ship between the distribution of the MP and the collateral circulation was appropriate. In two others (patients 16, 20), the distribution of the MP could not be explained by collateral circulation alone. When the perfusion pressure in the MCA declines, superficial BZ areas can be salvaged by the leptomeningeal collateral flow from the ACA and/or the PCA, provided this channel is functioning. This type of collateral flow is often insufficient to save the internal BZ because the perforators of MCA are terminal arteries. This reason is perhaps why the internal BZ was more vulnerable to ischemia than the superficial ones.

The present results do not support the PET observations by Leblanc et al (15) and Yamauchi et al (16) that the superficial BZ areas are hemodynamically vulnerable to ischemia in patients with ICA occlusive disease and good collateral flows. We found no significant differences in the superficial BZ/MCA ratio of CBV/CBF and OEF between the ICA stenosis/occlusion groups and the control group; this was consistent with the observation by Carpenter and colleagues (17). Several differences in methodology exist among these studies, and these may account for the differences in results. Leblanc et al selected patients with ICA stenosis, and Yamauchi et al selected those with ICA occlusion and good collateral circulation through the Acom artery. In contrast, Carpenter et al and we selected those with ICA/MCA occlusive disease, which has nothing to do with collateral circulation. As we mentioned earlier, the main route of blood flow to the affected MCA territory had a significant relationship to topographic pattern of the MP. It should be noted that, in our study, two patients with good collateral flow through the Acom artery also had MP in only the affected BZ areas. Furthermore, Carpenter et al and we used the BZ/MCA ratio to account for the hemodynamic status of the ipsilateral MCA territory. This approach allowed us to determine whether patients with abnormal MCA hemodynamics have a further selective abnormality localized to the BZs.

It has generally been thought that most BZ infarctions arise from hemodynamic events (2–4). However, some authors (5–14) have suggested that embolization may play an important role in the pathogenesis of these infarcts. Pollanen et al (7) reported three autopsy cases of the anterior BZ infarction caused by thromboemboli. In their autopsy series, Masuda et al (11) reported that atheromatous embolism in the brain frequently caused anterior and posterior BZ infarcts by occluding the terminal cortical branches. Thus, emboli of a certain small size might occlude terminal portions of the cortical branches and cause a so-called watershed infarction. Recently, Caplan et al (14) emphasized the interaction of hypoperfusion and embolization, that is, that decreased perfusion reduces the washout and clearance of emboli that enters the vascular bed of hypoperfused regions. In either theory, embolization may play an important role in the pathogenesis of superficial BZ infarctions. Our results provided further support for this concept.

A question remains as to why posterior BZ infarction occurs in ICA occlusive disease. The posterior BZ area can easily be supplied by a blood flow through the leptomeningeal collateral channels from the PCA. To take another example, superficial BZ infarctions often occur in MCA occlusive disease. The superficial BZ areas, however, are hemodynamically resistant to ischemia because of leptomeningeal collateral channels. Such BZ infarctions are not easily explained with the hemodynamic theory, and thus, they are more likely to be embolic in nature. Recently, some authors have reported that the patients with internal BZ infarction have hemodynamic impairment more severe than that of patients with superficial BZ infarctions (27–29). A hemodynamic mechanism may play an important role in the development of internal BZ infarction. We have to clinically observe the part of the brain that becomes necrotic in the case of certain hemodynamic infarctions associated with occlusive disease of a major cerebral artery. Furthermore, we also need to compare the present results obtained in patients without BZ infarcts with the PET findings in patients with BZ infarcts.

Conclusion

We found no evidence that selective hemodynamic failure consistently occurs in the internal and superficial BZ areas in patients with occlusive disease of the major cerebral arteries. A small number of patients, 25% in the present series, had elevated OEF localized in the BZ areas, which always included the internal one. Although the internal BZ area was more frequently accompanied by localized MP than were the other regions, no patients had elevated OEF in only superficial BZ areas. These results are inconsistent with the clinical observation that approximately 80% of BZ infarctions develop superficially. Thus, most superficial BZ infarctions may not be associated with the hemodynamic mechanism.

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Evacuation of Intracerebral Hematoma Is Likely to Be Beneficial

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A new era has begun for acute ischemic stroke since the success of a clinical trial of hyperacute thrombolytic therapy. By contrast, there is yet time before daybreak in the management of acute intracerebral hematoma (ICH). Although many therapeutic options, including surgical evacuation, are described in stroke textbooks and guidelines for patients with acute ICH, nothing has yet been proven in large-scale randomized clinical trials.[1,2] Only a few subgroups of patients with ICH are listed as candidates for surgical treatment. They are patients with large (>3 cm) cerebellar hematoma and young patients with a lobar hematoma who are clinically deteriorating. Patients with small hematoma and with deep coma should not be treated surgically. For all other ICH patients, the best therapeutic option remains unclear.[2]

In the first and largest controlled trial by McKissock et al,[3] no benefit from surgical evacuation was demonstrated in regard to either mortality or morbidity. However, many patients with ICH have been treated surgically since this negative study. For example, more than 7000 patients with ICH per year are estimated to receive surgical treatment for hematoma evacuation in the United States.[4] The situation is similar in Japan.

In a retrospective, nonrandomized study in Japan, Kanaya and Kuroda[5] compared the effects of surgical evacuation on mortality and morbidity in 3638 patients with putaminal hemorrhage to those of medical management in 3372. On the basis of the results, they recommended surgical treatment if the hematoma is larger than 30 mL in extent and the level of consciousness is somnolent to semicomatose. They also found that functional outcome was better in patients undergoing stereotaxic aspiration than in those with conventional evacuation, if the patient's preoperative consciousness was normal or stuporous. Most of neurosurgeons and neurologists in Japan accept their opinion that hematoma evacuation can reduce the early mortality. The conclusion of this study, particularly concerning the beneficial effect of surgical evacuation on functional outcome, has been criticized, mainly because of the lack of randomized comparisons.

Recently, results of several randomized clinical trials were published. Their sample sizes were small, and therefore their results were inconclusive. In a systematic review by Hankey and Hon,[6] the pooled results of the 3 randomized trials of open craniectomy and 1 trial of endoscopic evacuation for supratentorial ICH indicated a nonsignificant increase in odds of death and dependency at 6 months for patients treated surgically. More recent meta-analysis by Fernandes et al[7] suggested a benefit from surgery, with a reduction in the chances of death and dependency after surgical treatment by a factor of 0.63. This meta-analysis excluded the study by McKissock et al and a Chinese trial, because of problems of quality.

The Surgical Trial in Intracerebral Hemorrhage (STICH), a multicenter, randomized controlled trial, is in progress to evaluate the role of surgery in a total of 1000 patients with spontaneous supratentorial ICH.[8] Unfortunately, the study protocol is rather ambiguous. A patient can be included when the surgeon is uncertain about the need for surgical evacuation. The neurosurgeon can use the method preferred for surgical evacuation. The study may have a danger of surgeon's or institutional bias.

It is a reasonable concept that brain damage due to ICH may be minimized by removal of the hematoma. It may reduce the mass effect, block the release of toxic products from the hematoma, and prevent early hematoma enlargement occurring early after onset of ICH.[9] I believe that hematoma evacuation can reduce not only mortality but also morbidity if several critical conditions are optimized. They are clinical and neurological conditions of patients, the extent and site of hematoma, the method of hematoma evacuation (conventional versus stereotaxic or endoscopic evacuation), the time window of surgery, and additional medications to facilitate complete evacuation (use of thrombolytic agents). In order to establish the best therapeutic option for acute ICH patients, further studies will be needed even after the STICH study.

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THROMBOSIS RESEARCH

Regular Article

Correction of INR by prothrombin complex concentrate and vitamin K in patients with warfarin related hemorrhagic complication

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Abstract

We investigated the effect of prothrombin complex concentrate (PCC, median 500 IU) and vitamin K (10–20 mg) or either on blood coagulation and clinical findings in 17 patients with major hemorrhagic complication during warfarin treatment. Their international normalized ratio (INR) at admission was median 2.7 (2.0–above 10.0).

In 11 patients treated with PCC and vitamin K, INR decreased to median 1.13 (0.91–1.36) 10 min after the administration with elevation of plasma levels of coagulant factors II, VII, IX, X and protein C.

INR decreased abruptly after the administration of PCC without vitamin K in two patients but it increased again 12–24 h after, with decrease of coagulant factors levels. In one of them, a hematoma of the brain enlarged with INR re-increase 12–24 h after the administration.

In four patients treated with vitamin K alone, INR decreased slowly from 2.69 (1.03–3.35) to 1.28 (1.25–1.44) 12–24 h after the administration in parallel with gradual increase of the coagulant factors.

PCC administration with or without vitamin K seems to be more effective in rapidly correcting increased INR levels than vitamin K treatment without PCC. PCC without vitamin K may result in re-increase of INR and clinical deterioration.

Keywords: Intracranial hemorrhage; Warfarin; Prothrombin complex concentrate

1. Introduction

Hemorrhage is a major adverse effect of oral anticoagulant agents, which are widely used for prevention of thrombotic or embolic diseases [1–5]. Intracranial hemorrhage (ICH) is one of the most serious hemorrhagic complications associated with warfarin treatment. The relative risk of ICH during oral anticoagulant therapy is more than 10-fold in patients over 50 years of age [6]. More protracted bleeding and larger hematomas are found in patients treated with anticoagulants than in those with spontaneous ICH [7,8]. The annual risk of anticoagulant-related ICH was reported to be 1.1% per year when anticoagulant treatment is given for cerebrovascular disease [9]. Hylek and Singer [10] reported that the risk of intracerebral and subdural hemorrhage rises dramatically with an international normalized ratio (INR) value greater than 4.0.

In order to reverse the effect of warfarin, warfarin administration is discontinued, vitamin K or a combination of vitamin K and fresh frozen plasma (FFP) of 800–1000 ml are administered according to INR values. However, administration of FFP of 800–1000 ml has a risk of viral infection, needs a long preparation time and often causes volume overload. They may result in enlargement of ICH with deterioration of neurological deficit or heart failure [11,12]. Prothrombin concentrate complex (PCC) has been introduced as a faster method of correcting INR than FFP in warfarin-related coagulopathy [11–14]. However, several questions remain to be resolved in PCC treatment; how rapidly PCC is capable of correcting INR, whether PCC can actually prevent enlargement of hematoma or whether it has a danger of inducing a hypercoagulable state. Thus, in 17 patients treated with PCC and vitamin K or either for major hemorrhagic complication during warfarin treatment, we investigated hematoma size, neurological symptoms, INR, plasma levels of coagulation factors II, VII, IX, X, protein C, prothrombin fragment 1+2 (F1+2) and D-dimer after the treatment and compared them according to combination of

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the treatment, PCC with vitamin K, PCC without vitamin K, or vitamin K only.

2. Methods

From December 2000 to January 2002, 17 patients developed major hemorrhagic complication during warfarin treatment and were admitted into our hospital. The major hemorrhage was cerebral hemorrhage in 13, acute epidural hemorrhage, acute subdural hemorrhage, massive subcutaneous hemorrhage, and hemothorax suspected in one each. The patients were 12 men and 5 women with 33–83 years of age (median 69 years old). The underlying diseases for warfarin indication was NVAF in 9, prosthetic cardiac valves in 4, deep vein thrombosis in 2, dilated cardiomyopathy and myocardial infarction in 1 each. Past history of brain infarction was accompanied in 8, hypertension in 11, and diabetes mellitus in 6 of the 17 patients.

PCC with vitamin K, PCC without vitamin K, or vitamin K only were administered to them according to treatment decision of physicians in charge after informed consent was obtained from the patients or their family.

When PCC was administered, we initially had a plan of giving 50 IU/kg or 25 IU/kg of PCC in combination with vitamin K when INR values ≥ 4.5 or < 4.5, respectively [15]. However, in the first patient, the efficacy of PCC in correcting INR was greater than expected. Subsequently, PCC was administered first at 500 or 1000 IU, and an additional administration was considered according to the INR value just after the first PCC administration. We used a commercially available PCC "PPSB-HT Nichiyaku" produced by Nihon pharmaceutical, Tokyo, Japan, which contained 500 IU of II, VII, IX, X and 380 U of protein C in 25 ml. The PCC was derived from donated plasma, which was negative for HBs antigen, anti HCV antibody, anti HIV-1 antibody, anti HIV-2 antibody, anti-HTLV-I antibody and screened by ALT values. Heat at 65 °C for 96 h and nanofiltration were applied to inactivate viruses. PCC was extracted from a bottle through a filter to an injection syringe and infused through a venous line in 5–10 min. We administered 10 or 20 mg of vitamin K through the venous line with or without PCC.

Plasma levels of INR, factors II, VII, IX, X, protein C, fibrinogen, prothrombin fragment 1+2 (F1+2) and D-dimer were determined before and 10 min and 12–24 h after PCC administration.

INR, plasma levels of fibrinogen (normal value, 150–340 mg/dl), coagulant factors II (75–135%), VII (75–140%), IX (70–130%), and X (70–130%) were measured by a clotting assay method; plasma levels of antithrombin III (80–120%) and protein C activity (75–125%) were measured by a chromogenic assay method. Plasma levels of F1+2 (0.40–1.40 nmol/l) and D-dimer (< 1.0 μmol/ml) were determined by an ELISA method.

Intracranial hematoma size on CT and neurological deficits before and after PCC administration were also monitored. ICH volume was determined in the following manner [16]. On the CT slice with the largest area of ICH, the longest diameter (A) and the largest diameter (B) perpendicular to the longest diameter were measured using the centimeter scale on the film. The height of the hematoma (C) was calculated by multiplying the number of slices involved and slice thickness. Hemorrhage within the ventricular system was not measured. The three diameters were multiplied and then divided by two to obtain the volume of ICH ($A \times B \times C/2$) [10].

Neurological deficits were evaluated by the NIH stroke scale (NIHSS) score before and 12–24 after the administration of PCC [17]. The activity of daily living was

Table 1
Baseline characteristics of the subject

No.	Age	Sex	Hemorrhagic complication			NIHSS at adm.	Past history of HT	SBP at adm.
			Location	Size of hematoma (ml)	Ventricular expansion			
1	70	M	Thalamus	1	–	9	+	150
2	74	F	Thalamus	4	+	3	–	140
3	70	M	Thalamus	8	–	20	+	180
4	54	M	Caudate nucleus	6	+	3	+	140
5	62	M	Acute epidural hemorrhage	–	–	28	+	200
6	62	M	Acute subdural hemorrhage	–	–	5	–	160
7	80	F	Massive subcutaneous hemorrhage	–	–	0	–	140
8	83	M	Hemothorax suspected	–	–	0	+	150
9	33	F	fronto-parietal lobe	50	–	16	–	100
10	63	M	cerebellum	24	–	4	+	220
11	81	M	lateral geniculate body	1.5	–	3	+	150
12	65	F	Thalamus	10	+	8	+	148
13	55	M	Occipital lobe	72	–	6	–	120
14	65	F	frontal lobe	7.5	–	1	+	150
15	72	M	thalamus	1	–	1	+	192
16	72	M	thalmus+ putamen	157	+	28	+	190
17	69	M	thalamus	0.5	–	1	+	170

Table 2
Treatments and outcomes

No.	Anti-HT therapy after adm.	Correction of INR		Enlargement of cerebral hematoma	Rankin Scale	
		Method	Period from onset (h)		Before	At discharge
1	+	PCC+VK	18	–	3	3
2	–	PCC+VK	9	–	1	4
3	+	PCC+VK	8	–	4	4
4	+	PCC+VK	10	–	1	3
5	–	PCC+VK	4	–	1	death
6	–	PCC+VK	10	–	2	2
7	–	PCC+VK	6 days	no cerebral hematoma	1	1
8	–	PCC+VK	unknown	no cerebral hematoma	1	1
9	–	PCC+VK	3	–	0	3
10	–	PCC+VK	3	+	1	1
11	+	PCC+VK	11	–	1	2
12	+	PCC	6	–	1	4
13	–	PCC	15	+	1	death
14	–	VK	60	–	1	1
15	+	VK	14	–	1	1
16	+	VK	3	–	+	death
17	+	VK	18	–	1	0

assessed by the Rankin scale score before ICH and at discharge from the hospital [18].

Data were expressed as median and range. We used Wilcoxon's rank sum test for analysis of variables. A p-value less than 0.05 was considered significant.

3. Results

In 11 patients treated with PCC (500 IU in 9, 1000 IU and 1500 IU in 1 each, 7–27 IU/kg) and vitamin K (10 mg), INR significantly decreased from 2.70 (2.26–above10) to median 1.13 (0.91–1.36) 10 min after the administration ($p<0.01$, Wilcoxon's rank sum test) and remain low (median 1.06) 12 to 24 h after ($p<0.01$ vs. before treatment, $p=0.21$ vs. 10 min after the administration), while plasma levels of the coagulant factors II, VII, IX, X and the protein C significantly increased 10 min after ($p<0.01$) and 12–24 h after the administration ($p<0.01$ vs. before treatment, $p<0.05$ in protein C, VII, IX and $p<0.1$ in II, X vs. 10 min after, Tables 1 and 2, Figs. 1 and 2). Although clinical deterioration or enlargement of cerebral hematoma were not seen in 9 of them, a patient with severe epidural hemorrhage died and the other patient having cerebellar hemorrhage deteriorated with enlargement of hematoma while blood pressure was high (Tables 1 and 2). A patient with massive subcutaneous hemorrhage improved after reversal of warfarin with PCC and vitamin K (Tables 1 and 2, patient 7). In other patient with hemothorax suspected, warfarin was counteracted to perform pleural puncture with PCC and vitamin K (Tables 1 and 2, patient 8). With other examinations, he was diag-

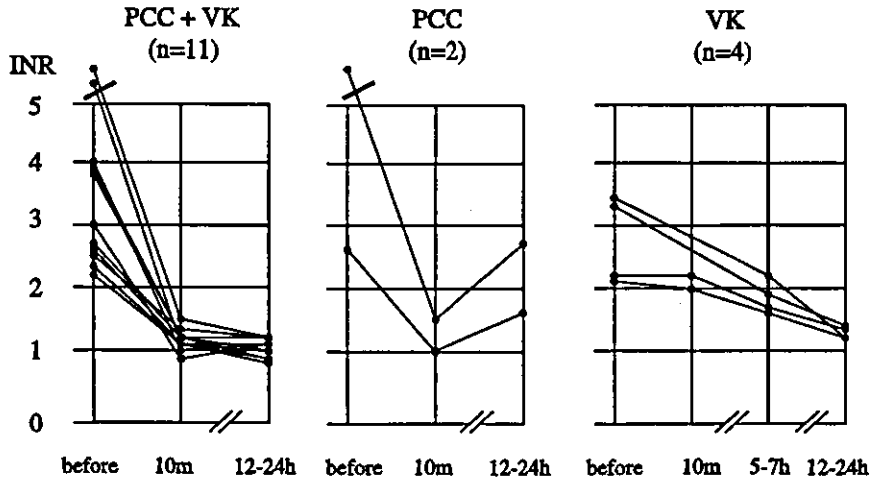

Fig. 1. INR values before and after PCC administration according to combination of PCC and vitamin K. VK: vitamin K, m: minutes, h: hours.

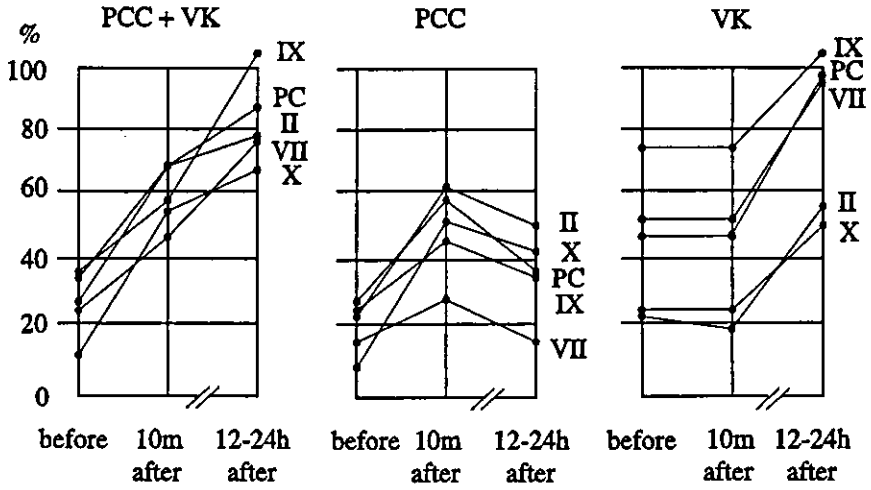

Fig. 2. Median values of coagulant factors II, VII, IX and X and protein C before, 10 min after, and 12–24 h after PCC administration according to combination of PCC and vitamin K. VK: vitamin K, m: minutes, h: hours.

nosed pleural effusion with pneumonia and improved by treatment of antibiotics.

INR decreased sharply 10 min after the administration of PCC without vitamin K in two patients from median 6.23 to 1.36 but it increased to 2.07 12–24 h after, in whom plasma levels of the protein C and the coagulant factors increased 10 min after and decreased 12–24 h after the administration (Figs 1 and 2). In one of them, a hematoma size unchanged after the treatment (Fig. 3). However, in the other one, a hematoma in the right occipital lobe enlarged and left hemiparesis was deteriorated with INR re-increase 12–24 h after the administration (Fig. 3). Then, combination of 500 IU of PCC and 10 mg of vitamin K was administered into him. After INR was corrected to be 1.45, his enlarged hematoma was evacuated surgically and neurological symptoms improved. However, he died on the fourth day due to infective endocarditis.

In four patients treated with vitamin K (10–20 mg), INR values of median 2.69 (2.03–3.35) before treatment were unchanged 10 min after the administration but decreased to 1.78 (1.54–2.19) 5–7 h after ($p=0.07$) and further decreased to 1.28 (1.25–1.44) 12–24 h after ($p=0.07$ vs. before treatment and 10 min after) in parallel with gradual increase of the protein C and coagulant factors (Figs. 1 and 2). One of them with severe parenchymal hemorrhage (157 ml) died but in the other three patients with small paren-

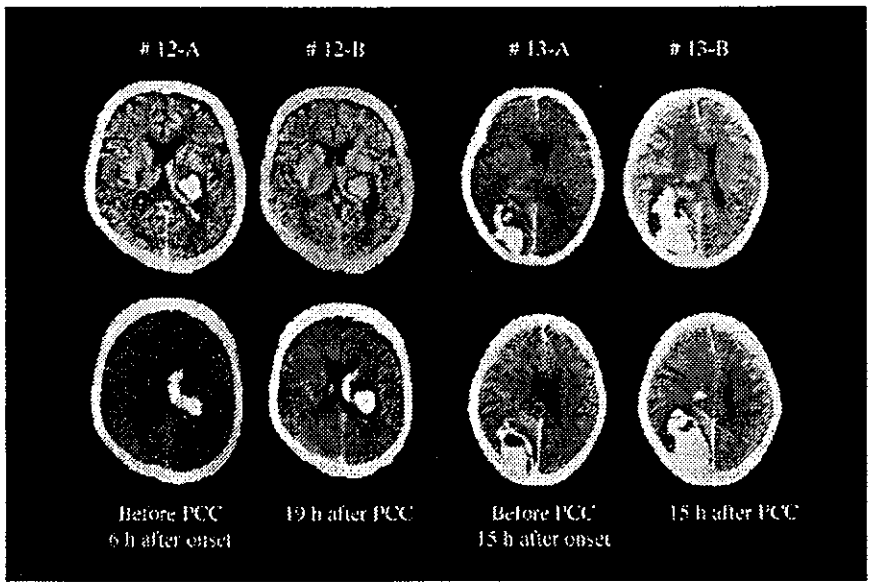

Fig. 3. Brain CT images of patients #12 and #13; #12-A, 6 h after onset and before PCC administration; #12-B, 19 h after PCC administration; #13-A, 15 h after onset and before PCC administration; #13-B, 15 h after PCC administration.

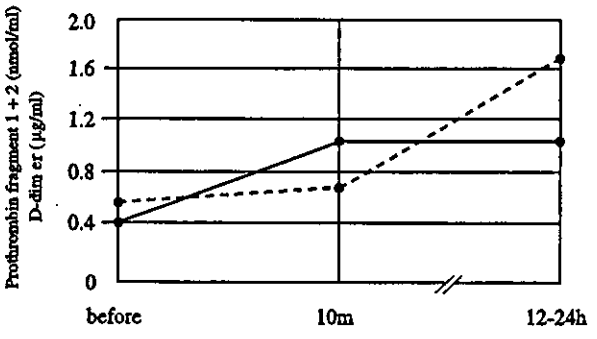

Fig. 4. Median values of prothrombin fragment 1+2 and D-dimer (broken line) before and after administration of PCC 10 min after, and 12–24 h after PCC administration; m: minutes, h: hours.

chymal hemorrhage (0.5–7.5 ml) at the start of the treatment 14–60 h after the onset, there was no clinical deterioration (Tables 1 and 2).

In 13 patients treated with PCC and with or without vitamin K, plasma levels of F1+2 increased significantly from the median 0.41 (0.047–3.94 nmol/ml) to 1.02 nmol/ml (0.41–3.90 nmol/ml) ($p<0.01$) 10 min after the treatment and those of D-dimer increased from the median 0.57 (0.05–4.06 μg/ml) before the treatment to 1.64 μg/ml (0.05–8.77 μg/ml) ($p<0.05$) 12–24 h after the treatment although there were no embolic episodes during hospitalization of 2–54 days (Fig. 4). In four patients with vitamin K treatment only, both F1+2 and D-dimer levels were unchanged after the treatment. There were no significant changes in plasma levels of fibrinogen nor antithrombin in any treatment combinations group.

4. Discussion

Reversing warfarin effects by 20–50 IU/kg of PCC with vitamin K in patients with life-threatening neurological emergencies has been reported to be more rapid and effective than FFP at a mean amount of 600–2712 ml with vitamin K in four studies [11–14]. Correction of INR values was confirmed 15 min, 2, or 4.8 h after PCC administration. Preston et al. [19] demonstrated rapid reversal of INR by measuring blood samples obtained at 20, 60, and 120 min after treatment. According to the present study, correction of INR seems to be accomplished more quickly, within 10 min after completion of PCC administration when compared to the previous four reports. Excessive INR values may be counteracted immediately with increase of coagulant factors II, VII, IX, and X by the PCC administration.

Butler and Tait [15] recommended administration of 50 or 25 IU/kg of PCC with vitamin K in the immediate management of oral anticoagulant-related intracranial hemorrhage when INR values are ≥ 4.5 or <4.5, respectively. However, the present study demonstrated that median 12.5 IU/kg (range 7–27 IU/kg) of PCC induced a rapid correction of INR. Therefore, if immediate measurement of INR is available, it may be appropriate to administer 500 IU of PCC at first followed by a second administration of PCC 500 IU according to the INR value measured just after the first administration.

The hematoma in a patient with cerebellar hemorrhage enlarged during systolic blood pressure >200 mm Hg although INR correction was commenced 3 h after the onset and immediately accomplished. Blood pressure control in acute phase of hemorrhage in patients treated with warfarin seems as important as brain hemorrhage in those not treated with warfarin [20].

Fredriksson et al. [13] reported bilateral renal infarction at autopsy in a case treated with PCC and noted the risk of general thromboembolism triggered by activated prothrombin complex. Although the F1+2 levels increased soon after the PCC administration and plasma levels of D-dimer increased 12–24 h after, no patients in the present study demonstrated thrombotic or embolic episodes after administration of PCC. Plasma levels of protein C, an inhibitor of factor V and VIII, increased with PCC administration, which may play a role to suppress excessive coagulopathy induced thrombosis or embolism. PCC has been used for replacement of PC in patients with PC deficiency [21]. We used smaller amount of PCC than previous reports, which might contribute to avoid thromboembolism [11–14].

PCC administration without vitamin K resulted in a rapid decrease of INR but a re-increase of INR 12–24 h after PCC administration in two patients, one of whom developed enlargement of intracerebral hematoma. It appears that rapid decrease of INR reflects a rapid increase in the plasma level of prothrombin complex, and the subsequent increase in INR was due to a decrease in the plasma level of prothrombin complex according to its relatively short half time. It has been reported that PCC has a biphasic half time, the first phase was 8 h and the second one was 20 h [22]. A subsequent increase in INR at 12–24 h may facilitate resumption of warfarin control so as to prevent ischemic events. However, in such an early phase of PCC administration, resumption of warfarin control seems to carry a risk of enlargement of hematoma. Thus, primary physicians might be reluctant of resume warfarin. Kazui et al. [20] reported that enlargement of hematoma was seen in 20% of intracranial hemorrhage patients not treated with antithrombotic agents and enlargement of hematoma had stopped by 6 h after the onset in 83% and by 24 h in 100%. Kawamata et al. [23] resumed anticoagulation in 12 patients with intracranial hemorrhage related to warfarin within 3 days and found no enlargement of hematoma or rebleeding. Therefore, in order to avoid worsening hemorrhagic complications, an interval of 3 days, wherein INR is fully corrected with PCC and vitamin K, may be required before resumption of anticoagulation.

Three patients with intracerebral hemorrhage did not deteriorate after reversal of warfarin by vitamin K only. Their size of hematoma was small (0.5, 1, and 7.5 ml) and period from onset to admission was more than half a day

(14, 18, 60 h). Therefore, vitamin K administration only may be enough in patients with brain hemorrhage if their size of hematoma is found small when more than half a day passes after the onset.

In order to determine the true effect of PCC treatment, optimal dose of PCC and the timing of anticoagulation resumption, further studies with a larger number of patients with intracranial hemorrhage treated with warfarin is needed.

In conclusion, PCC administration with or without vitamin K seems to be more effective in rapidly correcting increased INR levels than vitamin K treatment without PCC. PCC without vitamin K may result in re-increase of INR and clinical deterioration.

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Predisposing factors for enlargement of intracerebral hemorrhage in patients treated with warfarin

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Summary
To elucidate predisposing factors for enlargement of intracerebral hematoma (ICH) during warfarin therapy, we reviewed 47 patients on warfarin who developed acute ICH and determined relationships among ICH enlargement, INR reversal and clinical data. Among 36 patients treated to counteract the effects of warfarin within 24 h of onset, ICH increased in 10 patients (enlarged group), but remained unchanged in the remaining 26 (unchanged group), while ICH remained unchanged in another 11 patients in whom the effect of warfarin was reversed after 24 h. The international normalized ratio (INR) was counteracted immediately in 11 patients treated with prothrombin complex concentrate (PCC) but gradually in the other 36 treated by reducing the dose of warfarin, or by administering vitamin K or fresh frozen plasma. Multivariate analysis with a logistic regression model showed an INR value <2.0 at admission or for 24 h after immediate INR correction with PCC prevented ICH enlargement (OR 0.069, 95%CI 0.006-0.789, p = 0.031). An INR value of >2.0 within 24 h of ICH seems an important predisposing factor for ICH enlargement.

Keywords
Intracerebral hematoma, warfarin, prothrombin complex concentrate, international normalized ratio

Thromb Haemost 2003; 89: 278–83

Introduction

Intracerebral hemorrhage (ICH) is one of the most serious hemorrhagic complications associated with warfarin treatment. The relative risk of ICH during oral anticoagulant therapy increases more than ten-fold in patients over 50 years of age (1). Bleeding is more protracted and hematomas are larger in patients treated with anticoagulants than in those with spontaneous ICH (2, 3). The annual risk of anticoagulant-related ICH is 1.1% per year among patients who have cerebrovascular disease and who are treated with anticoagulants (4). Hylek et al. reported that the risk of intracerebral and subdural hematoma significantly increases when the international normalized ratio (INR) value was above 4.0 (5). Yamaguchi et al. reported that the standard intensity of warfarin (INR 2.2–3.5) carried a higher risk of severe hemorrhagic complication than a lower intensity (INR 1.5–2.1) in elderly patients with non-valvular atrial fibrillation (NVAF) (6).

Our prior study revealed that the predisposing factors to hematoma growth among patients with spontaneous intracerebral hemorrhage were acute phase within 6 h of onset, hypertension, diabetes mellitus, liver diseases and a history of brain infarction (7). However, such factors in patients treated with warfarin have not been fully investigated.

The effect of warfarin can be counteracted by administering vitamin K or a combination of vitamin K and 800–1,000 ml of

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fresh frozen plasma (FFP) depending on INR values, in addition to the discontinuation of warfarin. However, administration of FFP carries a risk of viral infection, requires long preparation time and often causes volume overload. These strategies may result in enlarged ICH accompanied by deteriorating neurological deficits or heart failure (8, 9). Prothrombin complex concentrate (PCC) has recently been introduced as an agent that can correct INR faster than FFP in warfarin-related coagulopathy (8-11). We have corrected high INR values using PCC since December 2000, because it counteracts the effects of warfarin within 10 minutes (12).

We examined the predisposing factors for ICH enlargement and determined whether PCC is useful to prevent it in patients treated with warfarin. We retrospectively investigated consecutive patients who developed acute ICH during warfarin treatment, from December 2000 to September 2002 when PCC was administered and from January 1992 to November 2000 when conventional treatment was applied.

Methods

We retrospectively reviewed the hospital records of 50 consecutive patients who developed ICH. These patients were admitted to our stroke care unit within five days of ICH onset and the diagnosis was confirmed by CT. Excluded from the study were three patients who were comatose upon admission and who died within three days of ICH onset due to brain herniation. We thus studied 47 patients (35 men and 12 women; median age, 69 [range 16–89] years) with acute ICH.

The primary underlying diseases requiring anticoagulation were NVAF in 22 patients, mitral or aortic valve replacement in 11, deep vein thrombosis in four, dilated cardiomyopathy in three, coronary artery bypass graft for ischemic heart disease in three, complicated atheromatous lesions at the aortic arch in two, and atherosclerotic obliterans and homograft-shunt operation for hemodialysis in one each. Twenty-four of the patients had a history of brain infarction.

The second CT examination was performed routinely within 24 h after starting treatment to counteract the warfarin effects and the third was implemented within a few days after that. An additional CT scan was also performed if a patient clinically deteriorated.

A parenchymal hematoma was located at the thalamus in 18 patients, the putamen in 8, the thalamus and putamen in one, the caudate head in two, the subcortex in 13, the cerebellum in four, and pons in one.

The volume of ICH was determined as follows (13). The longest diameter (A) and the largest diameter (B) perpendicular to A were measured using the centimeter scale on CT films of slices showing the largest area of ICH. The height of the hematoma (C) was calculated by multiplying the number of slices involved and slice thickness. Hemorrhage within the ventricular system was not measured. The three diameters were multiplied and then divided by two to obtain the volume of ICH ($A \times B \times C/2$) (10). When volume after treatment was 1.4-fold larger than that before, the parenchymal hemorrhage was considered to have enlarged.

The effects of warfarin were counteracted by stopping or reducing the amount of warfarin, administration of only vitamin K, or of fresh frozen plasma (FFP) with or without vitamin K, and 500–1,500 IU of prothrombin concentrate complex (PCC) with or without vitamin K. The effect on INR correction by each therapy was monitored by measuring INR more than twice from 10 min to 24 h after starting the treatment.

We determined relationships between ICH volume and age, gender, hypertension, diabetes mellitus, underlying disease for anticoagulation, liver disease, history of brain hemorrhage, antiplatelet medication, duration from ICH onset to commencement of treatment, INR, systolic blood pressure (SBP), and serum blood sugar level at the time of admission, as well as INR and SBP after the treatment.

Hypertension was defined as the use of antihypertensive agents or blood pressure with a systolic value of > or = 160 mmHg or a diastolic value of > or = 95 mmHg. Diabetes mellitus was defined as the use of insulin or oral hypoglycemic agents, fasting blood glucose levels of > or = 140 mg/dl, or random blood glucose levels of > or = 200 mg/dl. Liver disease was defined as a diagnosis of liver cirrhosis or active hepatitis.

Data are expressed as median and range. Univariate analyses were performed based on the Mann-Whitney U test, the chi square test, or Fisher's exact test for instances in which counts of individual cells in a 2×2 table were below five. We performed multivariate analyses with a logistic regression

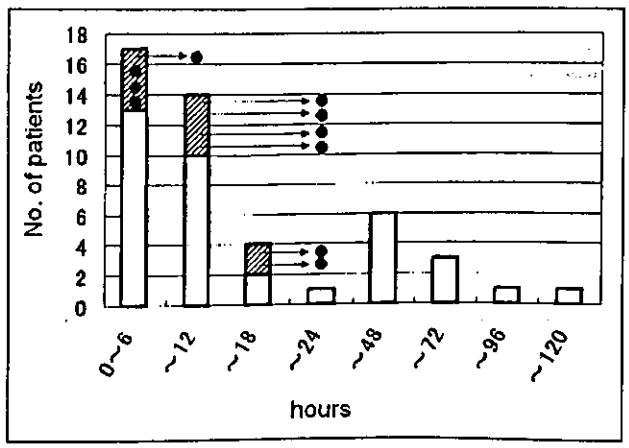

Figure 1: Number of patients with intracerebral hematoma during warfarin treatment stratified by time from onset to commencement of treatment, and by presence (shaded bar) or absence (white bar) of enlarged intracerebral hematoma. Closed circles indicate points in time when ICH enlargement was confirmed by CT

model using values of p <0.15 in univariate analyses. A p-value below 0.05 was considered significant, and values between 0.05 and 0.1 were considered marginally significant.

Results

Warfarin counteraction was commenced within 24 h of ICH onset in 36 patients and after 24 h in the remaining 11 patients. Among the 36 patients, ICH enlargement was confirmed in 10 (28%, enlarged group) but was not observed in the other 26 (unchanged group) and was definitely absent in the 11 patients who underwent treatment after 24 h of ICH (p = 0.0885). In four of the 17 patients in whom the treatment was commenced within six hours of onset, ICH enlarged, which was confirmed by CT within six hours in three patients and at six hours and a half in the other one (Fig. 1). In six of the 19 patients in whom the treatment was started between six and 24 h of onset, ICH enlargement occurred, which was confirmed by CT from 18 to 24 h after the onset of the ICH. Neurological deterioration was accompanied with eight of the ten patients with ICH enlargement (Fig. 2).

Patients tended to be younger (Mann-Whitney U test, p = 0.0961) and had liver diseases more frequently (Fisher's exact test, p = 0.0152) in the enlarged group than in the unchanged group (Table 1). Gender, history of hypertension, incidence of diabetes mellitus, hypercholesterolemia, ischemic stroke and brain hemorrhage did not significantly differ among the groups. Antiplatelet therapy accompanied warfarin administration in 20% of the enlarged group and in 35% of the unchanged group (p = 0.6880).

Although median ICH volume at the time of admission in the enlarged group was larger than that in the unchanged group, it was not significant (Mann-Whitney U test, p = 0.1288, Fig. 2 and Table 2).

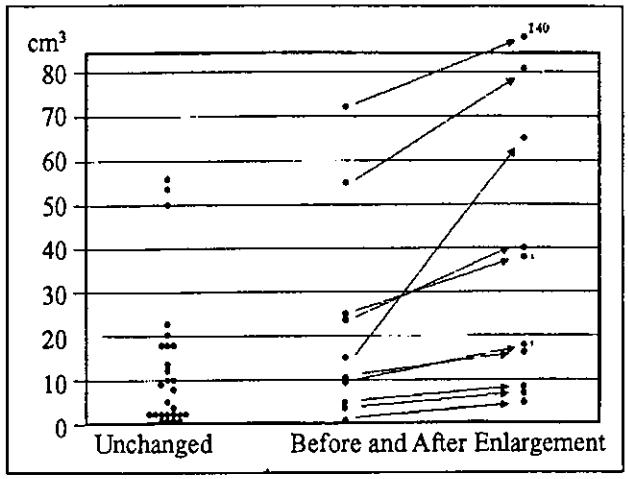

Figure 2: Hematoma volumes on admission in unchanged and enlarged groups, and those after enlargement in the latter group. * indicates patients without neurological deterioration.

The INR values on admission in the enlarged group were always above 2.0, which were higher than those in the unchanged group with significance (Mann-Whitney U test, p = 0.0217) (Fig. 3 and Table 2).

Duration from the onset of ICH and commencement of treatment was 1-109 h (median 9 h). The numbers of cessations or reductions of warfarin (40% vs. 35%), administration of vitamin K (30% vs. 27%), or FFP (10% vs. 4%), or PCC (20% vs. 35%) did not significantly differ between the enlarged and unchanged groups (Table 3).

The INR levels in eleven patients treated with PCC was corrected from a median of 2.64 (2.26–10) to 1.14 (0.91-1.63)

	Enlarged n=10	Unchanged n=26	p value
Male	8 (80)	20 (77)	>0.9999
Age*	63 [46-74]	71 [16-83]	0.0961
Hypertension	9 (90)	20 (77)	0.6454
Diabetes Mellitus	3 (30)	7 (27)	>0.9999
Hypercholesterolemia	2(20)	3 (12)	0.6034
Ischemic stroke	6 (60)	13 (50)	0.7169
Brain hemorrhage	2 (20)	3 (12)	0.6034
Liver disease	4 (40)	1 (4)	0.0152
Antiplatelet therapy	2 (20)	9 (35)	0.6880

Table 1: Demographics of patients. *, Mann Whitney U test; without *, Chi square test; ( ), % ; [ ], median and range.

Table 2: Clinical and laboratory data. SBP, systolic blood pressure; *, Mann Whitney U test; without *, Chi square test; ( ), % ; [ ], median and range; **, Number of patients with INR <2.0 at admission or rapid correction of INR with PCC and vitamin K.

	Enlarged n=10	Unchanged n=26	p value
At admission			
SBP (mmHg)*	161 [114-220]	162 [100-190]	0.7108
Blood sugar (mg/dl)*	160 [80-260]	125 [84-371]	0.1864
INR*	2.74 [2.1-10]	2.20 [1.11-4.0]	0.0217
INR >2.0	10(100)	17(65)	0.0394
Hematoma size (cm^2)*	12.2 [0.7-72]	6.0 [0.5-56]	0.1288
24 hours after treatment			
SBP (mmHg)*	150 [104-240]	142 [100-170]	0.9718
INR <2.0 **	1 (10)	18(69)	0.0023

10-60 minutes after an intravenous injection of PCC (500 IU in nine patients, 1,000 IU and 1,500 IU in one each) and a low INR level was maintained for at least 24 h in ten of them (Table 3). In the remaining patient, INR was decreased from 10.0 to 1.63 by 500 IU of PCC without vitamin K, but this value increased again to 2.60 and ICH enlarged 12 h after treatment. On the other hand, the amount of time required for INR values to decrease from > 2.0 to that between 1.2 and 1.9 was longer in patients treated without than with PCC.

The INR levels at admission were higher in the enlarged group than in the unchanged group (2.74 [2.1-10] vs. 2.20 [1.11-4.0], p = 0.0217, Table 2) and INR >2.0 at admission was more frequent in the enlarged group than in the unchanged group (100% vs. 65%, p = 0.0394, Fig. 3). The frequency of patients with INR <2.0 before treatment or for at least 24 h after PCC injection was significantly smaller in the enlarged group than in the unchanged group (10% vs. 69%, p = 0.0023).

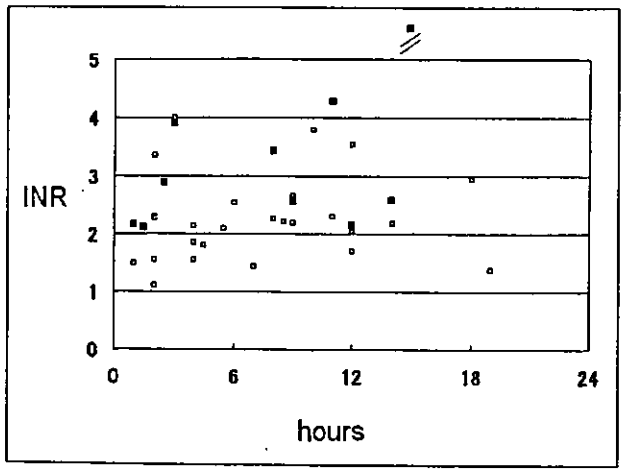

Figure 3: INR values on admission in patients admitted within the first 24 hours. Open squares, INR values of unchanged group; closed squares, INR values of enlarged group.

SBP and blood sugar at admission and SBP during the first 24 h after starting treatment did not significantly differ between the two groups (Table 2). The SBP was >200 mmHg at admission and during the 24 h after treatment in two patients of the enlarged group and in none of the unchanged group.

We selected the variables of liver disease, age, hematoma size and INR <2.0 before treatment or for at least 24 h after PCC injection as independent factors for multivariate analyses with a logistic regression model for hematoma enlargement. The analysis demonstrated that the INR <2.0 before treatment or for at least 24 h after PCC injection was significant (OR 0.069, 95%CI 0.006–0.789, p = 0.0312, Table 4).

Discussion

Although bleeding is more protracted and hematomas are larger in patients treated with warfarin than in those with spontaneous intracerebral hemorrhage (2, 3), the time window for ICH enlargement in patients treated with warfarin remains obscure. Fujii et al. retrospectively found enlarged hematomas in 14% of 627 patients with spontaneous intracerebral hemorrhage admitted within 24 h of onset (14). Kazui et al. reviewed the clinical records of 204 patients with spontaneous intracerebral hemorrhage and found enlarged hematomas in 41 (20%) of them within 24 h of onset in 34 (83%) of the 41 within 6 h and in 7 (17%) from 6 to 24 h (7). On the contrary, our study of patients treated with warfarin demonstrated a higher frequency of hematoma enlargement (28%). More than half of these

Table 3: Treatment to counteract warfarin and INR values. n*, Number of patients with available INR data; h, hours; min, minutes INR before, INR value before treatment; INR after, INR value after treatment.

	Enlarged	Unchanged	Adm. > 24 h	Total	n*	INR before		INR after		Duration	
						Median	Range	Median	Range	Median	Range
W	4	9	6	19	7	2.60	2.20-3.13	1.79	1.34-1.98	38 h	13-168 h
K	3	7	4	14	11	2.25	2.03-5.66	1.79	1.23-1.98	6 h	1-42 h
FFP	1	1	1	3	3	3.35	2.10-3.39	1.40	1.39-1.80	24 h	8-24 h
PCC	2	9	0	11	11	2.64	2.26- 10.0	1.14	0.91-1.63	10 min	10-60 min
Total	10	26	11	47							

enlargements (70%) were confirmed by CT between 6 and 24 h, but not thereafter. Therefore ICH patients treated with warfarin must be carefully monitored not only within six hours of onset but also within 24 h of onset. Although our subjects received treatment soon after admission, the period between ICH onset and the start of treatment was relatively long (median 9 h). To receive appropriate treatment to prevent ICH enlargement, patients should be educated about visiting an emergency hospital as soon as possible after stroke symptoms occur.

The size of small hematomas in patients with spontaneous intracerebral hemorrhage is unlikely to further increase (7). However, the present study found that 40% of the hematomas were smaller than 10 cm^2 on admission in the enlarged group. Therefore, the potential hazard of enlargement in patients treated with warfarin cannot be excluded, if a small hematoma is recognized within 24 h of ICH onset.

Our data showed that INR levels in the enlarged group were always above 2.0 and higher than those in the unchanged group. In addition, the number of patients with an INR value of <2.0 before treatment or for at least 24 h after immediate correction by PCC was significantly smaller in the enlarged group than in the unchanged group. Multivariate analyses with logistic regression model demonstrated that an INR value of <2.0 before treatment or for 24 h after PCC treatment is an independent factor that is negatively associated with ICH enlargement. Therefore, an INR value of ≥2.0 seems to be a predisposing factor for ICH enlargement. Rapid reversal of INR with PCC and vitamin K seems effective when INR at admission is above 2.0 and this may improve the outcome of patients with ICH.

Table 4: Logistic regression analysis for enlargement of hematoma. *, at admission or for 24 h after treatment with PCC and vitamin K.

Variable	OR	95%CI	P
INR <2.0 *	0.069	0.006 - 0.789	0.0312
Liver diseases	7.050	0.506 - 98.205	0.1461
Age	1.011	0.937 - 1.091	0.7736
Hematoma size	1.041	0.974 - 1.113	0.2340

Liver dysfunction can also affect the progression of ICH (7, 14, 15). Fujii and coauthors demonstrated that the incidence of hematoma enlargement significantly increases with the severity of liver dysfunction (14). Decreased levels of coagulant factors caused by both warfarin and liver disease may increase the risk of ICH enlargement.

Although SBP at admission and for 24 h after treatment did not differ between the enlarged and unchanged groups, SBP was >200 mmHg in only two of the enlarged group. Kazui et al. reported that an SBP value of > or = 200 mmHg was a predisposing factor to the enlargement of spontaneous intracerebral hemorrhage (7). Broderick and associates recorded an SBP value of > or = 195 mmHg during the first 6 h in 5 of 6 patients, whose neurological condition deteriorated with a >40% increase in hematoma volume (16). Hypertension is obvious in patients with active bleeding (17, 18). Controlling SBP below 200 mmHg may be helpful to prevent ICH enlargement during the acute phase.

In conclusion, the predisposing factors to enlargement of warfarin-related ICH appeared to be an INR value of >2.0 within 24 h of onset and the absence of rapid treatment to counteract INR. Because the present study was retrospective and the study populations were small, a prospective study should compare PCC with other conventional treatment modalities in a large number of patients.

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CASE REPORT

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Effect of prothrombin complex concentrate on INR and blood coagulation system in emergency patients treated with warfarin overdose

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Abstract We investigated the effect of prothrombin complex concentrate (PCC) on the international normalized ratio (INR) and blood coagulation system in two emergent patients treated with warfarin for secondary prevention of cardioembolic stroke due to nonvalvular atrial fibrillation. An 80-year-old woman developed massive subcutaneous hemorrhage and swelling on her right upper extremity with weak pulsation of the right radial artery and had an INR above 10. An 83-year-old man had pleural effusion with an INR value of 6.69 and pleural puncture was immediately required. We administered 500 IU of PCC to the two patients (17.2 IU/kg and 12.5 IU/kg) with 10 mg of vitamin K. The INR decreased to 1.12 and 1.85, respectively, with an increase of plasma levels of protein C and coagulant factors IIa, VIIa, IXa, and Xa 10 min after administration. The plasma levels of the thrombin-antithrombin III complex increased (from 4.0 to 12.0 μg/l and from 0.5 to 28.9 μg/l, respectively, normal value <3.0), but prothrombin fragment 1+2 increased minimally 10 min after administration (from 0.4 to 1.1 nmol/ml and from 0.4 to 0.7 nmol/ml, respectively, normal value 0.4–1.4 nmol/ml). Plasma levels of D-dimer remained unchanged. The massive subcutaneous hemorrhage in the former patient improved in 14 days. Anticoagulation was restarted in the latter patient after 14 days of PCC administration. There were no embolic episodes during the month after PCC administration. In conclusion, a small amount of PCC may be effective in immediately correcting increased INR levels with increased plasma levels of protein C and coagulant factors IIa, VIIa, IXa, and Xa and may partially activate the coagulation system without any effects on plasma levels of D-dimer.

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Keywords Prothrombin complex concentrate · International normalized ratio · Blood coagulation system · Warfarin overdose

Introduction

Hemorrhage is a major adverse effect of oral anticoagulant agents [5, 10, 11], which are widely used for prevention of thrombotic or embolic diseases. Since the efficacy of warfarin in the primary prevention of stroke in nonvalvular atrial fibrillation (NVAF) has been confirmed [1, 5, 7], the use of warfarin is recommended for NVAF patients with a high risk of stroke, such as a history of previous stroke or transient ischemic attack (TIA), diabetes mellitus, hypertension, advanced age (≥75 years), congestive heart failure, or coronary artery disease. The number of patients with hemorrhagic complication may be increased because a major hemorrhage often develops in elderly patients on anticoagulant therapy and the number of elderly people with NVAF has recently increased. We had two patients in emergency who were treated with a warfarin overdose and needed acute correction of the international normalized ratio (INR). We then administered 500 IU of prothrombin concentrate complex (PCC, commercially available PPSB-HT Nichiyaku, Nihon-Seiyaku Pharmaceutical Company, Tokyo, Japan), which contained 500 IU of coagulant factors II, VII, IX, and X and 380 U of protein C, and measured coagulation and fibrinolysis markers before and after administration. The effect of PCC administration on blood coagulation and the fibrinolysis system was discussed.

Case reports

Case 1

An 80-year-old woman developed massive subcutaneous hemorrhage on her right upper extremity after falling down. She had been on warfarin treatment because of secondary prevention of car-

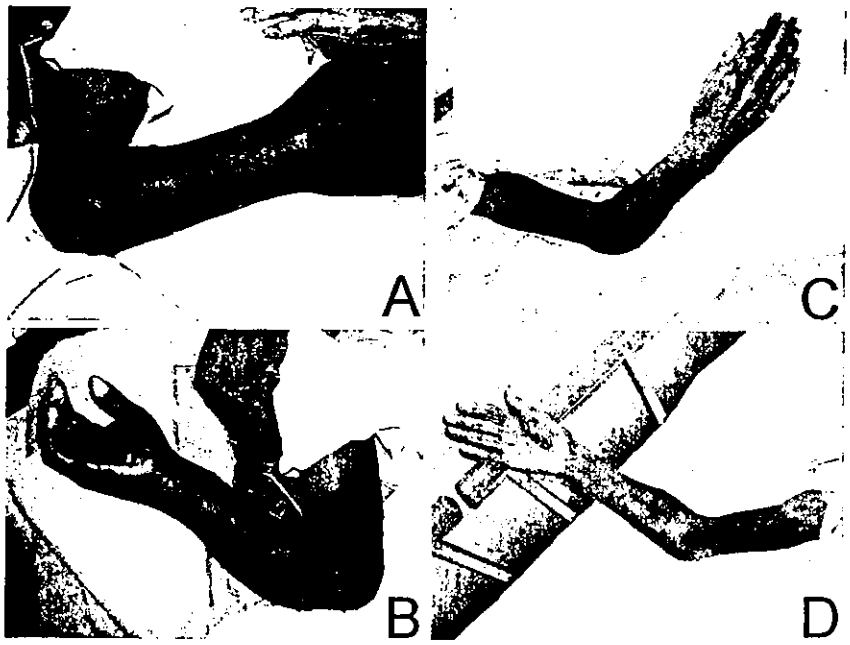

Fig. 1 Subcutaneous hemorrhage and swelling was observed in the right upper extremity (A, B) in case 1 and improved 14 days after the administration of PCC (C, D)

Table 1 Measurement of blood coagulation system

	Case 1			Case 2				Normal value
	Before PCC	10 min after PCC	20 h after PCC	Before PCC	10 min after PCC	60 min after PCC	4 days after PCC	
International normalized ratio (INR)	>10.0	1.12	0.94	6.69	1.85	1.85	1.19	0.90–1.14
Coagulant factor IIa (%)	10	69	68	22	62	61	83	75–135
Coagulant factor VIIa (%)	5	28	81	15	26	26	71	75–140
Coagulant factor IXa (%)	9	42	69	24	54	41	105	70–130
Coagulant factor Xa (%)	9	58	56	11	47	46	67	70–130
Prothrombin fragment 1+2 (nmol/ml)	0.4	1.1	0.8	0.4	0.7	0.5	1.0	0.4–1.4
Thrombin-antithrombin III complex (TAT, μg/l)	4.0	12.6	5.2	0.5	28.3	3.1	3.1	<3.0
Antithrombin III (%)	87.3	85.9	89.2	80.1	77.4	71.9	75.0	80–120
Protein C (%)	17.1	61.0	69.0	16.8	41.2	39.6	74.3	75–125
Fibrinogen (mg/ml)	249	253	238	608	592	576	469	150–340
D-dimer (μg/l)	<0.05	<0.05	0.32	4.1	3.8	2.8	2.7	<1.0

dioembolic stroke due to nonvalvular atrial fibrillation. At admission she had massive subcutaneous hemorrhage and subsequent tight swelling on her right upper extremity, which resulted in weak pulsation of the right radial artery (Fig. 1). Her INR at admission was above 10.0.

In order to prevent further subcutaneous bleeding, we administered 500 IU of PCC (17.2 IU/kg) with 10 mg of vitamin K. The INR value decreased to 1.12 10 min after administration and remained low 20 h thereafter with an increase in plasma levels of coagulant factors IIa, VIIa, IXa, and Xa (Table 1). Plasma levels of thrombin-antithrombin III complex (TAT) and protein C increased from 4.0 to 12.6 μg/l and from 17.1% to 61.0% after administration, respectively, but those of prothrombin fragment 1+2 (FP1+2) increased minimally from 0.4 to 1.1 nmol/ml. There was no increase in plasma levels of D-dimer. Further bleeding and swelling was not observed and after 14 days, her right upper extremity improved and she was discharged from the hospital without any thrombotic or embolic episodes.

Case 2

An 83-year-old man had pleural effusion with an INR value of 6.69. In order to perform pleural puncture for rapid exploration, 500 IU of PCC (12.5 IU/kg) with 10 mg of vitamin K were administered. The INR value decreased to 1.85 both 10 and 60 min after administration and remained low 4 days thereafter with an increase in plasma levels of coagulant factors IIa, VIIa, IXa, and Xa (Table 1). Plasma levels of TAT and protein C increased from 0.5 to 28.3 μg/l and from 17.1% to 61.0% after administration, respectively, but those of FP1+2 increased minimally from 0.4 to 0.7 nmol/ml (Table 1). Plasma levels of D-dimer were high before administration and did not increase thereafter. Based on pleural puncture findings, chest X-ray, blood chemistry, and peripheral blood counts, he was diagnosed as having bacterial pneumonia with pleural effusion. He was treated with antibiotics and improved. Anticoagulation was resumed 14 days after PCC administration, and there were no embolic or thrombotic episodes during 40 days of hospitalization.

Discussion

Reversal of warfarin by 20–50 IU/kg of PCC with vitamin K in life-threatening neurological emergencies has been reported to be more rapid and effective than fresh frozen plasma (FFP) at a mean amount of 600–2712 ml with vitamin K in four studies [3, 4, 6, 8]. Correction of INR values was confirmed 15 min, 2 h, or 4.8 h after PCC administration. According to the present reports, correction of INR seems to be accomplished more quickly, within 10 min after completion of PCC administration, when compared to the previous four reports.

Butler et al. recommended administration of 50 IU/kg or 25 IU/kg of PCC with vitamin K in the immediate management of oral anticoagulant-related intracranial hemorrhage when INR values are ≥4.5 or <4.5, respectively [2]. However, the present study demonstrated that 500 IU of PCC (12.5–17.2/kg) induced a rapid correction of the INR. Therefore, if immediate measurement of INR is available, it may be appropriate to first administer 500 IU of PCC followed by a second administration of 500 IU of PCC according to the INR value measured just after the first administration.

Fredriksson et al. reported bilateral renal infarction at autopsy in a case treated with PCC and noted the risk of general thromboembolism triggered by activated prothrombin complex [6]. However, blood coagulation and the fibrinolytic system have not been fully investigated before and after the administration of PCC. In the present two patients, TAT levels increased but PF1+2 levels increased minimally and D-dimer levels remained unchanged without any thromboembolic episodes after the administration of PCC. Excessive activation of coagulation and the fibrinolytic system with increased coagulant factors IIa, VIIa, IXa, and Xa may be suppressed by a sufficient amount of antithrombin III and protein C, an inhibitor of factors V and VIII, induced with PCC administration. PCC has been used for replacement of protein C in patients with protein C deficiency [9].

Recently, recombinant VIIa has been applied in the treatment of bleeding due to warfarin overdose [12]. Therefore, there is a possibility to treat patients with hemorrhagic complications due to warfarin overdose with the recombinant FVIIa. It is necessary that the efficacies of PCC and FVIIa be investigated and compared with those of conventional infusion of FFP or infusion of only vitamin K in a large number of patients with hemorrhagic complications due to warfarin overdose.

In conclusion, a small amount of the PCC may be effective in immediately correcting increased INR levels with increased plasma levels of protein C and coagulant factors IIa, VIIa, IXa, and Xa and may partially activate the coagulation system without any effects on plasma levels of D-dimer.

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□ CASE REPORT □

Disappearance of an Oscillating Intraluminal Thrombus in the Carotid Artery Demonstrated by Ultrasonography

Kiminobu YONEMURA, Kazumi KIMURA, Masahiro YASAKA and Kazuo MINEMATSU

Abstract

In a patient with acute cardioembolic stroke, ultrasonographic studies demonstrated the disappearance of an oscillating intraluminal thrombus lodged at the carotid bifurcation. Following the commencement of immediate anticoagulation, the thrombus completely dissolved over two weeks without further deterioration in the patient's symptoms. Neurosonographic studies are useful for the detection and follow-up of an intraluminal thrombus in acute stroke patients undergoing anticoagulant therapy.
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Key words: intraluminal thrombus, ultrasonography, carotid artery

Introduction

In patients with acute ischemic stroke, cerebral angiographic studies occasionally identify an intraluminal thrombus within the major cerebral arteries. An intraluminal thrombus can lead to complete arterial occlusion and distal embolization, and as a result is considered as a threatening finding (1, 2). However, a standard treatment protocol for an intraluminal thrombus has not yet been established.

Neurosonographic studies are a real-time, noninvasive technique to evaluate the extra- and intracranial arteries. They can be easily performed at the bedside and are suitable for follow-up examinations.

Using duplex carotid ultrasonography and transcranial Doppler (TCD), we herein present the findings of an oscillating intraluminal thrombus within the carotid artery in a patient with acute cardioembolic stroke and its disappearance while undergoing anticoagulant therapy.

Case Report

The patient was a 64-year-old man with dilated cardiomyopathy. He had no history of hypertension, diabetes mellitus, hyperlipidemia, or smoking, and he had never received antithrombotic therapy previously.

The patient abruptly developed weakness in the left extremities, and was admitted to our hospital the following day. He also had an episode of a transient weakness in the right extremities 10 days before admission. On admission, his blood pressure was 110/60 mmHg with a regular heart rate of 64 beats/min. Neurological examinations revealed mild dysarthria and left hemiparesis.

Laboratory blood tests revealed the following: leukocyte count, 6,310/μl; erythrocyte count, 4,530,000/μl; hemoglobin, 12.1 g/dl; hematocrit, 37.9%; platelet count, 138,000/μl; C-reactive protein, 5.85 mg/dl; prothrombin time expressed as an international normalized ratio, 1.10; activated partial thromboplastin time, 42 seconds; fibrinogen, 529 mg/dl; antithrombin III, 80.0%; protein C, 83.6%; fibrin degradation products, 12 μg/ml; D-dimer, 2.7 μg/ml; and thrombin-antithrombin III complex, 21.6 μg/*l*. Chest X-rays demonstrated an enlargement of the heart. Twelve-lead electrocardiogram showed normal sinus rhythm, but paroxysmal atrial fibrillation was detected on 48-hour electrocardiogram monitoring. Transthoracic echocardiography showed enlargement of the left ventricle with severely reduced contraction. No intracardiac thrombi were visualized.

A brain computed tomography (CT) on admission revealed a low-density area in the right parietal cortex (Fig. 1). A duplex carotid ultrasonographic examination using an ATL Ultramark 9 (Advanced Technology Laboratories, Bothell, WA) with the transducer operating at 5 to 10 MHz for B-mode and Doppler functions was performed just after the CT study. A B-mode scan demonstrated a mobile, echogenic intraluminal mass echo in the bifurcation of the right common carotid artery (CCA) through to the proximal site of the internal carotid artery (ICA) (Fig. 2A). The

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