August 2012

Washington University Emergency Medicine Journal Club
Risk of Delayed Traumatic ICH in Patients on Anticoagulation

Vignette

You are working a moonlighting shift at a local level II trauma center when you meet Mr. X, a 68 year old gentleman with a history of atrial fibrillation, for which he takes diltiazem for rate control and warfarin for anticoagulation. He see his primary care physician on a regular basis and has his international normalized ratio (INR) checked once a week. It has been between 2.0 and 3.0 consistently for the last 6 months. This morning, while walking his dog, a rare crossbreed known as a great doodle (a cross between a great dane and a poodle), he was tripped up by the leash and fell forward, striking his forehead on the concrete. He suffered no loss of consciousness, has a mild headache, and has had no nausea or vomiting. His wife states that he has had no altered mental status since the fall.

On exam he has a GCS of 15, a superficial abrasion to his forehead with a small 4 cm hematoma, no cervical spine pain or tenderness, and a normal neurologic examination. His INR today is 3.2. Being an astute reader of the literature, you remember that the studies on the Canadian Head CT rules excluded patients on anticoagulation, and proceed to order a head CT, which is read as normal by the attending radiologist (not a neuroradiologist).

After updating the patient's tetanus booster you discharge him home in the care of his wife. That night after your shift, you recall an Italian friend of yours telling you that in Italy, standard of care in patients with head injury on anticoagulation is 24 hours of observation followed by a repeat CT scan. You consider the efficacy of such a protocol, and begin asking yourself about the patient's risk of delayed intracranial hemorrhage. Unable to sleep, you head online and begin your search.

PICO Question
Population: Patients on anticoagulation therapy suffering minor head injury
Intervention: Observation and/or repeat CT scan of the head CT
Comparison: Discharge after normal initial head CT
Outcome: Risk of delayed intracranial hemorrhage leading to a change in management

Search Strategy

Search Strategy: You remember seeing two articles in a recent copy of Annals of Emergency Medicine on the topic, which you failed to read. You read both of these articles, and find references to a third article in the Journal of Trauma.

You then turn to PUBMED and enter a search strategy of ((((warfarin) OR coumadin) OR anticoagulation) AND trauma) AND intracranial hemorrhage, resulting in 275 articles (search strategy). In addition to the three articles already chosen, this strategy identifies a fourth article relevant to the PICO question.

Article 1: Menditto VG, Lucci M, Polonara S, et al. Management of minor head injury in patients receiving oral anticoagulant therapy: a prospective study of a 24-hour observation protocol. Ann Emerg Med 2012;59:451-455. ANSWER KEY.

Article 2: Kaen A, Jimenez-Roldan L, Arrese I, et al. The value of sequential computed tomography scanning in anticoagulated patients suffering from minor head injury. **J Trauma** 2010;68:895-898. ANSWER KEY.

Article 3: Nishijima DK, Offerman SR, Ballard DW, et al. Immediate and delayed traumatic intracranial hemorrhage in patients with head trauma and pre-injury warfarin or clopidogrel use. **Ann Emerg Med** 2012;59:460-468. ANSWER KEY.

Article 4: Peck KA, Sise CB, Shackford SR, et al.Delayed intracranial hemorrhage after blunt trauma: are patients on preinjury anticoagulants and prescription antiplatelet agents at risk? **J Trauma** 2011 Dec;71(6):1600-4. ANSWER KEY.

Bottom Line

Traumatic brain injury results in just over 1.3 million emergency department (ED) visits, 275,000 hospitalizations, and 52,000 deaths annually in the United States alone, with an increase in ED visits and hospitalization of 14.4% and 19.5%, respectively, from 2002 to 2006 (CDC TBI Report). In elderly patients suffering a fall, long-term anticoagulation has been shown to increase not only the incidence of intracranial hemorrhage (ICH) compared to those not on anticoagulation (8.0% vs. 5.3%, $p < 0.0001$), but to also increase mortality in those with ICH (21.9% vs. 15.2%, $p = 0.04$) (Pieracci 2007). Additionally, the use of warfarin prior to blunt head trauma has been shown to increase mortality compared to those not taking anticoagulants, with an odds ratio of 2.008 (95% CI 1.634-2.467) (Batchelor 2012). Unfortunately, the rate of pre-injury warfarin use has been increasing in trauma patients in the US, from 2.3% in 2002 to 4.0% in 2006 ($P < .001$); in patients older than 65 years, use increased from 7.3% in 2002 to 12.8% in 2006 ($P < .001$) (Dossett 2011).

Given the increasing number of head injury patients seen in the ED, and the increase in concomitant anticoagulant use, the clinical dilemmas surrounding these patients have become more and more relevant. Studies in patients taking warfarin who suffer minor head injury have shown incidences of ICH ranging from 6.2%-29% (Li 2001, Gittleman 2005, Brewer 2011), leading some authors to conclude that most, if not all, such patients should undergo routine cranial CT scanning on presentation

(Brewer 2011, Cohen 2006, Fabbri 2004). One important question surrounds the prognostic implications of a normal cranial CT in head injury patients on anticoagulant therapy. While some European guidelines suggest that all anticoagulated patients with head injury should be admitted for a period of routine observation (Vos 2002, Ingebrigtsen 2000), these recommendations are not based on studies of the prevalence of delayed ICH.

In the four studies reviewed, the incidence of delayed ICH following normal CT scan ranged from 0.6% to 6%. However, if a diagnosed ICH has no affect on the patient's outcome or treatment, then it would be considered a *surrogate outcome*, which is often "used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions or survives (Thomas 1995)." As such outcomes are often found to be clinically insignificant, their use has been questioned in the literature (Guyatt 2011, Fleming 1996), and the incidence of *patient important outcomes* should be considered instead. In these studies, the majority of patients found to have delayed ICH required no neurosurgical intervention and had no adverse outcome documented. The incidence of death or neurosurgical intervention ranged from 0 to 1.1%.

The authors of one of the articles suggest that "our data support the general effectiveness of the European Federation of Neurological Society's recommendations for 24-hour observation followed by a repeated head CT scan for anticoagulated patients with a minor head injury" (Menditto 2012). However, this conclusion is based on the incidence of delayed ICH (6%) rather than the incidence of clinically important outcomes (1.1%). In this study, only one patient out of 87 suffered clinically significant delayed ICH. It is mentioned in the study that one patient showed signs of neurologic deterioration, however they do not say if this was the same patient who required neurosurgical intervention. If so, this would suggest that observation alone would suffice to detect any clinically significant delayed ICH.

Additionally, the authors do not perform a cost-effectiveness analysis to support their conclusion. In a subsequent editorial appearing in the same journal, it is suggested that a protocol of 24-hour observation and routine repeat CT scanning would cost an average of just over $1 million per patient saved (Li 2012). The author of the editorial suggests that home observation and phone call follow-up would be more cost-effective, and likely as safe, though this has not been studied.

One difficulty in studies of prognosis involves homogeneity. It would be unfair to say that all head injury patients on warfarin carry the same risk for delayed ICH. There are many risk factors which need to be considered, and a one-size-fits-all approach may not be warranted. A prior study on warfarin use in head trauma showed that the degree of anticoagulation was predictive of risk of ICH, rather than the use of warfarin alone, with an odds ratio of 2.59 in patient with an INR greater than or equal to 2.0 (Pieracci 2007). Another retrospective study of 1493 patients admitted for traumatic brain injury with preinjury warfarin use showed both the risk of ICH and mortality were increased with higher INR (Franko 2006). Whether

this association can be applied to the risk of delayed ICH remains to shown, however one of the articles reviewed here suggests an increased risk in patients with an international normalized ratio (INR) greater than or equal to 3 (relative risk = 14; 95% CI 4 to 49) (Menditto 2012).

It is important to recognize the populations to whom the evidence applies. The current studies were predominantly (>80%) geriatric patients who had suffered a standing level fall. These were not young adults who were the victims of violence or motor vehicle accidents so the evidence should not be applied to younger populations. Elderly adults are not a homogenous population. Numerous occult geriatric syndromes exist that differentiate biological age from physiological age, most of which are unrecognized in today's ED. Geriatric syndromes include frailty, dementia, delirium, falls, functional status, and social isolation. As with any predictor variable, if one cannot measure a phenomenon then one cannot study or understand that phenomenon. In anticoagulated head injury patients, the decision to obtain a repeat CT scan and/or observe for a prolonged period of time incorporates clinicians' gestalt for many of these geriatric syndromes and future elderly patient head injury research will need to adjust prognostic models for these confounding variables.

An additional prognostic factor to consider is concomitant antiplatelet therapy. The risk of major bleeding is known to increase for those on combined anticoagulant-antiplatelet therapy, with hazard ratios of 1.83 (95% CI 1.72-1.96) and 3.08 (95% CI 2.32-3.91) for combined warfarin-aspirin and warfarin-clopidogrel use respectively, compared to warfarin therapy alone (Hansen 2010). It seems reasonable to assume that combined therapy would lead to increased rates of both initial and delayed ICH in head injury patients, and in one of the studies which identified 2 patients with delayed ICH, both were taking aspirin in addition to warfarin (Kaen 2010). Concomitant antiplatelet therapy in 3 of the studies ranged from 0-5.9% (Menditto 2012, Kaen 2010, Peck 2011), while the fourth paper specifically excluded such patients (Nishijima 2012). Studies in the US have demonstrated much higher rates of concomitant antiplatelet therapy in patients taking warfarin, ranging from 19.4-38.5% (Shireman 2004, Johnson 2007).

While the current literature does not support routine hospital observation for 24 hours or repeat cranial CT scans in all anticoagulated patients with head injury, this may be warranted in those at increased risk of delayed bleeding, such as those with supratherapeutic INR levels or concomitant antiplatelet therapy. Further studies are needed to identify these higher risk patients for delayed bleeding to determine appropriate management. Furthermore, as a result of the inherent difficulties in warfarin administration, including the need for strict dietary compliance and routine INR monitoring, attempts have been made to find alternative anticoagulants. As newer anticoagulants enter the market and begin to replace warfarin, such as apixaban, dabigatran, and rivaroxaban, further studies on the risk of delayed hemorrhage may be necessary to determine the best management strategy for patients on these medications.