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ORIGINAL ARTICLES

Warfarin-associated intracerebral hemorrhage occurs with lower intensification of anticoagulation in Chinese

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Abstract

Background and Objective: Intracerebral hemorrhage occurs more commonly in Asians than whites. This is to determine whether this racial difference extends to intracerebral hemorrhage associated with the use of warfarin. *Methods:* From a prospectively conducted stroke registry of 3,476 patients, we identified ten patients who developed intracerebral hemorrhage while on warfarin treatment. Their clinical features and laboratory investigations were compared with those from other published series. *Results:* The demographic features, indications, duration of warfarin therapy and size of hematoma in our patients were similar to other series. However, the mean INR in our patients was 2.3 which appeared lower than the reported range of 3 - 3.8 in other series. All except one patient had INR below 3. During the same period, 478 patients were hospitalized because of acute ischemic stroke and had atrial fibrillation but were not on warfarin therapy.
Conclusion- Intracerebral hemorrhage in Chinese patients occurs at a lower intensity of anticoagulation than in whites. Adding the propensity for intracerebral hemorrhage and increased sensitivity to warfarin, the benefit-to-risk ratio of warfarin for stroke prevention and optimal level of INR in Chinese population may be different from the published data.

INTRODUCTION

The efficacy of warfarin for the prevention of stroke in patients with atrial fibrillation is now firmly established, subsequent to the publication of a number of randomized controlled trials in Europe and North America.[1-7] Despite the clear evidence for its efficacy, the majority of suitable patients in North America do not receive warfarin for stroke prevention.[8,9] In other populations where hemorrhagic strokes occur much more commonly than in Europe and North America, physicians may be even more hesitant to use warfarin routinely because of the concern about developing intracerebral hemorrhage as a result. Little information is available on this risk in non-white populations. By using a prospectively conducted stroke registry based in Shatin, Hong Kong, we were able to identify ten patients who developed intracerebral hemorrhage while on warfarin therapy. Their clinical and laboratory features and outcomes were compared with those reported in other series.

METHODS

We searched the Shatin Stroke Registry from 1994 to 1996 to identify those patients who were admitted for intracerebral hemorrhage while they were taking warfarin. The diagnosis of intracerebral hemorrhage was confirmed by computed tomography (CT). We excluded patients who had hemorrhagic transformation of the infarct while having treatment for acute ischemic stroke. We reviewed the case notes to obtain the demographic details, past medical history, indication for and dosage of warfarin used. The International Normalized Ratio (INR) on admission was noted. The volume of the hematoma from the CT scan was measured by the formula $ABC/2$ as described by Broderick et al.[10] (*A* being the longest diameter of the largest area of hemorrhage; *B* being the diameter perpendicular to *A*; *C* being the number of 1-cm CT slices in which the hemorrhage was visible). Previous CT scans, if available, were reviewed to detect any prior cerebral infarct. For the survivors, we arranged a telephone interview to determine their functional outcome.

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RESULTS

Among 3,476 patients recorded in the Shatin Stroke Registry from 1994 to 1996, ten patients were noted to be on long term warfarin therapy when they were being admitted for intracerebral hemorrhage. In contrast, during the same period, 478 patients with history or electrocardiographic evidence of atrial fibrillation (AF) but not taking warfarin were hospitalized because of ischemic stroke. The sex and age of the ten patients, indication for and dosage of warfarin, duration of anticoagulation, INR on admission, history of hypertension and cerebrovascular disease, location and size of the hematoma, and functional outcome are tabulated in Table 1. The most common indication for taking warfarin was history of cerebrovascular disease plus additional risk factors such as non-valvular AF (4 patients), valvular replacement with AF (2) and chronic rheumatic heart disease with AF (1). Three patients without AF had aortic valve replacement (2) or deep venous thrombosis (1). History of hypertension was present in four patients. The mean dosage of warfarin was 2.2 mg daily and the mean INR was 2.3. Only one patient had an INR considered to be high (3.45). Duration of warfarin therapy ranged from 4 months to 8 years (mean 3 years). The location of the hematoma was nearly always different from the site of previous infarction if there was any, except in one patient with cerebellar hematoma. The size of the hematoma ranged from 3 ml to 178 ml (mean 55 ml).

The warfarin was stopped after admission and most patients were treated with vitamin K. None of the patient had a neurosurgical evacuation of the hematoma. Functional outcome was generally poor: four patients died in hospital while three were severely disabled at follow-up. None of the patients with a hematoma larger than 50 ml survived. Only three patients were able to live independently after the hemorrhagic stroke.

The results of our patients, together with a summary of other reported series, were tabulated in Table 2.[11-17]

DISCUSSION

Intracerebral hemorrhage is the most feared complication of taking warfarin. The risk of intracerebral hemorrhage increases more than ten-fold compared with untreated subjects.[11] The incidence is difficult to estimate because of its rarity. In a prospective study, 9 patients developed intracerebral hemorrhage among 555 patients who were treated with warfarin, resulting in an annual rate of 0.9% per year.[17] Any increase of this rate, even to one or two percent, may adversely affect the decision to give warfarin.[18,19] As concerns about cerebral hemorrhage is one of the main reasons preventing a higher rate of warfarin use to prevent strokes, a better understanding of the potential risk factors may improve the confidence of physicians prescribing warfarin. Previous studies have found that a history of stroke, advanced age and the intensity of anticoagulation are potential risk factors.

Although prior stroke is a risk factor for the development of warfarin-associated intracerebral hemorrhage,[15,20] patients with known cerebrovascular disease are prone to recurrent stroke and for them the benefits of warfarin outweighs its risks.[6]

Table 1: Summary of the clinical features and outcome

Sex	Age	Warfarin dosage (mg)	INR	Duration of treatment (months)	Intracerebral hematoma		Outcome
					Location	Size (ml)	
female	64	2.15	3.45	n/a	thalamus	3	disabled
female	68	3	1.96	48	pon	3	alive
male	62	3	2.66	84	basal ganglia	16	alive
male	67	2	2.35	31	cerebellum	17	disabled
male	57	1.5	2.81	7	cerebellum	26	alive
male	61	n/a	1.54	96	basal ganglia	46	disabled
female	72	1.5	2.15	7	parietal	56	died
female	82	1	0.98	12	occipital	60	died
female	59	3	2.61	4	thalamus	140	died
male	76	3	2.47	4	parietal	178	died
Mean	67	2.24	2.30	33		55	

Age is also a risk factor for the development of warfarin-associated intracerebral hemorrhage.[15,17] Compared with patients of a younger age, patients older than 75 years have a relative risk of 3.2 of developing this complication.[17] Hylek et al. found that age is a strong independent risk factor for subdural hemorrhage, but for intracerebral hemorrhage age carries only borderline significance.[15] In our patients, the mean age of 67 years is similar to those reported by other series, as is the mean duration of therapy.

The mortality in our patients is 40% and is lower than the mortality of other series, which range from 46-68%. This mortality of 40% is also lower than the previous reported mortality of 53% among patients with spontaneous intracerebral hemorrhage in our hospital.[21]

However, the difference between our series and others is relatively small and probably related to small number of patients in our series. Whether the use of warfarin is associated with increased mortality remains an unsettled issue. Radberg et al. found that the use of anticoagulant increased the volume and mortality of intracerebral hemorrhage when compared with untreated patients.[14] However, our results did not shown an increased mortality among warfarin users when compared with historical controls and is in keeping with the findings of Winzten et al.[11]

The main finding of this study is that the mean INR value in our series of patients is lower than other reported series. The intensity of anticoagulation has been shown to be one of the most significant risk factors for the development of warfarin-associated intracerebral hemorrhage. Hylek et al. reported that among whites there was a doubling of risk with each increase of 0.5 in the prothrombin time ratio, and the risk increased dramatically if the INR was greater than 4.[15] This observation was also supported by most other studies.[11,12,17,22] In our patients, the mean INR of 2.3 is much lower than that encountered in other series, which generally reported a mean INR of above 3. (Table 2) Thus, Chinese patients may develop intracerebral hemorrhage at a lower intensity of anticoagulation when compared with white patients. Although this observation could be biased by the fact that most physicians in Hong Kong aim at a lower range of INR, there are other epidemiological data which suggest that ethnicity plays a major role in the development of intracerebral hemorrhage. Although Helyk et al. did not found race (white Vs non-white) a significant risk factor,[15] the number of non-whites was small and constituted less than 10% of their patients. Studies of the epidemiology of stroke on the other hand suggest that there are large differences in the proportion of intracerebral hemorrhage among different racial groups. Intracerebral hemorrhage accounts for about 10% of all strokes in whites but up to 30% in Africans, Hispanics and Asians.[23-25] The mechanism of this difference remains unknown.[26]

Furthermore, Chinese patients are also more sensitive to warfarin. Yu et al. have shown that for the same INR, Chinese patients require a lower dose of warfarin than whites.[27] Physicians treating Chinese patients tend to be more reserved in the use of warfarin and usually keep the intensity of anticoagulation at a low level. There is also a distinct lack of enthusiasm in using warfarin for primary prevention of stroke in patients with non-valvular AF. Under-dosage and under-utilization of warfarin may have denied some

Table 2: Summary of reported series of warfarin-associated intracerebral hemorrhage

Reported Series	n	Mean INR	Mean Age	Duration of Treatment (months)	Hematoma Volume (mls)	Mortality (%)
Wintzen et al, 84[11]	38	3.7	84%>60	66%>12	n/a	68
Kase et al, 85[12]	24	n/a	62	22*	47*	63
Franke et al, 90[13]	79	3.5	67	51	50	67
Radberg et al, 91[14]	28	3.3*	71	30	72	57
Hylek et al, 94[15]	77	n/a	69	3 to 48	n/a	46
Mathiesen et al, 95[16]	41	3.8	70	15	50	68
SPAF II, 96[17]	9	3	76	9	n/a	n/a
Current series	10	2.3	67	33	55	40

*calculated from published data; n/a indicates not available

patients from the benefits of anticoagulation. During the period of our study, only 10 patients had warfarin-associated intracerebral hemorrhage while 478 patients not on warfarin were hospitalized for ischemic stroke and AF. If the published relative risk reduction of 68% were applicable to our population, then up to 325 of these ischemic strokes (or approximately 10% of all strokes) might have been prevented. In order to encourage the wider use of anticoagulation, there is a need to determine the safety and efficacy of warfarin and optimal level of INR in Chinese. A randomized controlled trial comparing warfarin with aspirin in patients with non-valvular AF may be justified in our population.

In conclusion, this study suggests that apart from a lower mean INR, there is no major difference in the pattern of warfarin-associated intracerebral hemorrhage between Chinese patients and others. Further studies are needed to determine the significance of the difference in INR and to clarify the risk-benefit ratio of long term anticoagulation for the prevention of stroke in our population.

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