entiate the MO group from the MB group. A P value of $< .05$ was accepted as indicating a significant difference.

Results

We performed intra-arterial DSA in 55 patients (46 men and nine women; mean age, 63.8 ± 13.1 years). TCCS depicted bilateral MCA flow signals in 43 patients. However, TCCS depicted only unilateral MCA flow signal intensity in the other 12 patients. Consequently, the EDV of 98 vessels was measured. Occlusive lesions were present in 10 patients with a unilateral mid-to-distal occlusion of MCA stem, seven patients with a unilateral MCA branch occlusion, one patient with bilateral MCA branch occlusions, and 37 patients without a significant occlusion or stenosis. Thus, the groups consisted of patients with an occlusion of the MCA stem (MO group, $n = 10$), those with an occlusion of the MCA branch (MB group, $n = 8$), and patients with no occlusive lesions (control group, $n = 37$).

We did not detect MCA flow on the right side in the patient with bilateral MCA branch occlusions. Typical waveforms obtained in the MO and MB groups are shown in Figure 1.

The end-diastolic ratio was calculated for all patients in whom bilateral MCAs were detected. Scattergrams of the EDV and the end-diastolic ratio for each group are shown in Figure 2. EDV was significantly higher in the control group (40.5 ± 11.5 cm/s) than in the MO group (12.2 ± 3.6 cm/s, $P < .001$) or MB group (19.6 ± 4.8 cm/s, $P < .001$). The end-diastolic ratio (4.2 ± 1.5) of the MO group was significantly greater than that of the MB group (1.8 ± 0.5, $P < .001$) or control group (1.2 ± 0.1, $P < .001$).

On sensitivity-specificity curve analysis, the optimal threshold value of EDV for differentiating the MO and MB groups from the control group was 25 cm/s (Fig 3A). A positive predictive value of 81.0%, a negative predictive value of 98.4%, and an accuracy of 93.9% were calculated for the optimal threshold value. The optimal threshold value of the end-diastolic ratio for discriminating the MO group from the MB group was 2.7 (Fig 3B), with a positive predictive value of 100%, a negative predictive value of 100%, and an accuracy of 100%.

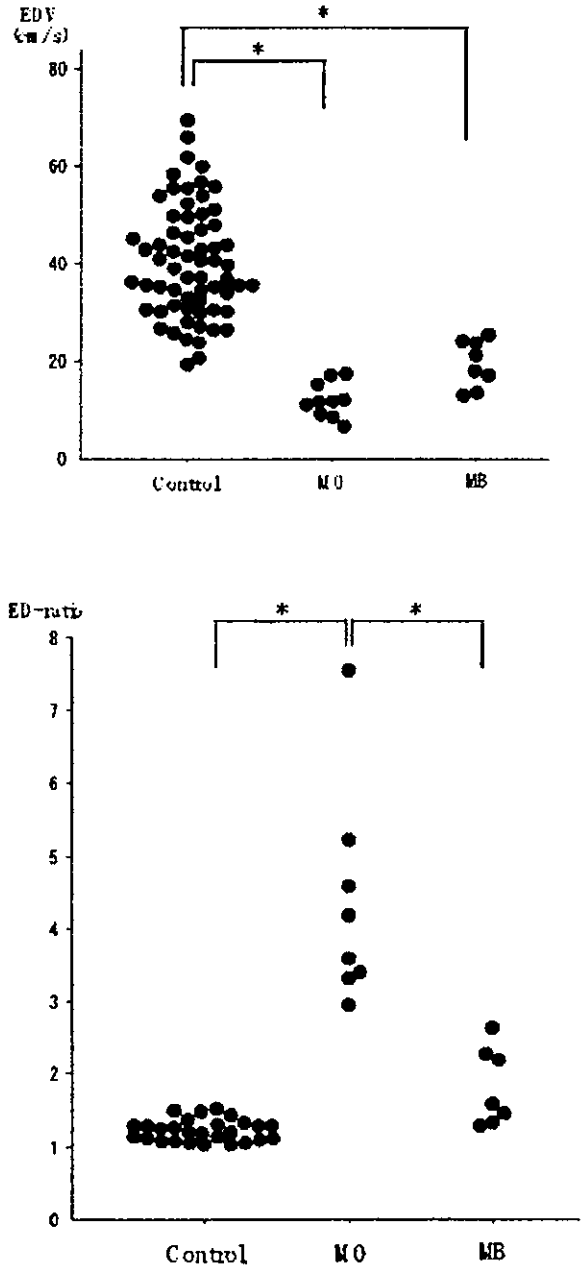

FIG 2. Scattergrams. *Top*, Mean EDVs (±2 SDs) for the control, MO, and MB groups are 40.5 ± 11.5, 12.2 ± 3.6, and 19.6 ± 4.8, respectively ($P < .001$, Scheffé test). *Bottom*, Mean end-diastolic ratios (±2 SDs) for the control, MO, and MB groups are 1.2 ± 0.1, 4.2 ± 1.5, and 1.8 ± 0.5, respectively ($P < .001$, Scheffé test).

Discussion

To our knowledge, this is the first study to develop TCCS criteria for diagnosing MCA stem occlusion and MCA branch occlusion. Kimura et al (7) reported that the end-diastolic ratio of patients with an MCA stem occlusion might increase to >1.9. In the present study, the end-diastolic ratio in the MO group was higher than 1.9, and this is compatible with the previous report by Kimura et al. Because they did not report TCCS criteria for determining MCA branch occlusion, the results of our MB group cannot be compared with their results.

Sensitivity-specificity curve analysis demonstrated an optimal threshold EDV value of 25 cm/s for differentiating MO and MB patients from control patients. In the MO and MB groups, 17 (94.4%) of 18 patients had an EDV <25 cm/s. However, of 37 patients in the control group, four (10.8%) had an EDV < 25 cm/s. Therefore, if the EDV is <25 cm/s, one cannot always identify the group (MO, MB, or control) to which the patient belongs. This is a limitation of our study. We have already reported that the end-diastolic ratio of control group patients was <1.9, even if EDV was under 25 cm/s (7). Therefore, the

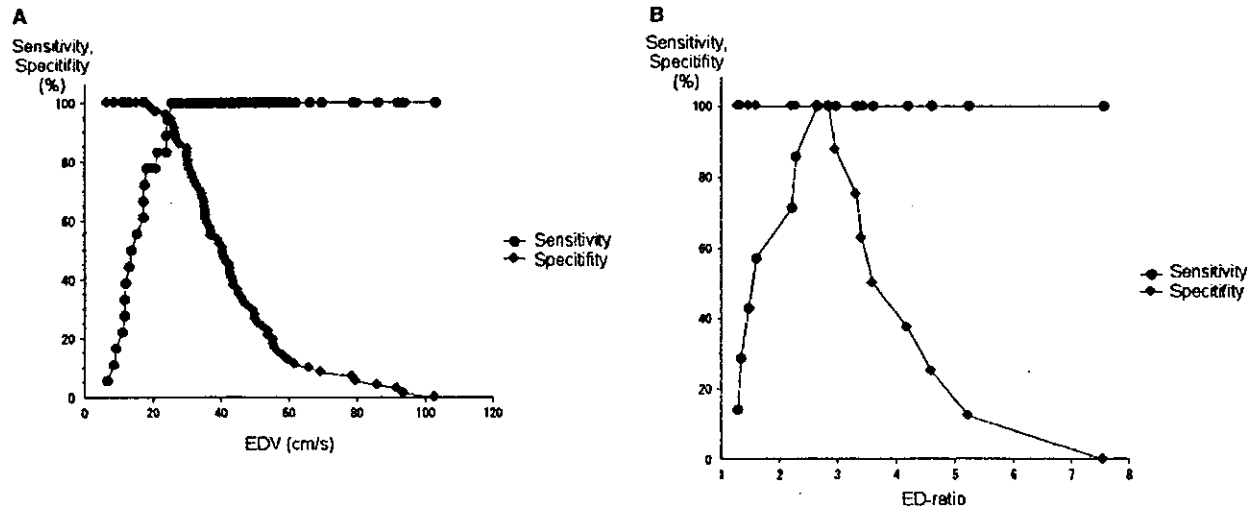

FIG 3. Sensitivity-specificity curves.
A, Predicting MO or MB by EDV. Optimal threshold value for EDV is 25 cm/s.
B, Differentiating MO from MB by the end-diastolic ratio. Optimal threshold value for the ratio is 2.7.

end-diastolic ratio should be useful in deciding if patients with EDV of ≤25 cm/s have an occlusive MCA lesion.

In the present study, we observed no differences in the end-diastolic ratio between the MB group and the control group. Therefore, the end-diastolic ratio alone is insufficient to diagnose an MCA branch occlusion. However, an end-diastolic ratio of 2.7 perfectly distinguished the MO group from the MB group. By using both the EDV and the end-diastolic ratio, we could distinguish the MB group from the control and MO groups. These results can be explained by the differences in the peripheral resistances among the MO, MB, and control groups. We conclude that the TCCS criteria of an EDV of ≤25 cm/s and an end-diastolic ratio of <2.7 indicates an MCA branch occlusion and that an EDV of ≤ 25 cm/s and an end-diastolic ratio of ≥2.7 indicates an MCA stem occlusion. The diagnostic algorithm for MCA stem and branch occlusion is shown in Figure 4.

A few patients could not be examined because of inadequate insonation windows during TCCS. The failure rate increased with age and was higher in women because of the higher prevalence of temporal hyperosteosis (8). Furthermore, the detection rate of intracranial artery flow signal intensity by using transcranial Doppler imaging is lower in Japanese patients than in white patients (9). Contrast agents can increase the detection rate of the MCA with TCCS (8, 10–13). Therefore, use of a contrast agent may help in diagnosing MCA diseases if the MCA flow cannot be detected with conventional TCCS.

When intravenous thrombolysis with tissue plasminogen activator (t-PA) is given to ischemic stroke patients within 3 hours of stroke onset, long-term outcomes improve (14). The Prolyse in Acute Cerebral Thromboembolism (PROACT) II study (15) demonstrated a significant benefit from treatment with intra-arterial prourokinase in patients with MCA occlusion treated within 6 hours of stroke onset.

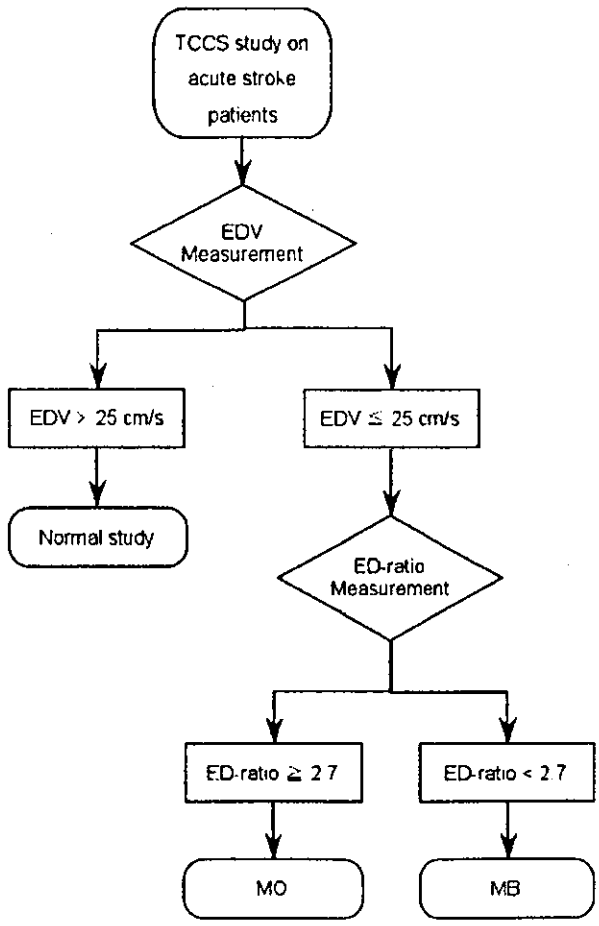

FIG 4. Algorithm for diagnosing MO and MB by using the EDV and end-diastolic ratio on TCCS.

Therefore, our TCCS criteria for MCA diseases may be useful in determining whether we perform the intra-arterial or venous thrombolysis in patents with hyperacute stroke. Furthermore, Eggers et al (16)

reported that the use of sonography with t-PA therapy improved outcomes in patients with hyperacute ischemic stroke. Therefore, in the near future, TCCS may be useful not only as a diagnostic tool but also as a treatment in patients with MCA disease.

Conclusion

To our knowledge, we are the first group to develop TCCS criteria for diagnosing MCA stem occlusion and MCA branch occlusion. TCCS is a useful tool in the assessment of MCA diseases in patients with acute stroke.

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□ ORIGINAL ARTICLE □

Is Stroke a Paradoxical Embolism in Patients with Patent Foramen Ovale?

Masahiro YASAKA, Ryoichi OTSUBO, Hiroshi OE and Kazuo MINEMATSU

Abstract

Objective **Purpose was to assess the stroke mechanism in patients with patent foramen ovale (PFO).**

Methods **We reviewed the medical records of 111 stroke patients with PFO and sinus rhythm (PFO-S group), 25 with PFO and atrial fibrillation (AF) (PFO-AF group) and 67 with AF but not PFO (AF group), who had received contrast transesophageal echocardiography. The clinical and neuroradiological findings were then compared among the three groups. Deep vein thrombosis was investigated in 93 patients with PFO. We determined the number of patients with definite paradoxical embolism who met three criteria: deep vein thrombosis, neuroradiological features indicating embolic stroke, and the absence of other sources of emboli. We also evaluated those with probable paradoxical embolism who met two of the three criteria.**

Results **The PFO-S group more frequently exhibited hypercholesterolemia ($p<0.0001$) and lesions limited to the posterior circulation ($p<0.0004$), and less frequently exhibited large or cortical lesions in the anterior circulation ($p=0.0008$, $p<0.0001$, respectively), than the PFO-AF and AF groups. In the PFO-S and PFO-AF groups, other sources of emboli such as a cardiac source of emboli, cerebral artery stenosis ≥50%, or complicated atheroma in the aortic arch were identified in 72 cases (52.9%). In the 93 patients with examination for deep vein thrombosis, the definite and probable criteria of paradoxical embolism were fulfilled only in three (3.2%) and 33 cases (35.5%), respectively.**

Conclusion **In stroke patients with PFO, not only paradoxical brain embolism through the PFO but also other causes of stroke may contribute to the development of stroke.**

(Internal Medicine 44: 434–438, 2005)

Key words: stroke, patent foramen ovale, atrial fibrillation, paradoxical brain embolism

Introduction

Patent foramen ovale (PFO) is found in about 30% of autopsies and may be associated with paradoxical brain embolism (1). The prevalence of PFO in patients with stroke is higher than in control subjects and PFO is more frequently detected in cryptogenic stroke than in stroke of known etiology (2–4). Contrast transesophageal echocardiography (TEE) enables the detection of PFO with a higher degree of sensitivity, which has contributed to the diagnosis of paradoxical brain embolism (5).

Typical patients with paradoxical brain embolism through PFO demonstrate a venous thrombus as the direct source of emboli and neuroradiological features of cerebral embolism. However, numerous stroke patients with PFO do not have a venous thrombus or neuroradiological findings of brain embolism. Therefore, the contribution of paradoxical embolism through PFO to the development of stroke may be smaller than previously thought. Although clarifying the causes of stroke in patients with PFO is important, the clinical characteristics of stroke patients with PFO have not been fully elucidated. Thus, we retrospectively reviewed the medical records of stroke patients having PFO with or without atrial fibrillation (AF) and those of stroke patients with AF but not PFO, and compared their clinical and neuroradiological findings. In addition, we proposed definite and probable criteria for paradoxical brain embolism and determined how many stroke patients with PFO met the criteria.

For editorial comment, see p 401.

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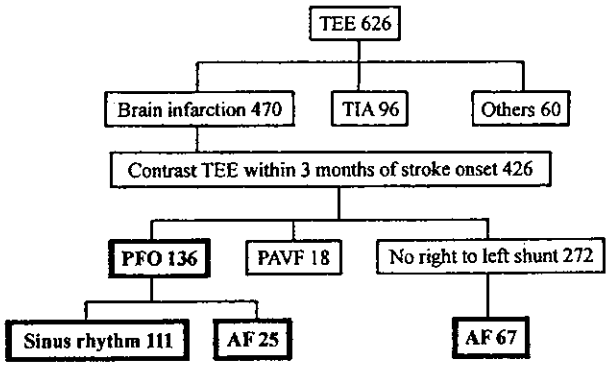

Figure 1. Diagram of the study subjects. TEE: transesophageal echocardiography, TIA: transient ischemic attack, PFO: patent foramen ovale, PAVF: pulmonary arteriovenous fistula, AF: atrial fibrillation. Arabic numerals indicate number of patients.

Methods

From January 2000 to December 2001, we performed TEE in 626 patients (Fig. 1); 470 with brain infarction, 96 with TIA, and the remaining 60 with other neurological disorders. In 426 of the 470 patients with brain infarction, contrast TEE was performed within 3 months of onset. PFO was demonstrated in 136 patients and pulmonary arteriovenous fistula was suspected in 18. We divided the 136 patients with PFO into 111 patients with sinus rhythm (PFO-S group) and 25 patients with AF (PFO-AF group). No right to left shunt was observed in the other 272 patients, and of these patients, AF was noted in 67 patients (AF group) at the time of TEE. We compared the clinical background, atherosclerotic risk factors, vascular territory of the brain infarction, site and size of the infarct, and cerebral angiographic findings among the PFO-S, PFO-AF and AF groups.

We performed contrast TEE using a commercially available real-time two-dimensional echocardiography system (model SSD-2200, Aloka, Tokyo) equipped with a 5.0 MHz phased array omniplane transesophageal transducer. Without any contrast medium, we inspected the left atrium for debris appearing inside the left atrium during the Valsalva maneuver and after release of the maneuver. Next, the contrast medium, a mixture of 9 ml saline and 1ml air, was infused into the right antecubital vein during the Valsalva maneuver. When the right atrium was opacified by the contrast medium as seen on the monitor, we asked the patient to release the Valsalva maneuver. When contrast medium different from the debris was found in the left atrium within three cardiac cycles after the release of the Valsalva maneuver, we diagnosed the patient with PFO, and when the medium was observed after three cardiac cycles, we suspected the presence of pulmonary atriovenous fistula (5–8).

Previously diagnosed hypertension, diabetes mellitus and hypercholesterolemia were considered atherosclerotic risk factors. Patients taking antihypertensive medicine and with a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg were considered hypertensive, while diabetic patients were defined as those taking insulin or oral antidiabetic agents, and exhibiting a fasting plasma glucose level of ≥126 mg/dl or plasma glucose at any time of ≥200 mg/dl. Patients taking antihypercholesterolemic medicine, or with a plasma total cholesterol of ≥220 mg/dl were defined as having hypercholesterolemia.

We investigated the circulation territory, either anterior or posterior circulation, responsible for the infarction, whether the lesions involved cortical areas, and whether the lesions were larger than 3.0 cm in diameter in patients with infarctions of the anterior circulation (9–11).

We also compared the incidence of cervical or cerebral artery stenosis ≥50% demonstrated by carotid ultrasonography, MRA, or cerebral angiography, in the major artery proximal to the responsible infarction, intraluminal filling defect indicating an embolus on angiogram, reopening of the previously occluded artery confirmed by MRA, and atherosclerotic lesions thicker than 4.0 mm at the aortic arch among the three groups. We reviewed medical records for other sources of emboli, such as arterial dissection, ulcerative plaque at the carotid artery, and cardiac and cerebral catheter manipulation.

In the 136 patients having PFO with or without AF, we investigated underlying heart diseases by electrocardiography, TEE and transthoracic echocardiography. Thrombus in lower leg veins was investigated by ultrasonography in 86 patients, by RI scintigraphy in 46 patients, and by either procedure in 93 patients. Using the diagnostic criteria given in Table 1, we ascertained the number of patients who met the definite or probable criteria for paradoxical embolism.

Continuous data were expressed as mean ± SD. We used the Chi squared test for analysis of discrete variables and analysis of variance with the multiple comparison test with Scheffe's test for analysis of continuous variables.

Results

Patients in the PFO-S, PFO-AF, and AF groups were 63.5±11.7 years old, 68.0±11.7 years old, and 70.7±7.8 years old, respectively (ANOVA, $p<0.0001$). Patients in the PFO-S were significantly younger than those in the AF group (multi comparison test with Scheffe, $p<0.0001$, Table 2). Hypercholesterolemia was noted in 54.1%, 20.0%, and 38.8% of the PFO-S, PFO-AF, and AF groups, respectively ($p<0.0001$) and was significantly more frequent in the PFO-S group than the PFO-AF and AF groups ($p<0.0001$).

Infarction occurred in the anterior circulation in 68.5%, 84.0%, and 79.1%, in the posterior circulation in 31.5%, 8.0%, and 11.9%, and in both in 0%, 8.0% and 9.0% of the PFO-S, PFO-AF and AF groups, respectively (Table 2). Patients in the PFO-S group had a significantly higher incidence of lesions restricted to the posterior circulation than did the PFO-AF and AF groups ($p=0.0004$).

Table 1. Diagnostic Criteria for Paradoxical Brain Embolism

1) Brain infarction demonstrated by CT or MRI.
2) Patent foramen ovale diagnosed by TEE.
3) Intravenous thrombus demonstrated by ultrasonography or RI venography.
4) Neuroradiological features of brain embolism,
   such as cortical infarction demonstrated by CT or MRI and angiographic findings of intraluminal filling defect (embolus shadow) or reopening of previously occluded arteries.
5) Absence of other sources of embolism, such as
   heart disease (atrial fibrillation, prosthetic valves, rheumatic heart disease, dilated cardiomyopathy, sick sinus syndrome, acute myocardial infarction, ventricular aneurysm), atherosclerotic plaque at the aortic arch thicker than 4.0 mm, and arterial stenotic lesion (≥50%) proximal to the lesion.

Diagnosis of paradoxical brain embolism.

Definite	1)+2)+3)+4)+5)
Probable	1)+2)+3)+4)
	1)+2)+3)+5)
	1)+2)+4)+5)

Table 2. Demographics

Number	PFO-S group 111	PFO-AF group 25	AF group 67	p
Age (years)	63.5±11.7	68.0±11.7	70.7±7.8*	<0.001
Gender, male	84 (75.7)	22 (88.0)	47 (70.1)	0.21
Hypertension	71 (64.0)	11 (44.0)	45 (67.2)	0.11
Diabetes Mellitus	42 (37.8)	6 (24.0)	24 (35.8)	0.52
Hypercholesterolemia	60 (54.1)	5 (20.0)	14 (20.9)	<0.0001 (<0.0001)+
Territory of the infarction				
Anterior circulation	76 (68.5)	21 (84.0)	53 (79.1)	0.24
Posterior circulation	35 (31.5)	2 (8.0)	8 (11.9)	0.0018** (0.0004)+
Both	0 (0)	2 (8.0)	6 (9.0)	
Stenotic lesion***	31 (22.8)	2 (8.0)	5 (7.5)	0.0011 (0.0002)+
Aortic arch atheroma	10 (9.0)	10 (40.0)	20 (30.0)	<0.0001 (<0.0001)+
Number of patients with infarction located in the anterior circulation.				
	76	23	55	
Infarction >3.0 cm diameter	21 (27.6)	13 (56.5)	34 (61.8)	0.0002 (0.0008)+
Cortical infarction	35 (46.0)	22 (95.7)	46 (83.6)	<0.0001 (<0.0001)+
Number of patients with cerebral angiography.				
	28	13	19	
Embolic shadow	2 (8.8)	2 (15.4)	2 (10.5)	0.71
Intracranial artery occlusion	14 (50.0)	11 (84.6)	16 (84.2)	0.017 (0.0046)+
Follow-up MRA	7	9	7	
Reopening on MRA	0	8 (88.9)	7 (100)	<0.0001 (<0.0001)+

(%), *multi comparison test with Scheffe p<0.0001 vs. PFO-S group, **vs. anterior circulation, ***at the artery proximal to the infarction. +PFO-S group vs. PFO-AF and AF groups.

In patients with infarction in the anterior circulation, lesions larger than 3.0 cm in diameter were seen in 27.6%, 56.5%, and 61.8% (p=0.0002), and cortical lesions were observed in 46.0%, 95.7%, and 83.6% (p<0.0001) of the PFO-S, PFO-AF and AF groups, respectively. Large infarcts and cortical lesions were significantly less frequent in the PFO-S group than in the PFO-AF and AF groups (p=0.0008, p<0.0001, respectively, Table 2).

We performed carotid ultrasonography in all patients, MR angiography (MRA) in 77 (69.4%) of the PFO-S group, in 20 (80.0%) of the PFO-AF group, and in 50 (74.6%) of the AF group. Cerebral angiography was carried out in 28 (25.2%), 13 (52.0%), and 19 (28.4%) of the PFO-S, PFO-AF, and AF groups, respectively. The incidence of arterial stenotic lesion proximal to the infarction was 22.8%, 8.0%, and 7.5% of the PFO-S, PFO-AF, and AF groups, respectively (p=0.0011). The stenotic lesions were significantly more commonly complicated in the PFO-S group than in the PFO-S and AF groups (p=0.0002, Table 2).

The incidence of intracranial arterial occlusion demonstrated by cerebral angiography was 50.0%, 84.6%, and 84.2% (p=0.017), and reopening of a previously occluded artery detected by follow-up MRA was demonstrated in 0%, 88.9%, and 100% (p<0.0001) of the PFO-S, PFO-AF and AF groups, respectively. The incidence of intracranial arterial occlusion and reopening phenomenon was significantly less frequent in the PFO-S group than in the PFO-AF and AF groups (p<0.0043 and p<0.0001, respectively, Table 2). The incidence of embolic shadow was low in all three groups (Table 2). All patients with findings of intraluminal filling defect or reopening phenomenon had cortical infarction.

TEE revealed complicated atheroma at the aortic arch in 9.0%, 40.0%, and 30.0% of the PFO-S, PFO-AF, and AF groups, respectively (p<0.0001). In the 136 patients with PFO, an underlying heart disease was demonstrated in 26 patients (19.1%); non-valvular atrial fibrillation in 25 and sick sinus syndrome in one. Other sources of emboli in the PFO group were ulcerative carotid plaque (n=1), arterial dissection (n=2), and cardiac catheter manipulation (n=1).

In total, sources of emboli including a cardiac source of emboli (n=26), cerebral artery stenosis ≥50% (n=33), complicated aortic atheroma (n=20), and other sources mentioned above (n=4) except for PFO and deep vein thrombosis were demonstrated in 72 (52.9%) of the 136 patients with PFO (eight had both AF and aortic atheroma, one had both AF and stenotic lesion, and one had AF, stenotic lesion and aortic atheroma). Deep vein thrombosis was found in 25 of the 93 patients (26.9%) who were examined by ultrasonic examination or RI scintigraphy. Of these 93 patients, the definite and probable criteria for paradoxical brain embolism were fulfilled in only 3 (3.2%) and 33 cases (35.5%), respectively.

Discussion

Several studies have revealed that paradoxical embolism through PFO is an important stroke mechanism (2–4). However, in the present study, we found that 3.2% and 35.5% of stroke patients with PFO fitted the criteria for definite and probable paradoxical brain embolism, respectively. We also found that a considerable number of stroke patients with PFO had other sources of emboli (52.9%) and risk factors of atherosclerosis. Neuroradiological features of embolic stroke such as large or cortical infarction, or reopening of a previously occluded artery were less common in the PFO-S group than in the PFO-AF and AF groups. On the other hand, the clinical and neuroradiological features in the PFO-AF group were similar to those in the AF group. These distinguishing characteristics of the PFO-S and PFO-AF groups suggest that a considerable number of patients developed stroke not only by paradoxical embolism through PFO but also by other embolic mechanisms from a cardiac source, proximal arterial stenosis, atherosclerotic lesions in the aortic arch, or thrombotic or hemodynamic mechanisms in the large or small arteries. Therefore, the risk of stroke and other sources of emboli in stroke patients with PFO must be investigated to determine if they meet the criteria for paradoxical embolism, which requires anticoagulant therapy against recurrent attacks. The present study was retrospective, and thus prospective studies examining consecutive stroke patients are required to obtain an accurate prevalence rate for paradoxical embolism in stroke.

PFO is an important mechanism by which stroke develops in the young (2, 3), whereas in the elderly, non-valvular atrial fibrillation (NVAF) is the most frequent embolic source of brain infarction (12). Recent population-based surveys have revealed that 10% of people over 80 have AF (13). Thus, the differences in several features of stroke patients among the PFO-S, PFO-AF, and AF groups may be reflected by a difference in age.

Infarction in the posterior circulation was common in the PFO-S group. Small emboli passing through the PFO may enter the vertebral arteries more easily than the common carotid arteries. Otsubo et al reported that aortogenic infarction tends to occur at the posterior circulation (14). Therefore, emboli from atherosclerotic lesions in the aortic arch may play an important role in developing stroke in the PFO-S group, although aortic atherosclerotic lesions were also reported to play an important role in the development of stroke in patients with NVAF (15).

Exploration for deep vein thrombus is essential for proper diagnosis of paradoxical embolism. The detection rate of thrombus was 26.9% among the cases investigated in the present study. Recently, echo examination was applied to small veins for detecting thrombi. The more widely the echo examination is applied, the higher the detection rate of venous thrombi in stroke patients with PFO. If thrombi are detected, anticoagulant therapy should be applied and if not, antiplatelet treatment may achieve prevention to the same extent as the anticoagulant therapy (16).

In conclusion, the clinical features of patients having PFO with sinus rhythm appear to differ from those of patients

with AF. Other causes of stroke should be considered in stroke patients with PFO because not only paradoxical brain embolism through the PFO but also other causes of stroke may contribute to development of the stroke.

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to significant increases in prostacyclin as well as PGE_2 levels following 24 hours of ischemia, though significant increases in COX-2 mRNA persisted during the 24 h of ischemia, though significant increases in COX-2 protein were not observed. This latter finding may be attributable to the severe ischemic injury that was caused by reduced CBF, which likely affected protein synthesis[2]. In spite of these effects on COX-2 protein, significant increases were seen in the concentration of prostaglandins in the ischemic core 24 hours after ischemia. Local increases in neuronal COX-2 expression in the ischemic core, as determined by immunohistochemical analysis, could have accounted for this increase in prostaglandin concentration.

The induction of neuronal COX-2 is important for the regulation of prostaglandin signaling in post-ischemic regions, and the magnitude of COX-2 activity and prostaglandin production is determined by the degree and duration of CBF reduction. Before novel therapeutic options for stroke patients can be developed, further clarification of the effects of COX-2 during and after ischemia will be required.

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REGULAR ARTICLE

Optimal dose of prothrombin complex concentrate for acute reversal of oral anticoagulation

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KEYWORDS
Hemorrhagic complication;
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Abstract We investigated optimal dose of prothrombin complex concentrate (PCC) for acute reversal of oral anticoagulation in patients with major hemorrhagic complications or who required invasive procedures. We also checked how rapidly international normalized ratio (INR) was reversed after PCC administration.

INR was measured before and 10–60 min after administration of PCC with or without vitamin K in 42 patients (men 28, women 14, median age of 70 years old) who had received warfarin but required rapid reversal of INR because of a hemorrhagic complication or medical procedure. The amount of PCC administered was 200 IU in six patients, 500 IU in 30, 1000 IU in 3, and 1500 IU in the other 3. Additional administration of PCC was performed when the correction of INR was inadequate. In 10 of the 42 cases, INR was measured serially, before, 10 and 60 min and 12–24 h after the administration of PCC and vitamin K.

In the six patients who received PCC of 200 IU, INR values of 3.34 median (range 2.06 to 5.08) decreased to 1.85 (range 1.23 to 2.43) significantly (Wilcoxon's rank sum test, p=0.028), but in three patients (50%), INR values were still above 2.0 after the administration. In 30 patients treated with PCC of 500 IU, values decreased from 2.49 median (range 1.54 to 10.00) to 1.19 (range 0.87 to 1.55) significantly (p<0.0001). The corrected INR values were below 1.5 in 25 of 26 patients (96%) who had initial INR values from 2.0 to 4.9. In four patients with initial INR of 5.0 or more, the reversed INR was below 1.5 in one (25%), between 1.5 and 2.0 in two (50%), and above 2.0 in one (25%) who had additional administration of 500 IU PCC lowering INR from 2.01 to 1.48. Values of INR in the six patients receiving 1000 IU or 1500 IU, INR decreased from 2.33 median (range 1.96 to 4.00) to 0.96 (range 0.87 to 1.24, p=0.028).

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In the 10 patients with serial measurement, INR changed from 2.67 median (range 2.05 to 10.00) to 1.17 (range 0.99 to 1.60) 10 min after the administration. The INR values remained stable 60 min and 12–24 h after the PCC administration.

The 500 IU of PCC is likely to be optimal dose of PCC for emergent reversal of INR in patients requiring rapid correction of INR below 5.0, but to be inadequate dose in patients with INR of 5.0 or more. PCC administration with vitamin K may finish reversing INR rapidly within 10 min and keep the reversed INR values for 12–24 h.

Introduction

Hemorrhagic complication is a major adverse events in patients with oral anticoagulant therapy [1,2], and often requires reduction in dose or discontinuation of the therapy, administration of vitamin K, fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC). The PCC contains coagulant factors II, VII, IX, and X and can reverse the effect of warfare more rapidly than FFP in warfarin-related coagulopathy [3–7]. We reported earlier that rapid correction of international normalized ratio (INR) prevented enlargement of intracranial hematoma in patients with INR values above 2.0 within 24 h of hemorrhagic stroke onset [8].

However, several questions remain to be resolved in the PCC treatment; how much PCC should be administered initially and how rapidly the PCC treatment can reverse INR. The present study was carried out to solve these questions.

Material and methods

From December 2000 to August 2003, PCC was administered in 42 patients who were given warfarin treatment, but required rapid correction of INR because of a major hemorrhagic complication or invasive procedures, an insertion of drainage tube into the thoracic cavity due to acute pneumothorax in two patients and an operation to remove a part of skull bone due to local infection. The major hemorrhagic complications were cerebral hemorrhage in 27, acute epidural hemorrhage in seven, acute bleeding from the gastrointestinal system in two, acute subdural hemorrhage, massive subcutaneous hemorrhage, and intramuscular hemorrhage in one each.

They were 28 men and 14 women with 24–90 years of age (median 70 years old). The underlying diseases requiring warfarin treatment were atrial fibrillation in 22, prosthetic cardiac valves in 9, deep vein thrombosis in 4, left ventricular assist systems in 2, Buerger disease, basilar stenosis, old myocardial infarction, dilated cardiomyopathy, and aortic arch atherosclerosis in 1 each. Hypertension, brain infarction, hypercholesterolemia, diabetes mellitus and hepatitis was complicated in 32 (76.2%), 24 (58.5%), 14 (34.1%), 8 (19.5), and 2 (4.8%) patients, respectively.

The pharmaceutical council in our hospital discussed the administration of PCC including ethical issue and approved it for emergent INR reversal after obtaining informed consent. Then written informed consent was always obtained from the patients or their family. For each patient, administration and amount of the PCC were decided by physicians in charge according to our previous studies [7,8]. The initial amount of PCC was 200 IU in 6, 500 IU in 30, 1000 IU in 3 and 1.500 IU in the other 3. We administered vitamin K of 10 mg in 20 patients and 20 mg in 11 with PCC. Additional PCC was given if the INR value was still high 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.

INR values were measured before and 10 to 60 min after administration of PCC with or without vitamin K in 42 patients. In 10 of the 42 cases, they were measured serially, before, 10 and 60 min and 12–24 h after the administration of PCC (500 IU in nine and 1000 in the other one) and vitamin K (10 mg in seven and 20 mg in the other three).

Data were expressed as median and range. We used Wilcoxon's rank sum test for analysis of

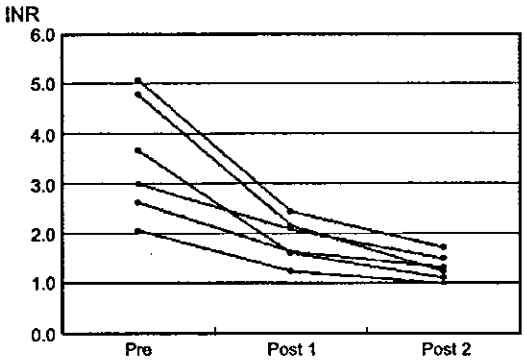

Figure 1 INR values before (Pre) and after PCC administration of 200 IU (Post 1), and those after additional administration of 300 IU (Post 2).

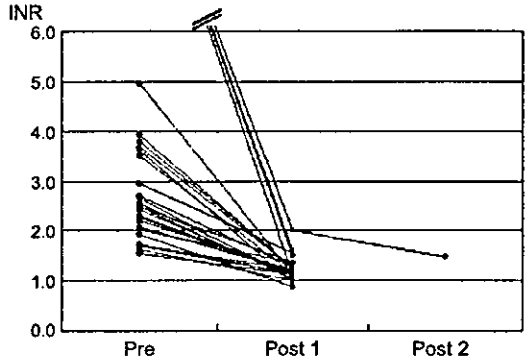

Figure 2 INR values before (Pre) and after PCC administration of 500 IU (Post 1), and those after additional administration of 500 IU (Post 2).

variables. A p-value less than 0.05 was considered significant.

Results

In six patients who received PCC of 200 IU (median 3.3 IU/kg, range 2.6 to 5.3 IU/kg), INR values decreased from 3.34 median (range 2.06 to 5.08) to 1.85 (range 1.23 to 2.43) significantly (p=0.028), but INR values after the PCC administration were still above 2.0 in three patients and between 1.5 and 2.0 in two patients (Fig. 1). Additional 300 IU was administered into the six patients, and INR values decreased to 1.28 (range 0.99 to 1.71).

In 30 patients treated with PCC of 500 IU (median 8.8 IU/kg, range 6.0 to 17.9 IU/kg), INR values decreased from 2.49 median (range 1.54 to 10.00) to 1.19 (range 0.87 to 1.55) significantly (p<0.0001, Fig. 2). INR values after PCC administration were below 1.5 in 25 of 26 patients (96%) who had initial INR values from 2.0 to 4.9 and between 1.5 and 2.0 in two (50%) and above 2.0 in the one (25%) of the four patients that had initial INR of 5.0 or more (Table 1). Only one patient with INR value of 2.01 after 500 IU of PCC administration received additional 500 IU of PCC (1000 IU in total) and his INR decreased to 1.48.

Values of INR in patients receiving 1000 IU (median 18.4 IU/kg, range 18.1 to 18.7 IU/kg) or 1500 IU (median 26.0 IU/kg, range 25.2 to 26.8 IU/kg), INR values decreased from 2.33 median (range 1.96 to 4.00) to 0.96 (range 0.87 to 1.24, p<0.028, Fig. 3).

In 10 patients with serial measurement, INR changed from 2.67 median (range 2.05 to 10.00) to 1.17 (range 0.99 to 1.60) 10 min after the administration (p=0.0051, Fig. 4). The INR values remained stable after 60 min and 12–24 h after the administration.

Symptoms did not deteriorate and hematoma volume did not enlarge in 25 patients of the 27 with cerebral hemorrhage. Deterioration of symptoms with enlargement of hematoma volume was noted in only two, one of whom re-increase of INR from 1.48 to 2.72 half a day after INR reversal by administration of 1000 IU of PCC without vitamin K, and the other one of whom systolic blood pressure after admission remained above 200 mm Hg while INR was kept low. Evacuation of hematoma in six patients with acute epidural hematoma and in a patient with acute subdural hematoma was successfully performed and easy hemostasis during operation was noted by neurosurgeons while a patient with severe epidural hematoma at admission died despite INR reversal. Insertion of drainage

Table 1 Reversed INR according to the initial INR

Amount of PCC administered initially (%)									
	200 IU			500 IU			1000 or 1500 IU		
Reversed INR	≧2.0	≧1.5 & <2.0	<1.5	≧2.0	≧1.5 & <2.0	<1.5	≧2.0	≧1.5 & <2.0	<1.5
Initial INR									
5.0–	0	0	0	1 (25)	2 (50)	1 (25)	0	0	0
3.0–4.9	3 (75)	1 (25)	0 (0)	0	0	6 (100)	0	0	1 (100)
2.0–2.9	0	1 (50)	1 (50)	0	1 (8)	12 (92)	0	0	3 (100)
1.5–1.9	0	0	0	0	0	7 (100)	0	0	2 (100)
									(%)

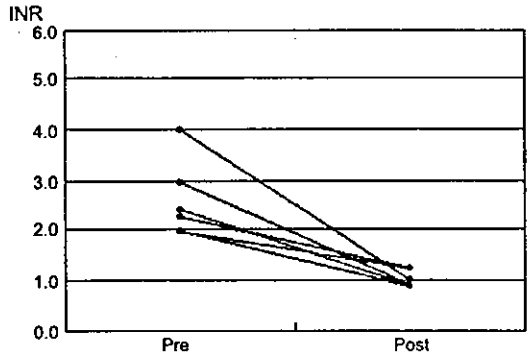

Figure 3 INR values before (Pre) and after PCC administration of 1000 or 1500 IU (Post).

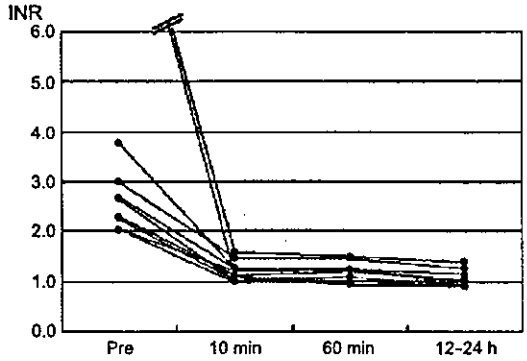

Figure 4 INR values before (Pre) and 10 min, 60 min, 12–24 h after PCC administration of 500 or 1000 IU. min: minutes, h: hours.

tube into the thoracic cavity and an operation to remove a part of skull bone were also successfully done. Subcutaneous, intramuscular and gastrointestinal bleeding stopped after the INR reversal by the PCC administration.

Any adverse effects including shock, allergy, or thrombotic or embolic episodes were not observed in the 42 patients.

Discussion

Previously we reviewed 47 patients on warfarin who developed acute intracerebral hematoma, 10 of whom had PCC treatment within 24 h of onset, and determined relationships among enlargement of the hematoma, INR reversal and clinical data [8]. Multivariate analysis showed an INR value <2.0 at admission or for 24 h after immediate INR reversal with PCC prevented the enlargement of hematoma. Fredriksson et al. retrospectively compared laboratory data and clinical features in 17 patients of anticoagulant-related intracerebral hemorrhage treated with PCC or FFP, and found that clinical progression within 12 h occurred in five of six patients with reversed INR of 1.46 or more [5]. Therefore, it seems that immediate reversal of INR and upkeep of INR values below 2.0 or below 1.5 is necessary to prevent progression of intracerebral hemorrhage.

Effect of 20–50 IU/kg of PCC on reversing INR was reported to be more rapid and effective than FFP [3–6]. Butler et al. [9] 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. The present study demonstrated that 500 IU (median 8.8 IU/kg, range 6.0 to 17.9) of PCC induced a rapid reversal of INR into below 1.5 in 96% of 26 patients who's initial INR values were below 5.0. Because, in the patients with INR above 5.0, INR values remained above 1.5 in 75% after the initial administration of 500 IU PCC and one of them had 1000 IU PCC in total to reverse INR fully, 500 IU PCC may be inadequate and initial administration of 1000 IU or 1500 IU PCC seem required to reverse INR fully in patients with INR above 5.0 (Tables 1 and 2).

Fredriksson et al. [5] reported bilateral renal infarction at autopsy in a case treated with 3000 IU PCC and noted the risk of general thromboembolism triggered by activated prothrombin complex. We did not find any adverse effects in patients treated with smaller amount of PCC (200–1500 IU) than in previous reports [3–6]. Therefore, the smaller amount of PCC might contribute to avoid

Table 2 Amount of PCC and INR change

Investigator	Number	PCC			VK (mg)	INR change	Time
		Amount (IU)	IU/kg	(median)			
Fredriksson et al. [[5]]	5		40–50		10	3.1–1.3	2 h
Makris et al. [[6]]	6		50		10	4.9–1.3	15 min
Boulis et al. [[3]]	10		25.8		10–20	2.8–1.2	4.8 h
Cartmil et al. [[4]]	16		20–50		1–5	5.8–1.3	15 min
Current study	6	200 IU	2.6–5.3	(3.3)	0–20	3.3–1.9	10–60 min
	30	500 IU	6.0–17.9	(8.8)	0–20	2.5–1.2	10–60 min
	3	1000 IU	18.1–18.7	(18.4)	0–10	2.3–1.0	10–60 min
	3	1500 IU	25.2–26.8	(26.0)	0–10	2.4–0.9	10–60 min

thrombotic or embolic adverse effects including disseminated intravascular coagulation. However, the present study showed that initial amount of 200 IU was so inadequate to reverse INR that we had better to administer 500 IU or more initially.

Correction of INR values was reported to be confirmed 15 min, 2 h, or 4.8 h after PCC administration [3–6]. Preston et al. [10] 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 than indicated in the previous five reports. Excessive INR values may be counteracted immediately with increases of coagulant factors II, VII, IX, and X by the PCC administration.

Because the present study was not a randomized one, we need prospective randomized research to confirm optimal initial dose of the PCC according to INR.

In conclusion, 500 IU of the PCC is likely to be optimal for rapid correction of INR below 5.0 but to be inadequate in patients with INR of 5.0 or more. PCC administration with vitamin K may finish correcting INR rapidly within 10 min and keep the lower INR values for 12–24 h.

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抗血栓療法施行患者の抜歯における出血管理に関する検討

Hemostatic management of tooth extraction in patients undergoing antithrombotic therapy

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木村和美***　矢坂正弘***　峰松一夫***

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Abstract

We examined hemostatic management for tooth extraction in Japanese patients undergoing antithrombotic therapy.

The subjects consisted of 57 patients aged from 18 to 91 years old. Forty patients received warfarin therapy including 15 receiving additional antiplatelet drugs. The remaining 17 patients received antiplatelet drugs (aspirin, tichlopidine hydrochloride and cilostazol). In patients receiving warfarin therapy, 19 patients were controlled in International Normalized Ratio (INR)<2.0, 14 in INR 2.0-2.5 and 7 in INR 2.5-3.0.

One-hundred and six teeth were extracted on 65 occasions. All teeth were extracted without reducing the usual antithrombotic therapy, oxidized cellulose was applied and suturing was performed for local hemostasis.

Three of 65 cases of tooth extraction showed postoperative hemorrhage (4.6%); two occurred in patients under warfarin therapy, with INR of 2.15 and 2.49, respectively. The other case was a patient who received both aspirin and tichlopidine hydrochloride. In these patients, because gingivitis, alveolar and gingival abscess were observed, postoperative hemorrhage appeared to be caused by local inflammation rather than antithrombotic therapy.

These results suggest that sufficient hemostasis can be obtained in most cases of tooth extraction under anticoagulant therapy with warfarin (INR<3.0) and antiplatelet drugs. An appropriate local hemostatic method can obtain hemostasis in case of postoperative hemorrhage.

Key words : Antithrombotic therapy (抗血栓療法), Warfarin (ワルファリン), Antiplatelet drug (抗血小板薬), Tooth extraction (抜歯), Local hemostasis (局所止血)

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緒　言

近年，欧米では抗血栓療法施行患者の抜歯を，抗凝固療法薬であるワルファリンまたは抗血小板薬を中止・減量することなく維持量投与下に行うことが推奨されている。特にワルファリンについては，International Normalized Ratio（INR）が3.0以下（報告によっては4.0以下）であれば，維持量投与下の抜歯でも，中止した場合と比べて，後出血の発生率に差はみられないとの報告[1-13]が多い。

一方，日本においては，抜歯の際に抗血栓療法を，その程度にかかわらず中止・減量することが慣習化されており，それに伴う血栓症の報告[14]もみられる。しかし，抗血栓療法を受けている日本人の抜歯における出血管理に関する研究は数少ない。また，抗血栓療法の効果は欧米人と日本人とでは異なっているといわれているため，欧米の抜歯時の基準をそのまま日本人にあてはめることはできない。

そこで，本研究では，抗血栓療法を受けている日本人の抜歯の出血管理を調査し，適切な基準について検討した。

研究対象および方法

1.　対象症例

対象は，2002年4月～2003年9月の間に，大阪大学歯学部附属病院歯科麻酔科および国立循環器病センター歯科において抜歯を受けた抗血栓療法施行患者57名である。これらの患者の患者背景（性別，年齢，基礎疾患および歯科疾患の種類），抗血栓療法の使用薬剤と投与量，ワルファリン投与患者については抗血栓効果の程度，抜歯の内容，術後出血の有無とその内容を診療録から調査した。

対象患者57名のうち，男性35名，女性22名で，年齢分布は18～91歳であった。

基礎疾患としては，心筋梗塞20名，脳梗塞18名，心房細動15名，心筋症11名，人工弁置換術後10名，高血圧症4名，原発性肺高血圧症3名などであった（重複あり）。歯科疾患としては，辺縁性歯周炎48歯（うち歯肉膿瘍7歯），根尖性歯周炎52歯（うち埋伏した残根9歯，歯槽膿瘍1歯，歯根嚢胞2個），智歯周囲炎6歯であった（表1～4）。

ワルファリン投与患者は40名で，ワルファリンの投与量は1～4 mg/日であった。そのうち15名は抗血小板薬を併用していた。抗血小板薬のみの投与患者は17名で，投与量は，アスピリンは81～300mg/日，塩酸チクロピジンおよびシロスタゾールはそれぞれ200mg/日であった（表1～4）。

抗血栓効果の程度は，ワルファリン使用例では，抜歯当日に測定したプロトロンビン（PT）活性およびINRにて評価した。ただし，症例29の2回目の抜歯は，1回目の抜歯の1週間後に行ったものであるが，当日の凝血学的検査は行われていなかった。

2.　抜歯と局所出血管理

ワルファリンおよび抗血小板薬は，維持量を継続して抜歯を行った。抜歯後の局所止血法としては，萌出歯の抜歯では，抜歯窩に酸化セルロース綿（サージセル綿™）を挿入し，脱落防止のために4-0絹糸で1糸水平マットレス縫合した。また必要に応じて止血床を使用した。埋伏歯の抜歯では，抜歯窩に酸化セルロース綿を挿入し，創は4-0絹糸で縫合閉鎖した。他の止血剤は使用しなかった。

3.　出血の程度の判定

出血の判定は新美らの基準[15]を用い，抜歯創からの出血を，抜歯直後（抜歯約30分後）から1週間後まで評価した。出血の程度は，出血なし（Grade 0），湧出性の出血（Grade 1），顕著な出血（Grade 2）とし，Grade 1および2を後出血ありとした。

結　果

抜歯はのべ65回，合計106歯に行った。そのうち萌出歯は91歯，埋伏歯は15歯であった。後出血は，Grade 1が3回（4.6%）認められたが，Grade 2はみられなかった。

ワルファリン投与患者のうち，INRが2.0未満の19名において，21回（萌出歯32歯，埋伏歯5歯）の抜歯を行い，後出血は1回もみられなかった（表1）。

INRが2.0～2.5未満の14名において，16回（萌出歯18歯，埋伏歯3歯）の抜歯および嚢胞摘出術1回を行い，2回に後出血（Grade 1）を認めた（表2）。

症例19は，ワルファリン1.0mg/日の投与で，INRは2.15であった。$\overline{65}$|は根尖性歯周炎による歯槽膿瘍を伴っていたため，抗菌薬を投与し，急性炎症がやや軽減した後に，抜歯をした。しかし，抜歯2日後から出血がみられ，ガーゼによる圧迫のみでは止血が得られず，出血をくりかえし，7日後には抜歯窩には血腫が認められた。抜歯窩を再掻爬後に酸化セルロース綿を挿入し，1糸縫合し止血がえられた。症例30は，ワルファリン2.5mg/日の投与で，INRは2.49であった。抜歯した|$\underline{3}$は辺縁性歯周炎による歯肉発赤を伴っていた。抜歯後，酸化セルロース綿の挿入および縫合のうえ，歯周包帯（COE-PAK™）を用いて義歯を装着した。しかし，抜歯6日後から間欠的に出血をきたし，7日後には抜歯窩から持続的な湧出性出血を認めた。この時点で，INR 3.5とワルファリンの効果が増強していたため，ワルファリンを一時中断のうえ，抜歯窩を再掻爬し，酸化セルロース綿を挿入し，縫合して止血がえられた。

表 1 INR 2.0 未満の症例

症例	性別	年齢	基礎疾患名	歯科疾患名	歯科処置	抗凝固療法（/日） ワルファリン（mg）	アスピリン（mg）	シロスタゾール（mg）	INR	PT（%）	後出血	備考
1	M	63	CI, DM	1|23 P	抜歯	3.0	100		1.33	74		
				32| P	抜歯	3.0	100		1.15	59		
				32|							
2	F	46	PPH	|5 per	抜歯	2.5			1.29	60		
				7|							
3	M	35	AVR	8| *perico*	埋伏抜歯	2.0			1.29	60		
4	F	58	MVS	|6 per	抜歯	3.5			1.57	48		
5	F	48	AVR, TAA	6| per	抜歯	2.5			1.68	44		
			Marfan Synd	7|							
				|457 per	抜歯	2.5			1.52	50		
6	M	78	MVR	7| P, GA	抜歯	2.5			1.80	39		
7	F	56	Af, CHF	4| P	抜歯	1.0	100		1.52	46		
8	M	89	OMI, CI	87| P	抜歯	3.0			1.80	39		
9	M	70	AMI, CI, HT, ASO	6| per	抜歯	1.0	81	200	1.60	43		
10	M	60	OMI	|35 per	抜歯	3.0	81		1.55	48		
11	M	82	Af, CI	1|1 P	抜歯	3.0			1.83	38		
12	M	58	HT, CI	|6 P	抜歯	2.0	200		1.65	44		
13	F	73	CI, Vf, SSS, MVR	|1 per, |45 P	抜歯	4.0			1.77	40		
14	F	18	DCM, PPH	|4 *per RR*	埋伏抜歯	2.5			1.59	49		
15	M	53	DCM, CHF, DM	|7 per	抜歯	2.0			1.70	36		
16	M	35	DCM, Af, CHF	8| *perico*	埋伏抜歯	1.5			1.74	41		
17	M	11	TOF	|C per	抜歯	1.4			1.20	60		
18	M	26	HCM, OMI	8| *perico*	埋伏抜歯	3.0	81		1.82	38		
19	M	75	OMI, Af, CI	3|*per RR*, 21| P	埋伏抜歯，抜歯	4.0			1.90	35		

P：辺縁性歯周炎，GA：歯肉膿瘍，per：根尖性歯周炎，perico：智歯周囲炎，RP：埋伏残根，italics：埋伏歯，
AMI：急性心筋梗塞，OMI：陳旧性心筋梗塞，AVR：大動脈弁閉鎖不全，MVR：僧房弁閉鎖不全，MVS：僧房弁狭窄，
CI：脳梗塞，Af：心房細動，DCM：拡張型心筋症，HCM：肥大型心筋症，HT：高血圧症，DM：糖尿病，
PPH：原発性肺高血圧症，TAA：胸部大動脈瘤，ASO：動脈閉塞症，CHF：慢性心不全，SSS：洞不全症候群，
Marfan synd：マルファン症候群，Vf：心室細動，TOF：ファロー四徴

INR が 2.5～3.0 未満の 7 名において，9 回（萌出歯 17 歯，埋伏歯 1 歯）の抜歯および嚢胞摘出術 1 回を行い，後出血はみられなかった（表 3）。

ワルファリン投与患者で後出血をきたしたのは，46 回の抜歯のうち 2 回（4.4%）であった。

抗血小板薬のみを投与されていた患者 17 名では，抜歯を 19 回（萌出歯 24 歯，埋伏歯 6 歯）行い，後出血を 1 回（5.3%）認めた（表 4）。後出血をきたした症例 40 は，アスピリン 81mg/日およびシロスタゾール 200mg/日の投与をうけていた 85 歳の患者で，抜歯した 5432| は，辺縁性歯周炎による歯肉膿瘍を伴っていた。抗菌薬の投与により急性炎症がやや軽減した後に，抜歯を施行した。抜歯翌日から間欠的な出血を認め，7 日後には抜歯窩に小血腫を認めたが，ガーゼによる圧迫のみで止血した。

考 察

現在，国際的には，ワルファリンの抗凝固作用を評価する基準として，International Normalized Ratio（INR）が用いられる。これは，各社の市販トロンボプラスチン試薬にて測定したプロトロンビン（PT）比を，WHO が標準品としたヒト脳トロンボプラスチンを用いた場合の PT 比に換算した値として示される。この各社の試薬には，標準品との活性を比較して得られた指数がつけられており，これを International Sensitivity Index（ISI）と称する。

表 2　INR 2.0～2.5 未満の症例

症例	性別	年齢	基礎疾患名	歯科疾患名	歯科処置	抗凝固療法（/日） ワルファリン (mg)	アスピリン (mg)	チクロピジン (mg)	INR	PT (%)	後出血	備考
20	M	65	AVS, CI	⌊6 per, WZ	抜歯，摘出	3.5	100		2.25	30		
21	M	61	AMI, Af	8 *perico*, 7⌋per	埋伏抜歯	3.0	100		2.27	29		
22	F	82	AMI, PVC	65⌋ per, AA	抜歯	1.0			2.15	32	+	
23	M	35	TVR, Af	7⌋ per	抜歯	3.0			2.08	32		
24	M	63	HCM, VT, CI	7⌋ per	抜歯	2.5			2.27	29		
25	M	58	DCM, VT	⌊3 P	抜歯	4.0			2.12	26		
26	F	48	DCM	⌊4 P	抜歯	2.5	162	200	2.36	30		
				65⌋ P	抜歯	2.5	162	200	2.32	31		
27	F	34	DCM	1⌋ P	抜歯	2.0	81		2.01	32		
28	M	77	AVS, MVR, Af, ASO	⌊5 per	抜歯	2.0	81		2.03	29		
29	M	45	DCM	⌊8 *perico*, ⌊7 P	埋伏抜歯，抜歯	2.5			2.30	26		
				6⌋6 P	抜歯	2.5						
30	M	91	Af, CI	1⌋ P	抜歯	1.0			2.20	26		
31	F	52	CS	⌊7 per	抜歯	2.0			2.13	32		
32	F	57	PPH, HT	⌊6 *per RR*	埋伏抜歯	2.5			2.41	27		
33	M	57	MVR, AVR, Af	3⌋ P	抜歯	1.5			2.49	26	+	止血床

P：辺縁性歯周炎，GA：歯肉膿瘍，per：根尖性歯周炎，AA：歯槽膿瘍，perico：智歯周囲炎，RP：埋伏残根，WZ：歯根嚢胞，italics：埋伏歯，AMI：急性心筋梗塞，AVR：大動脈弁閉鎖不全，AVS：大動脈弁狭窄，MVR：僧房弁閉鎖不全，CI：脳梗塞，Af：心房細動，DCM：拡張型心筋症，HCM：肥大型心筋症，HT：高血圧症，PPH：原発性肺高血圧症，VT：心室頻拍，ASO：動脈閉塞症，PVC：心室性期外収縮，CS：心サルコイドーシス

表 3　INR 2.5～3.0 未満の症例

症例	性別	年齢	基礎疾患名	歯科疾患名	歯科処置	抗凝固療法（/日） ワルファリン (mg)	アスピリン (mg)	チクロピジン (mg)	INR	PT (%)	後出血	備考
34	M	71	AMI	1⌋1 P, GA	抜歯	1.0	100		2.58	25		
35	F	53	CI	⌊23 per	抜歯	3.0			2.62	24		
36	F	66	Af, CI	21⌋12 P	抜歯	2.5			2.68	24		
				⌊5 P	抜歯	2.5			2.80	20		
37	M	63	Af, CI	⌊67 per, WZ	抜歯，摘出	3.0			2.67	22		
			AV block（Ⅲ）	76⌋ per	抜歯	3.0			2.51	24		
38	F	67	Af, CI	1⌋1 P	抜歯	3.0			2.63	21		
39	M	73	HCM, Af	⌊4 P	抜歯	2.0			2.51	24		
40	M	64	Af, CI	⌊1 *per RR*, 2⌋ per	埋伏抜歯，抜歯	3.0	81		2.55	24		

P：辺縁性歯周炎，GA：歯肉膿瘍，per：根尖性歯周炎，perico：智歯周囲炎，RP：埋伏残根，WZ：歯根嚢胞，italics：埋伏歯，AMI：急性心筋梗塞，CI：脳梗塞，Af：心房細動，AV block：房室ブロック，HCM：肥大型心筋症

したがって，INR は，INR＝

［患者血漿の PT（秒）/正常血漿の PT（秒）］^{ISI} で算出される[16]。

抗血栓療法施行患者の抜歯における出血管理について，Souto ら[2]，Devani ら[5]，Compbell ら[9]，Evans ら[11]は，ワルファリンを継続した群と中止した群で，出血量や後出血の発生頻度に差はなかったと報告した。Blinder ら[10]は INR が 1.5～4.0 までの患者にワルファリンを継続して抜

表 4 抗血小板薬の症例

症例	性別	年齢	基礎疾患名	歯科疾患名	歯科処置	抗凝固療法 (/日) アスピリン (mg)	チクロピジン (mg)	シロスタゾール (mg)	後出血	備考
41	F	63	UAP, DM	⌈45 per	抜歯	162				
42	F	77	AVR, MVR, VT	⌊7 per	抜歯	162				
43	F	72	OMI, DM	⌈5 P	抜歯	100				
44	M	85	MI, RA	5432⌋ P, GA	抜歯	81		200	+	
45	M	58	AMI	6⌋P	抜歯	100				
46	F	67	AMI	⌈76⌋per	抜歯	100				
				⌊4 P	抜歯	100				
47	M	63	OMI, HT	⌈3 P	抜歯	100				
48	M	50	CI	3⌋⌊23 per	抜歯	100	200			
49	M	35	DCM	⌈5 per	抜歯	81				
50	M	64	AMI	⌊6 P, GA	抜歯	300	200			
51	F	65	OMI, DM, HT	6⌋per	抜歯	81				
52	M	29	CHF	*8⌋perico*	埋伏抜歯	100				
53	F	77	TAA	⌊1 P	抜歯	162				
54	M	60	CI	⌊4 P	抜歯	100				
55	F	69	AMI	*32⌋per RR*	埋伏抜歯	81		200		
56	M	72	Af, CI	*5⌋per RR*, 4⌋per 5⌋	埋伏抜歯，抜歯	100				
				⌈*5 per RR*, ⌈7 per	埋伏抜歯，抜歯	100				
57	F	70	CI, DM	4⌋P, GA	抜歯		200			

P：辺縁性歯周炎，GA：歯肉腫瘍，per：根尖性歯周炎，perico：智歯周囲炎，RP：埋伏残根，italics：埋伏歯，
UAP：不安定狭心症，AMI：急性心筋梗塞，OMI：陳旧性心筋梗塞，AVR：大動脈弁閉鎖不全，MVR：僧房弁閉鎖不全，
CI：脳梗塞，DCM：拡張型心筋症，HT：高血圧症，DM：糖尿病，VT：心室頻拍，TAA：胸部大動脈瘤，CHF：慢性心不全，
RA：リューマチ

歯を行い，INR の値により後出血の発生率には差はないと報告した。Beirne ら[1]，Webster ら[8]は，普通抜歯では INR が 4.0 未満，埋伏歯や多数歯の抜歯では 3.0 未満，Meehan ら[3]は INR が 2.5 未満，Herman ら[4]，Scully ら[12]，Little ら[13]は INR が 3.5 未満であれば，ワルファリンを継続して抜歯をしても後出血が増加することはないと報告した。また Wahl は，抜歯にあたり抗血栓療法を中止すると，0.95%に血栓症を生じ，その大多数が死亡の転帰をとる[6,7]ことを報告し，抗血栓療法中止の危険性を示した。

一方，日本人の抗血栓療法施行患者の抜歯について，式守はトロンボテスト（TT）が 8.7～44.8%（INR 3.0～1.24 に相当[17]）の患者 23 名に 46 回の抜歯を行い，通常よりは止血しにくいが，最終的にはガーゼ圧迫のみで止血可能である[18]と報告した。新美らは INR が 3.0 までの患者 25 名にワルファリンを継続して抜歯を行い，局所止血法に線状アテロコラーゲンを使用したところ，抜歯直後に 4 名，翌日に 1 名の湧出性出血を認めたが，ガーゼ圧迫または線状アテロコラーゲンの再挿入にて止血可能であった[15]と報告した。

日本人は欧米人に比較して，抗血栓療法をやや軽度に維持しても血栓症を発症することが少なく，逆に欧米人と同じ程度で維持すると出血傾向が出やすいことが経験的に知られており，欧米の基準よりも軽度に抗血栓療法が行われている。最近では，ワルファリンの代謝酵素の活性が，欧米人と日本人では異なることがこれに関与する[19,20]といわれている。したがって，抗血栓療法下の抜歯に際し，日本人に欧米人と同様の基準をあてはめることの正当性についても報告が少なく，日本人独自のデータが必要である。

本研究では，INR が 3.0 までのワルファリン服用患者に対し，ワルファリンの維持量を継続しながら 1 回につき 1～4 歯の抜歯を 46 回行い，2 回(4.4%)に後出血を認めた。これは，Devani ら[5]が報告した後出血発生率 3.0%と同程度であり，Blinder ら[10]の 12%や Evans ら[11]の 26.3%と比較しても低い発生率である。後出血を認めた症例は，INR が 2.15 および 2.49 と過度に高くはなかった。しかし，

症例19では 65| 歯槽膿瘍，症例30では 3| 辺縁性歯周炎のため，急性炎症を伴っていたと考えられる。したがって，後出血はワルファリンの影響よりも，むしろ局所の炎症が原因で生じたものと推察された。

Scullyらは，ワルファリン投与患者では，歯肉炎が出血の危険性を増加させる[12]と述べ，Hermanらは，歯肉切除術や歯周外科手術ではINRを2.5未満でコントロールすべきである[4]と述べ，抜歯時よりも厳しい基準を示している。これは炎症を伴う部位では局所止血処置が奏功しにくいと考えたためであり，抜歯においても局所の炎症の有無が止血の成否に関係するといえる。

ワルファリンとアスピリンの併用は出血の危険性が高くなる[12]と報告されている。しかし，本研究結果からは，ワルファリンと抗血小板薬1ないし2剤を併用している症例について，これらを継続しても抜歯後の出血は生じていないことから，ワルファリンと抗血小板薬1ないし2剤を併用している場合でも，抜歯時の出血管理はINRを基準に判断すればよいと考えられた。

抗血小板薬のみを服用している患者において，1回につき1～4歯の抜歯を19回行い，後出血を1回認めた（5.3%）。後出血を認めた症例40では，5432| 歯肉膿瘍のため，急性炎症を伴っていたと考えられ，後出血は抗血小板薬の影響ではなくむしろ局所の炎症が原因で生じたものと推察された。本症例は高齢者であり，アスピリンとシロスタゾールの2剤が併用されているため，外科処置にあたってはより慎重な出血管理が必要であったと考えられた。

以上より，日本人のワルファリン服用患者（INRが3.0まで）または抗血小板薬服用患者において，維持量を継続して抜歯を行っても大部分の症例では止血可能であると考えられる。約5%の患者に後出血を認めたが，重篤な出血はみられなかったことや局所止血法にて止血可能であったこと，さらに抗血栓療法の減量または中止をした場合には，重篤な血栓症を生じることが少なくないとの報告があることから，抗血栓療法を継続して抜歯を行う方針が妥当であると考えられた。

本研究では，主に酸化セルロース綿の挿入と縫合のみを行ったが，この方法で局所の出血管理は良好に行えた。萌出歯では，酸化セルロース綿の脱落を防止する目的で，4-0絹糸で1糸のみ水平マットレス縫合を行った。抗血栓療法患者の抜歯における局所止血法としては，酸化セルロースやゼラチンスポンジの挿入と縫合のほか，フィブリン糊[21,22]や線状アテロコラーゲン[15]の使用が記載されているが，これらは高価であるため日常的に用いることは困難である。酸化セルロースやゼラチンスポンジとフィブリン糊では局所止血作用に差がない[21,22]ことから，本研究で用いた酸化セルロース綿と縫合を用いる方法が適切であると考えられる。

結　語

1. 抗血栓療法を受けている日本人に対し，抗血栓薬の維持量継続下での抜歯における出血管理について検討した。
2. 抗血栓療法施行患者は57名で，65回の抜歯のうち後出血を3回（4.6%）認めた。
3. 日本人のワルファリン服用患者（INRが3.0まで）および抗血小板薬服用患者においては，維持量を継続して抜歯を行っても大部分は止血可能である。また，後出血を生じた場合でも，局所止血法で止血可能であると考えられた。

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