Prevalence and Clinical Characteristics of Intracerebral Hemorrhages Associated with Clopidogrel

Abstract

Background: As clopidogrel is being increasingly used, intracerebral hemorrhage (ICH) associated with clopidogrel are expected to increase. We assessed the prevalence and clinical characteristics of of ICH with clopidogrel in a consecutive series of patients in two hospitals.

Methods: We retrospectively reviewed the medication history of 204 patients (112 in one hospital and 92 in another – both individually consecutive) admitted with ICH. We identified the patients who were using clopidogrel prior to ICH occurrence. The etiology of the ICH was categorized on the basis of clinical history and diagnostic imaging, and outcome was subsequently evaluated.

Results: A total of 8 (4%) of the 204 patients were using clopidogrel prior to onset of ICH. Clopidogrel was the only medication in 3 patients and was used with aspirin or warfarin in 3 and 2 patients, respectively. Aspirin or warfarin was the only medication in 23 (%) and 14 (%) patients associated with ICH, respectively. The hematoma was located in the basal ganglia (n=2), lobes (n=2), thalamus (n=1), intraventricular (n=2), and cerebellar (n=2). One patient had secondary intraventricular extension. All patients using a combination of clopidogrel and warfarin prior to ICH died.

Conclusion: The prevalence of ICH associated with clopidogrel is approximating the prevalence of aspirin- or warfarin-associated ICH. The mortality with clopidogrel related ICH appears to be high particularly when in combination with another antithrombotic agent.

Keywords: Clopidogrel, warfarin. aspirin. hypertension. intracerebral hemorrhage. intraventricular hemorrhage. mortality. neurological outcome.

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Steve M Cordina, MD
Ameer E Hassan, MD
Mustapha A. Ezzeddine MD

Address correspondance to:
Steve M Cordina, MD
Department of Neurology
University of Minnesota, 420 Delaware St SE,
Minneapolis, MN 55455

scordina@umn.edu

Clopidogrel is thienopyridine inhibitor of the platelet P2Y12 adenosine diphosphate (ADP) receptor. Clopidogrel is an agent that irreversibly inhibits adenosine diphosphate (ADP) induced platelet aggregation.[1] The interaction of ADP with the platelet P2Y12 receptor induces platelet shape change, reversible aggregation, initial glycoprotein (GP) IIb/IIIa activation, phospholipase C activation, and calcium flux.[1] Regular use of clopidogrel (75 mg daily) can produce 40-50% inhibition of adenosine diphosphate induced platelet aggregation.[1,2] This function makes it one of the drugs of choice for secondary stroke prevention, and also part of dual antiplatelet therapy in patients undergoing angioplasty and/or stent placement and acute coronary syndromes. As clopidogrel is being increasingly used in clinical practice, the incidence of associated hemorrhagic complications is expected to rise. Intracerebral hemorrhage (ICH) is a well known complication of antiplatelet and antithrombotic therapy. Although the rate and clinical characteristics of ICH with warfarin and aspirin is a well studied phenomenon, limited information is available regarding the rate, clinical characteristics, and outcome of ICH associated with clopidogrel. Our aim in this retrospective study was to analyze the prevalence and clinical characteristics of ICH associated with clopidogrel in a consecutive series of patients in two hospitals.

Methods

The records of a total 204 patients in two university affiliated hospitals were retrospectively reviewed. Both facilities are teaching hospitals with established neurocritical care services. There were 112 patients reviewed from one hospital and another 92 from the second hospital; both series were temporally consecutive within each facility. The patients were identified using the primary International Classification of Disease, 9th revision (ICD-9 CM) code was either 431 (intracerebral hemorrhage) or 432 (other and unspecified intra-

From the Zeenat Qureshi Stroke Research Center, University of Minnesota Medical Center, MN (SMC, MAE, AIQ), University of Medicine and Dentistry of New Jersey (AEH)

cranial hemorrhage). Subsequently, the clinical and imaging data for each identified patients was reviewed for confirmation of the accuracy of the discharge diagnosis. Patients who had subarachnoid hemorrhage, traumatic ICH, and hemorrhagic conversion of an ischemic stroke were excluded. A chart review was performed to identify use of any antithrombotic medication prior to occurrence of ICH using the emergency department notes, emergency department laboratory results, and history recorded by the admitting physicians and nurses. Additional patient information that was collected included other medication on admission, age, gender, race/ethnicity, history of hypertension, diabetes mellitus, ischemic heart disease, drug abuse, alcohol use, cigarette smoking, and elevated blood pressure on admission with no previous history of hypertension. Discharge functional outcome was determined by modified Rankin Scale (mRS). A mRS of 0 to 2 was defined as independent functional status. Dependent functional status was defined by mRS of 3 to 5.

Results

A total of 8 (3.9%) of the 204 patients were using clopidogrel prior to onset of ICH. Clopidogrel was the only medication in 3 patients and clopidogrel was used with either aspirin or warfarin in 3 and 2 patients, respectively. Aspirin or warfarin was the only medication in 23 (11.3%) and 14 (6.9%) patients associated with ICH, respectively. All patients who had ICH associated with clopidogrel had a history of chronic hypertension. The details are provided in Table 1.

One patient (12.5%) had a history of cigarette smoking, while two patients (25%) had diabetes mellitus. Of the diabetic patients, one had a concurrent history of cocaine abuse. The hematoma was located in the basal ganglia (n=2, 25%), lobes (n=2, 25%), thalamus (n=1, 12.5%), pure intraventricular (n=2, 25%), and cerebellar (n=1, 12.5%). One patient (12.5%) had secondary intraventricular extension. There was one patient (12.5%) in whom an incidental posterior cerebral artery aneurysm was discovered on magnetic resonance angiography. One patient (12.5%) received platelet transfusion during admission. In those patients on concurrent warfarin therapy (n=2, 25%) , INR was elevated (›3.0) in all patients. Platelet function assays and/or bleeding time was assessed in 4 of the 8 patients (abnormal in one patient). Four out of these 8 patients (50%) died after admission. All patients using a combination of clopidogrel and warfarin prior to ICH died (n=2).

Discussion

Approximately 7000 intracerebral hemorrhages annually in the United States are estimated to be caused by use of antithrombotic therapies.[3] Schalenkamp et al.[4] suggested that the use of oral anticoagulants in addition to clopidogrel may have similar rates of hemorrhagic complications compared to oral anticoagulants in addition to aspirin. The prevalence of ICH associated with clopidogrel is approximating the prevalence of aspirin- or warfarin-associated ICH. The mortality with clopidogrel related ICH appears to be higher than that

Table 1 Demographic, clinical, and radiological characteristics of patients with intracerebral hemorrhage associated with clopidogrel.

Patient Age /sex/race (ethnicity)	Other antithrombotic agents used	Risk factors	Location of ICH	Other imaging findings	PFA	Bleeding time	INR	Platelet transfusion	Status at discharge
85, F,AA	None	HTN	Left cerebellar + IVH	None	Not tested	Normal	Normal	No	Deceased
58, F, H	none	HTN	Right IVH	None	Normal	High	Normal	No	Deceased
51, M, AA	none	HTN	Left basal ganglia	None	Not tested	Normal	Normal	No	Dependent
54,M, W	ASA	HTN, DM, Cocaine abuse	Left frontal	None	Not tested	Not tested	Normal	No	Dependent
82, F, AA	Warfarin	HTN, DM	IVH	Left PCA Aneurysm	Not tested	Normal	5.4	Yes	Deceased
65,M, AA	Warfarin	HTN	Right basal ganglia	None	Not tested	Not tested	3.6	No	Deceased
61,F, W	ASA	HTN	Right temporal lobe	None	Not tested	Not tested	Normal	No	Dependent
64,M, W	ASA	HTN, smoking	Right thalamus	Not tested	Not tested	Not tested	Normal	No	Independent

Abbreviations used: M = male; F = Female; AA = African American; W = White; H = Hispanic; HTN = Hypertension; ASA = Aspirin; PCA = Posterior cerebral artery; PFA = Platelet function assay; INR = International normalized ratio; ICH = Intracerebral hemorrhage; IVH = Intraventricular hemorrhage

observed with aspirin related ICH. The rate of hemorrhages in patients treated with clopidogrel and aspirin in both the MATCH (Management of Atherothombosis With Clopidogrel in High-Risk Patients) and CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) trials were higher than in patients on single antiplatelet therapy.[1] In MATCH, rate of life threatening hemorrhage was 2.6% vs 1.3% with an absolute risk increase of 1.3% [95% CI 0.6 to 1.9]. In CHARISMA, moderate bleeding was significantly increased at 2.0% versus 1.3% (HR 1.60; 95% CI: 1.16 – 2.20; p=0.004). It is also known that a risk of ICH exists among patients with recent cerebral ischemic events undergoing neurointerventional procedures, particularly when aggressive antithrombotic treatment is used.[5] There is a lower risk of ICH in patients on single oral antithrombotic therapy.[6] The combination of aspirin and warfarin appears to increase the risk of intracerebral hemorrhage.[3,7]

Platelet function recovers gradually 3-5 days after clopidrogrel withdrawal.[2] The presence of aspirin seems to be an independent predictor of mortality in patient with ICH[8] and reversal of the antiplatelet effect might have a place in these patients.[9] No specific agent is documented except platelet transfusion.[2,9] The use of clopidogrel is increasing in the general population, especially in patients with previous strokes who suffer recurrent ischemic event who are already on an antiplatelet agent, usually aspirin.[4,10] It is of interest that other methods of clopidogrel action reversal may be available such as the use of methylprednisolone.[11] We had previously described a patient with ICH following endovascular treatment in whom platelet functional assay approached normal values after an injection of 25mg of intravenous methylprednisone. Rapid reversal of antiplatelet activity may prevent hematoma expansion[12] and consequent mortality in such patients[5]. Furthermore, in view of the recent description of genetic polymorphisms that affect clopidogrel absorption and metabolism,[13,14] it would be of interest to assess whether the possession of these polymorphisms which render clopidogrel less effective but also decreases the risk of ICH.

Conclusion

The use of clopidogrel is increasing in the general population, especially in patients with previous strokes who suffer recurrent ischemic event. An increasing number of clopidogrel associated ICHs are expected to be seen in United States with the increasing use of clopidogrel. Further studies need to elaborate the occurrence and risk factors for clopidogrel associated ICHs.

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