REPEATED INTRACEREBRAL HEMORRHAGE AFTER WARFARIN THERAPY FOR ATRIAL FIBRILLATION: A CASE REPORT

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Abstract

Stroke prophylaxis in patients with atrial fibrillation (AF) has been examined extensively in randomized trials, metaanalyses, and review articles. The clinical trials show that treatment with vitamin K antagonists significantly decreases the risk of stroke in AF patients. However oral anticoagulant use has a greater likelihood of complications, especially increasing the bleeding. We reported a 67-year-old man of atrial fibrillation treated with warfarin who developed right intracerebral hemorrhage (ICH) first. Craniotomy was given due to increased intracranial pressure (IICP). Another ICH over brainstem occurred during craniotomy for the first right ICH, no further operation was given, and the patient expired 4 days later. We suggest considerable dose adjusting of warfarin is required to keep patients within the therapeutic range, even the dose of warfarin is very low.

Key words: Stroke, Atrial fibrillation, Vitamin K antagonist, Intracerebral hemorrhage

Introduction

Atrial fibrillation (AF) is a significant marker for both a higher incidence of stroke and increased mortality. In the Framingham Cohort Study, the risk of stroke was 5.6 times greater in patients with atrial fibrillation than that in comparably aged patients with sinus rhythm.¹ Treatment with vitamin K anticoagulant (VKA) significantly decreases the risk of stroke in AF patients, but many physicians hesitate to prescribe it to elderly patients because of the associated risk for bleeding and the inconvenience of frequent blood tests for the patients. We reported a patient of atrial fibrillation treated with warfarin who developed right large intracerebral hemorrhage (ICH) first due to poor monitored international normalized ratio (INR), and another ICH over brainstem later during craniotomy for the right ICH.

Case Report

A 67-year-old man visited cardiovascular (CV) outpatient service of a community teaching hospital on March 10th, 2009, with the chief complaint of severe vertigo. Hypertension was noted and anti-hypertensive medications were prescribed there. Three days later, vertigo did not improve and unsteady gait with deviation to
right occurred. He visited our CV outpatient service and atrial fibrillation was found. He was admitted to our hospital immediately under the impression of atrial fibrillation and suspected stroke. Brain computerized tomography (CT) revealed no intracranial hemorrhage or recent infarction (Fig 1). Cardiac echo revealed dilated atrium, good left ventricular contractility, and no thrombus. Carotid Doppler study revealed mild diffuse atherosclerosis. His neurological function improved on the second day of admission. Under the impression of atrial fibrillation and transient ischemia attack (TIA), warfarin was prescribed on March 16th. The initial dose of warfarin was 5 mg and the maintenance dose was 2.5 mg everyday. On March 19th the follow-up INR was 1.62, and he was discharged with a maintenance dose of warfarin 2.5 mg everyday. He was followed up in our CV outpatient service and the warfarin was prescribed with the same dose. On April 8th, the follow up INR was >5, and the warfarin was stopped immediately. The liver function test revealed the AST 31U/L and the ALT 31U/L. The INR gradually returned to normal range and the follow up INR on April 24th was 1.04. Therefore, the warfarin was prescribed again on April 29th, and the dosage was decreased to 2.5 mg every other day. The same dose of warfarin was given thereafter in our CV outpatient service, and the other medications included Bisoprolol (Concor), Amlodipine (Norvasc), Telmisartan (Micardis), Piracetam (Nootropil), and Tamsulosin (Harnalidge) were given. No other problems were noted during this period and no further follow

Fig. 1. Brain CT scans revealed no intracerebral hemorrhage or infarction. The patient’s neurological function completely recovered the second day of attack.
up of INR was given. On the early morning of July 21st, sudden onset left limbs weakness occurred, and he was sent to our emergency room (ER). The checked prothrombin time (PT) was > 60 sec the INR was >5. The liver function test revealed the AST 30U/L and the ALT 16U/L. The Glasgow coma scale (GCS) initially was E3V5M6 and down to E1V1M5 in our ER. Brain CT revealed right large ICH with midline shift (Fig 2). Urgent craniotomy was done immediately under the diagnosis of right ICH with increased intracranial pressure (IICP). The ICH was removed and blood transfusion with fresh frozen plasma was given during the operation. After operation was completed, fixed dilated pupils were noted. Brain CT follow-up immediately revealed a new ICH over brainstem (Fig 3). After the second attack of brainstem ICH, only supportive treatment was given and the patient expired on July 25th.

**Discussion**

A number of randomized controlled trials (RCTs) have consistently demonstrated the efficacy of warfarin in preventing stroke in patients with nonvalvular atrial fibrillation (NVAF). The major complication of anticoagulant therapy is bleeding. Studies varied in their definition of bleeding complications. Bleeding was generally classified as major if it was intracranial or retroperitoneal, if it led directly to death, or if it resulted in hospitalization or transfusion. The increase in risk of major bleeding in patients

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**Fig. 2.** Brain CT scans revealed right large ICH with midline shift. Brainstem was not involved at this time. Urgent Craniotomy for right ICH was done due to IICP.
treated with VKA compared to control was low in well-controlled patients. In the pooled analysis of the trials with warfarin in atrial fibrillation, the annual rate of major bleeding was 1.0% in control patients versus 1.3% in patients treated with warfarin.²

In a case-control analysis of intracranial hemorrhage using anticoagulant, the prothrombin time ratio (PTR) was the dominant risk factor for intracranial hemorrhage. For each 0.5 increase in PTR over the entire range, the risk for intracranial hemorrhage doubled.² The response to oral anticoagulant therapy is affected by gut flora, variations in hepatic function, interactions with several drugs and diet.⁶ The risk for ICH is increased among older patients, especially those ≥ 75 years old when the INR is supratherapeutic.⁷ The target intensity of the treatment with VKA is strongly associated with the risk of bleeding (Table 1). Most randomized studies⁷-¹⁴ revealed that in VKA therapy, targeted international normalized ratio (INR) of 2.5 (range, 2.0-3.0) was associated with a lower risk of bleeding than therapy targeted at an INR > 3.0. Only in one of these studies, the patient with INR lower than 2.1 had less bleeding risk and same ischemia stroke prevention. In this Japanese randomized study, they made conclusion that for secondary prevention of stroke in persons with NVAF, especially in old patients, the low-intensity warfarin (INR 1.5 to 2.1) treatment seemed to be safer than the conventional-intensity (INR 2.2 to 3.5) treatment.¹¹ This may be due to people variation, but it needs more prospective studies.

Fig. 3. Brain CT scans revealed a new ICH over brainstem, more in the left side, and right residual ICH after craniotomy.
to prove the high tendency of bleeding of VKA treatment in Asian people.

Although in well-controlled patient the annual rate of major bleeding is low, the bleeding complication of anticoagulant usage has been a problem of medication safety. In 2008, the Joint Commission Accreditation of Healthcare Organization (JCAHO) in the National Patient Safety Goals (NPSGs) added medication safety regarding anticoagulant therapy. In 2009, they required the accredited hospital should provide education regarding anticoagulant therapy to prescribers, staff, patients and their families (NPSG.03.05.01).

In the SPINAF study using a standardized protocol, they demonstrated a 79% reduction in stroke rate among the warfarin-randomized patients without an increase in bleeding complications. In that study, monitoring was performed weekly during a 12 weeks induction period and monthly thereafter during a maintenance period for a total follow-up of 36 months, with a goal of maintaining the INR within 1.4 to 2.8. Dose adjustments of 1-mg increments or decrements were suggested by them.

In our case the final maintenance dose of warfarin was only 2.5 mg every other day. The dosage was very low, but major bleeding occurred. We suggest even with lower dose anticoagulation treatment, considerable dose adjusting is required to keep patients within the therapeutic range, particularly during the initiation phase. In addition, participation of patients and their families is also important to achieve the goals of safety usage of anticoagulant.

### References

3. Gulløv AL, Koefoed BG, Petersen P. Bleeding during
心房顫動使用 Warfarin 發生連續性腦內出血：
案例報告

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摘要

心房顫動病人的中風預防已經在很多文獻上被確認其重要性，很多臨床試
驗也顯示使用維他命K阻斷劑顯著的減少中風發生。但是使用抗凝血劑可能造
成其他併發症，尤其是增加出血機率。我們報告一位六十七歲心房顫動病人使
用warfarin後，先發生右腦腦內出血，在給予緊急開顱手術摘除腦內血腫時，
另外發生新的腦幹出血，最後不治死亡的案例。我們建議即使warfarin劑量很
低，也要嚴密監控及調整抗凝血剤的劑量。

關鍵詞：中風，心房顫動，維他命 K 阻抗剤，腦內出血

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