95% CI]	p
Reversal time	0.35 [0.04, 3.14]	.348	0.38 [0.14, 0.98]	.043
Age	0.99 [0.93, 1.05]	.651	1.01 [0.96, 1.05]	.770
GCS score	0.78 [0.58, 1.06]	.117	1.27 [0.91, 1.76]	.159
ISS	1.00 [0.79, 1.28]	.983	1.16 [0.99, 1.35]	.069
Head AIS score	2.65 [0.34, 20.7]	.354	0.72 [0.23, 2.25]	.567
		AUROC = 0.78		AUROC = 0.73

Note. AIS = Abbreviated Injury Scale; AUROC = area under the receiver operating characteristic (curve); GCS = Glasgow Coma Scale; INR = international normalized ratio; ISS = Injury Severity Score.

to the traumatic brain-injured population at large. Prospective research is warranted to further elucidate the relationship between early INR reversal and intracranial hemorrhage evolution.

CONCLUSION

Patients with TBI taking prehospital AC medication are at increased risk for worse outcomes. Overall, the results of this investigation suggest that reversing elevated INR in these patients in less than 10 hr may decrease the probability of intracranial hemorrhage evolution. These results are consistent with the national trend to expedite INR reversal in the setting of TBI patients taking AC medication in an attempt to improve outcomes.

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KEY POINTS

- INR reversal in less than 10 hr is associated with decreased intracranial hemorrhage evolution.
- Timely INR reversal is difficult to achieve and requires a team approach to minimize delays in treatment.
- Further prospective research is needed to elucidate a causal relationship between INR reversal and intracranial hemorrhage evolution in TBI patients.

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