CJEM Journal Club

Traumatic intracranial hemorrhage in patients using warfarin or clopidogrel

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Clinical question
What is the prevalence of immediate and incidence of delayed intracranial hemorrhage in patients with blunt head trauma who use warfarin or clopidogrel?
Article chosen
Nishijima DK, Offerman SR, Ballard DW, et al. Immediate and delayed traumatic intracranial hemorrhage in patients with head trauma and preinjury warfarin or clopidogrel use. *Ann Emerg Med* 2012;59:460-8.e7.
Study objective
To assess the prevalence of immediate and the cumulative incidence of delayed traumatic intracranial hemorrhage in patients using warfarin or clopidogrel.

Keywords: bleeding, clopidogrel, intracranial hemorrhage, warfarin

BACKGROUND

The use of warfarin and clopidogrel is increasing, particularly in the elderly population.[1–3] Several studies have demonstrated an increased risk of intracranial hemorrhage (ICH) in patients who use anticoagulation or antiplatelet therapy and suffer even minor blunt head trauma.[4–6] These studies are retrospective and provide limited data to guide clinical practice, especially with respect to patients taking clopidogrel.[7–9] Further information about investigations and the need for follow-up or hospitalization is required.

POPULATION STUDIED

This study enrolled adult (aged > 18 years) emergency department (ED) patients with blunt head trauma (defined as any blunt head injury regardless of loss of consciousness or amnesia) and preinjury warfarin or clopidogrel use within the previous 7 days. As expected, the large majority suffered mild traumatic brain injury (TBI). The study excluded patients who were transferred from outside facilities or using warfarin and clopidogrel concomitantly.

STUDY DESIGN

This was a prospective, observational, multicentre study conducted at two trauma centres and four community hospitals in northern California. Data were collected on patients' history, medication use, injury mechanism, and clinical examination, including the initial Glasgow Coma Scale (GCS) score and evidence of trauma above the clavicles. The ordering of computed tomographic (CT) scans and the decision to admit to the hospital were determined by the treating physicians. Patients with normal cranial CT scan results and therapeutic international normalized ratio (INR) levels did not have their anticoagulation reversed. Patients were followed for 2 weeks. Delayed bleeding was ascertained either through revision of electronic medical records for patients admitted for more than 14 days or through a standardized telephone survey for patients discharged from the ED or admitted for less than 14 days. Follow-up CT scans were done at the discretion of the treating physicians.

OUTCOME MEASURES

Immediate traumatic ICH was defined as the presence of any ICH or contusion on the initial cranial CT scan.

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Patients without a cranial CT scan during the initial ED evaluation were excluded from the immediate traumatic ICH calculation. Delayed traumatic ICH was defined as ICH visible on a cranial CT scan that occurred within 14 days after an initial normal CT scan result and in the absence of repeated head trauma. Stratified analysis was performed to ensure that differences in outcome between cohorts were not due to differences in injury severity, age, sex, INR level, etc.

RESULTS

A total of 1,064 patients were enrolled between April 2009 and January 2011. Nearly three-quarters of the patients (768) were using warfarin (72.2%), whereas 296 patients were using clopidogrel (27.8%). There were 364 patients (34.2%) from level I or II trauma centres and 700 patients (65.8%) from community hospitals. One thousand patients underwent cranial CT scanning in the ED. Both warfarin and clopidogrel groups had similar demographic and clinical characteristics, although concomitant acetylsalicylic acid (ASA) use was more prevalent among patients receiving clopidogrel (8.1% for clopidogrel versus 2.5% for warfarin). The prevalence of immediate traumatic ICH was higher in patients receiving clopidogrel (33 of 276, 12.0%; 95% confidence interval [CI] 8.4−16.4) than in patients receiving warfarin (37 of 724, 5.1%; 95% CI 3.6−7.0) with a relative risk of 2.31 (95% CI 1.48−3.63). Delayed traumatic ICH was identified in 4 of 687 (0.6%; 95% CI 0.2 −1.5) patients receiving warfarin and 0 of 243 (0%; 95% CI 0−1.5) patients receiving clopidogrel. Four patients were lost to follow-up. Forty-four patients (5.7%) in the warfarin group and 20 patients (6.8%) in the clopidogrel group did not have immediate CT and were excluded from the calculation. Follow-up was obtained for 63 of these 64 patients. None subsequently received a diagnosis of traumatic ICH.

Stratified analysis confirmed an increased risk of immediate traumatic ICH in those patients receiving clopidogrel compared to warfarin across all strata. Sensitivity analysis of the four patients lost to follow-up and the single death from unknown causes assumed that all patients had a delayed traumatic ICH. The cumulative incidence increased to 6 of 687 patients (0.9%; 95% CI 0.3−1.9) in the warfarin group and 3 of 243 (1.2%; 95% CI 0.3−3.6) in the clopidogrel group.

COMMENTARY

This is the largest study to date evaluating the prevalence of immediate and the incidence of delayed traumatic ICH in patients using either warfarin or clopidogrel prior to their injury. It was conducted at two trauma centres and four community hospitals, with the majority of subjects selected from the latter. The results seem to be generalizable to the population seen at any average ED. The study was designed as a prospective, observational study and was meant as a real-world study. Not all patients (1,000 of 1,064; 94%) had CT scans, which might have resulted in an underestimation of the true prevalence of immediate hemorrhage. Those patients who did not have CT scans during their initial ED visit might have had an undiagnosed traumatic ICH, although none were identified in follow-up, suggesting that any such hemorrhage was not clinically significant. Follow-up CT scans were obtained at the physician's discretion and not a mandatory part of the study. Some patients with a negative initial CT scan result may therefore have developed a delayed traumatic ICH, but here again the clinical significance appears to be minimal. CT scans were read by only one staff radiologist, so the reliability and accuracy of the interpretations are unknown.

The study divided participants into two groups, warfarin or clopidogrel use. Both groups had similar demographic and clinical characteristics. A stratified analysis was performed to account for known potential confounders and showed that significant differences between groups were maintained across the different strata. Concomitant use of ASA was found to be more common in patients using clopidogrel, which might have explained the increased prevalence of immediate traumatic ICH in this group. The stratified analysis for patients in the clopidogrel group not using concomitant ASA maintained a higher prevalence of hemorrhage, so the clopidogrel association remains true (11.5% for clopidogrel versus 5.1% for warfarin). Although the prevalence of immediate bleeding and neurosurgical intervention among patients using clopidogrel was higher, in-hospital mortality after immediate traumatic ICH remained similar among both groups (21.2% for clopidogrel versus 21.6% for warfarin).

It is important to note that the majority of participants had a relatively benign presentation with a GCS score of 15 (87.6%) and an apparently

nondangerous mechanism of injury (ground-level fall or fall from own height, 86.8%). Two of the four patients who were identified to have delayed ICH presented with a GCS score of 15 yet suffered catastrophic ICH within 3 days, leading to death.

It would be of great clinical value if the study had addressed the need for reversing or withholding of warfarin after a negative CT scan; information about the impact of varying INR levels (subtherapeutic, therapeutic, or supratherapeutic) would also have been of value. Notably, three of the four patients who had delayed traumatic ICH presented with a subtherapeutic INR (1.15, 1.5, and 1.9) and one patient with a supratherapeutic INR (4.95). It was not clear what action was done for the latter (no reversal for negative scans and therapeutic INR as per the study). Further studies will be required to answer these outstanding questions.

CONCLUSION

Despite the limitations of this study, the results support a careful approach when evaluating patients using either warfarin or clopidogrel who suffer even minor blunt head trauma. Benign mechanism of injury and normal physical examination do not eliminate the risk of intracranial bleeding. In addition, the use of clopidogrel was associated with double the risk of bleeding compared to warfarin. As stated in current guidelines discussing head injury and warfarin use, liberal CT scanning of the head seems to be a reasonable strategy, even for those who present with normal mental status and a GCS score of 15.[10–13] The risk of delayed bleeding appears to be very close to zero with clopidogrel, suggesting that routine hospitalization and follow-up scanning might not be necessary. Patients taking warfarin are not without risk and probably do require follow-up but not necessarily routine (second) CT.

Competing interests: None declared.

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