Intracranial Hemorrhages Related with Warfarin Use and Comparison of Warfarin and Acetylsalicylic Acid

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Background: Acetylsalicylic acid (ASA) and warfarin are used to prevent ischemic cerebrovascular events. They have serious complications including intracranial hemorrhages (ICHs). Warfarin-related intracerebral hemorrhage (ich) incidence is .2%-5% in population that accounts for 10%-12% of all ichs. In this article, we investigated the profile of ASA and warfarin-related spontaneous ICHs in comparison with ICHs without any drug use (WADU) with their clinical, radiological, and biochemical properties. *Methods:* In all, 486 patients aged 18-101 years with spontaneous ICHs were included. Patients constituted 4 separate groups: users of warfarin, ASA, ASA + warfarin, and WADU. Clinical, neurological, etiological, and radiological data of these patients were compared. *Results:* There were 32 patients in warfarin, 58 patients in ASA, and 7 in warfarin + ASA group. Most of the patients were in no drug group (389 patients). The most frequent type of hemorrhage was supratentorial intraparenchymal hemorrhage. The most common accompanying disease was hypertension. The number of female patients was statistically significant in the warfarin group. Glasgow Coma Scale (GCS), accompanying diseases, opening of the hematoma to the ventricle, localization of the hemorrhage, age of the patient, and activated partial thromboplastin time level are all related to the outcome of patients. Warfarin users had worst mortality rate. *Conclusions:* Use of warfarin, low GCS score, opening to ventricle, older age, accompanying diabetes, and/or hypertension were worse prognostic factors. It is possible that patients with these unfavorable prognostic factors cannot survive. **Key Words:** Warfarin—ASA—intracranial hemorrhage—anticoagulation.

Introduction

Anticoagulant and antiplatelet treatment (or antiaggregants) with oral agents are widely used to prevent ischemic cerebrovascular and cardiac events. The most common indication for warfarin as oral anticoagulant treatment is prevention of ischemic stroke in patients with atrial fibrillation. Warfarin is also used to prevent complications of thromboembolic events in patients with artificial heart valves or deep vein thrombosis.[1] Warfarin use increased in the world during 1990s after publication of treatment trials about showing that it is more effective for stroke prevention than acetylsalicylic acid (ASA) in patients with atrial fibrillation.[2] Risk reduction of all strokes is significantly higher with warfarin than antiplatelet agents.[3] The median age of patients with atrial fibrillation is approximately 75 years.[4] Because atrial fibrillation increases with aging, warfarin use increases mostly in elderly population; although they are useful in these aspects, they have a severe complication of intracranial hemorrhage (ICH). Very elderly atrial fibrillation patients (>75 years old) not only have higher rates of major bleeding during warfarin treatment but also have higher rates of ischemic stroke if not anticoagulated.[3] They have caused an increase of intracerebral hemorrhage (ich) incidence after a temporary decrease that

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was because of the improvement of hypertension treatment after 1980s.[2] There are several etiological factors for ICH such as genetic properties, gender differences, vascular abnormalities, fibrinolytic treatment, and trauma, and warfarin-related ich (WRICH) incidence is .2%-5% in population that accounts for 10%-12% of all ich.[5-7] In large hospitals, it is stated that one fourth of ich is WRICH.[8] Mortality rate is as high as 50%[5] and increases with higher international normalized ratio (INR),[9] older age, and increased duration of therapy.[6] Overall, the risk of warfarin-associated ich may reach 1%-2% every year and the risk increases to 4.2% in patients older than 75 years.[10,11] This means WRICH is an important issue for both neurology practice and public health.

In this article, we investigated the profile of antiaggregant drug ASA and anticoagulant drug (warfarin)–related spontaneous ICH in comparison with ICH without any drug use (WADU) with their clinical, radiological, and biochemical properties. We also discussed the possible preventive measures with available literature data.

Materials and Methods

This study was performed in the Neurology Department of Izmir Atatürk Research and Training Hospital from January 2005 to December 2011. This is a retrospective case series of patients from our Neurology Department. The institutional review board approved the study protocol.

Four hundred eighty six patients aged 18-101 years who had spontaneous ICH were included in this study. Patients coming to our hospital's emergency room who had determined spontaneous ICH with cranial imaging (computed tomography or magnetic resonance imaging) were examined by consulting neurologist, and they were admitted to our Neurology Department. All patients were followed in our Neurology Department either in neurology ward or in neurologic intensive care unit according to their Glasgow Coma Scale (GCS), metabolic and cardiovascular state, and other neurological findings. These patients followed in our department were included in the study. Patients' data from their records were evaluated and used for all analysis. When ICH patients were admitted to our department, if patients were able to give information, they were questioned about their disease history, warfarin or ASA use and indications of these drugs, cigarette smoking, alcohol consumption, and other accompanying diseases such as cerebrovascular disease in the past, diabetes mellitus (DM), lipoprotein metabolism disorders, hypertension, atrial fibrillation and other cardiac problems, carotid disease, and deep venous thrombosis; otherwise, available family members answered aforementioned questions about the patients. ICH was classified as supratentorial (lobar and nonlobar) and infratentorial intraparenchymal hemorrhages, subarachnoid hemorrhage (SAH), subdural hemorrhage (SDH), and primary intraventricular hemorrhage. GCS was scored in every patient, and they all had a detailed neurological and systemic examination with regular blood pressure controls. Laboratory examinations including biochemical and coagulation parameters especially INR, activated partial thromboplastin time (aPTT), prothrombin time (PT), and blood glucose levels were performed. In the follow-up period, prognoses of patients were evaluated. All data mentioned earlier were recorded to the patient's folders, and these data were used retrospectively for the statistical analysis.

There were 4 groups of patients, namely warfarin, ASA, ASA + warfarin, and WADU groups. The groups were also evaluated in a yearly basis. Statistical analyses were performed for each group separately and as a whole. SPSS for Windows 17.0 programme with 95% confidence interval was used, and parametric student t test, 1-way analyses of variance, nonparametric Mann–Whitney U test, Kruskal–Wallis test, and Tukey test were performed. For comparison of categorical data, Pearson chi-square test was applied. Statistical results of $P < .05$ were accepted statistically significant.

Results

Four hundred eighty six spontaneous ICH patients, 270 men (55.6%) and 216 (44.4%) women aged between 18-101 years (mean 62.22 ± 16.46), were included in the study. Warfarin group included 32 patients (6.6% of total ICH) aged between 31 and 89 years (mean 64.40 ± 13.24), 21 women (65.6%) and 11 men (34.4%). ASA group included 58 patients with 21 women and 37 men (11.9% of total ICH) (33 patients, 100 mg ASA; 24 patients ASA, 300 mg ASA; and 1 patient, 150 mg ASA) aged between 46 and 97 years (mean 68.22 ± 11.78) and warfarin + ASA group included 7 patients, 3 women and 4 men (1.4% of total ICH, 1 patient, 300 mg ASA, and 6 patients, 100 mg ASA) aged between 42 and 82 years (69.0 ± 16.05) (Table 1). The number of female patients was more than males in warfarin group compared with other groups, which was statistically significant ($P < .05$). We have 486 patients totally from 2005 to 2011; when it is evaluated year by year, total increase in the number of patients in 7 years is 67%, but the number of patients in subgroups is nearly stable (ie, warfarin group in 2008: 8 patients; 2009: 4; 2010: 5; 2011: 5). According to years, although the total increase of hemorrhage was remarkable, the number of patients in drug-using subgroups was nearly stable which meant that the number of patients in WADU group increased within this period.

The warfarin indications of 39 patients (warfarin group and warfarin + ASA group) were heart valve replacement (48.7%), atrial fibrillation (41%) and dilated cardiomyopathy, deep vein thrombosis, carotid artery stent, and pulmonary thromboembolism (last 4, each 2.5%).