Emergency Reversal of Anticoagulation After Intracerebral Hemorrhage

Kent Fredriksson, MD; Bo Norrving, MD; and Lars-Göran Strömblad, MD

Background and Purpose: Although intracerebral hemorrhage is one of the most serious complications during oral anticoagulant therapy, there are no guidelines on emergency treatment with respect to reversal of anticoagulation effect in these patients.

Methods: We retrospectively compared laboratory data and clinical features in 17 cases of anticoagulant-related intracerebral hemorrhage treated with prothrombin complex concentrate (n=10) or fresh-frozen plasma (n=7).

Results: In the group of patients treated with prothrombin complex concentrate, the mean prothrombin time decreased from 2.83 to 1.22 International Normalized Ratio within 4.8 hours, compared with a decrease from 2.97 to 1.74 within 7.3 hours in those given fresh-frozen plasma (i.e., four to five times more rapidly after treatment with prothrombin complex concentrate) (p<0.001). Symptoms and signs of intracerebral hemorrhage, measured on an eight-graded Reaction Level Scale, progressed on average 0.2 grades in patients given prothrombin complex concentrate compared with 1.9 grades in those given fresh-frozen plasma (p<0.05). In patients with prothrombin values above 1.46, clinical progression within 12 hours occurred in five of six cases.

Conclusions: Treatment with prothrombin complex concentrate reverses anticoagulation more rapidly than fresh-frozen plasma, which might be of importance for the prevention of further bleeding. (Stroke 1992;23:972-977)

KEY WORDS • anticoagulants • cerebral hemorrhage

Hemorrhage within the central nervous system during oral anticoagulant treatment is a serious complication with high morbidity and mortality rates. Anticoagulant-related intracerebral hemorrhages are larger, and protracted bleeding is more common, than in patients with spontaneous hematomas.1,2 Early reversal of anticoagulation would therefore seem to be essential in order to improve the outcome. However, there are no guidelines in the literature on emergency treatment of anticoagulant-related intracerebral hemorrhage (ICH). Both prothrombin complex concentrate2 and fresh-frozen plasma1 have been used in addition to vitamin K, but the relative efficiency of different treatments has not been determined. We retrospectively analyzed clinical and laboratory data in patients treated with prothrombin complex concentrate and fresh-frozen plasma at the University Hospital of Lund, Sweden, with respect to reversal of anticoagulation and the course of symptoms and signs of ICH.

Subjects and Methods

We retrospectively analyzed patients with anticoagulant-related ICH admitted to the Departments of Neurology and Neurosurgery, University Hospital of Lund, Sweden, between 1987 and 1990. In all patients, the diagnosis of ICH was established by computed tomographic (CT) scan (Toshiba, Tokyo; 512×512 matrix, 10-mm slice thickness) within a few hours after the onset of the symptoms. During the study interval, there were 29 patients with anticoagulant-related ICH. Twelve patients, the majority of whom were already in a comatose stage at the time of arrival at the hospital, were given no specific treatment or intravenous injections of vitamin K only. The sites of bleeding in these 12 patients, all of whom died within 4 days of onset, were as follows: large hemispheric, six patients; putaminal, four patients; and lobar and thalamic, one patient each. The present analysis concerns those 17 patients who, in addition to receiving vitamin K, received therapy with either prothrombin complex concentrate or fresh-frozen plasma.

The patients had been treated with warfarin or dicumarol. Prothrombin time (PT) testing (Nycotest PT, Nycomed) was used to determine the intensity of anticoagulation. In the text, PT values are expressed both as percentage of normal coagulative activity in control plasma (using a saline dilution curve) and as International Normalized Ratio (INR).3 The choice between prothrombin complex concentrate and fresh-frozen plasma therapy, as well as the dosage, were decided by the case physician after consultation with a hematologist at the Department of Coagulation Disorders, Malmö General Hospital. The average doses given were 0.43 ml (25.8 IU) prothrombin complex concentrate and 8.0 ml fresh-frozen plasma per kilogram of body weight, taking PT value on arrival into

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TABLE 1. Indications for Institution, Duration, and Degree of Oral Anticoagulant Treatment

<table>
<thead>
<tr>
<th>Condition</th>
<th>Duration of treatment</th>
<th>PT value at arrival</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>8 months</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>5 years</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>3 years</td>
<td>22</td>
<td>1*</td>
</tr>
<tr>
<td>Repeated</td>
<td>5 years</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3 years</td>
<td>9</td>
<td>1*</td>
</tr>
<tr>
<td></td>
<td>6 years</td>
<td>14</td>
<td>1*</td>
</tr>
<tr>
<td>Valve prosthesis</td>
<td>6 months</td>
<td>&lt;10</td>
<td>1</td>
</tr>
<tr>
<td>Atrial fibrillation + valve prosthesis</td>
<td>3 months</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Atrial fibrillation + brain infarct (or TIA)</td>
<td>3 years</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>10 years</td>
<td>17</td>
<td>1*</td>
</tr>
<tr>
<td></td>
<td>unknown</td>
<td>&lt;10</td>
<td>1*</td>
</tr>
<tr>
<td>Mitral valve prolapse + brain infarct</td>
<td>2 months</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Arterial disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe carotid artery stenosis + brain infarct (or TIA)</td>
<td>5 months</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>1 year</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>Brain infarct (or TIA)</td>
<td>2 years</td>
<td>12</td>
<td>1*</td>
</tr>
<tr>
<td></td>
<td>10 years</td>
<td>22</td>
<td>1</td>
</tr>
</tbody>
</table>

PT, prothrombin time measured in percent of normal plasma and as International Normalized Ratio (INR); n, number of patients; TIA, transient ischemic attack.

*Patients treated with fresh-frozen plasma.

Results

Table 1 shows the indications for institution, duration, and intensity of anticoagulation therapy. Tables 2 and 3 give clinical features, size, and location of ICH, and PT values at the time of onset of ICH in the two treatment groups.

Immediately after the diagnosis of ICH had been established by an emergency CT scan, vitamin K was given (10–20 mg i.v.) and an intravenous infusion was started with prothrombin complex concentrate (32±17 ml; 1,930±996 IU) or fresh-frozen plasma (600±306 ml). The time of infusion (Table 3) tended to be more protracted for patients treated with fresh-frozen plasma because of larger fluid volumes, which also restricted the total amount given. A significant correlation be-
TABLE 3. Prothrombin Time and Reaction Level Before and After Emergency Reversal of Anticoagulation

<table>
<thead>
<tr>
<th></th>
<th>Prothrombin complex concentrate</th>
<th>Fresh-frozen plasma</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin time (PT)</td>
<td>(n=10)</td>
<td>(n=7)</td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>16.7 (2.83)±5.5</td>
<td>15.7 (2.97)±6.3</td>
<td>NS</td>
</tr>
<tr>
<td>After treatment</td>
<td>63.1 (1.22)±20.1</td>
<td>33.6 (1.74)±21.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Time (hours)</td>
<td>4.8±5.1</td>
<td>7.3±5.5</td>
<td>NS</td>
</tr>
<tr>
<td>PT increase/hour</td>
<td>13.0±6.7</td>
<td>2.8±1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reaction level grade (1–8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>1.6±1.0</td>
<td>2.7±1.8</td>
<td>NS</td>
</tr>
<tr>
<td>After treatment</td>
<td>1.8±2.2</td>
<td>4.6±2.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Maximal difference after–before treatment</td>
<td>0.2±1.4</td>
<td>1.9±1.5</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Values are mean±SD. $n$, Number of patients; PT, prothrombin time in percent of normal plasma and (in parentheses) converted to International Normalized Ratio. Reaction level grades according to Reaction Level Scale 85. Statistical differences were evaluated with Wilcoxon's rank sum test.

between dose and response (change in PT per hour) was found for prothrombin complex concentrate but not for fresh-frozen plasma (Figure 1). The PT values reversed 4.6 times more rapidly after treatment with prothrombin complex concentrate compared with fresh-frozen plasma (Table 3).

Within 12 hours after their arrival, a decrease in reaction level (i.e., increased score according to RLS 85) was observed in six patients, five of whom had PT values below 45% (above 1.45 INR), more frequently observed in patients treated with fresh-frozen plasma than with prothrombin complex concentrate (Table 3). Occurrence of further intracranial bleeding was objectively assessed in four patients by repeated CT scans (two patients) or autopsy (two patients). Residual neurological deficits at discharge from the hospital tended to be less severe in patients treated with prothrombin complex concentrate (five patients in grades 0–3) than in those treated with fresh-frozen plasma (one patient in grades 0–3), but the difference did not reach statistical significance. Two patients in each treatment group died.

Selected Case Reports

Case 1. A 68-year-old hypertensive man treated with oral anticoagulants for 5 years after a single episode of pulmonary embolism suddenly experienced left-sided hemihypesthesia and hemiparesis but was fully awake upon arrival at the hospital (grade 1, RLS 85). CT scan revealed a small (0.5 cm) hematoma in the right thalamo-capsular region (Figure 2A). The patient was treated with vitamin K (10 mg i.v.) and prothrombin complex concentrate (2,000 IU i.v.; 28 IU/kg body weight), and his PT value increased from 17% to 68% (decreased from 2.8 to 1.2 INR) within 3 hours. The patient was discharged from the hospital a few days later with minimal neurological deficits.

Case 2. A 58-year-old man treated with oral anticoagulants for 5 months after implantation of mechanical prosthetic aortic and mitral heart valves suddenly experienced headache and weakness of his left arm and leg. On admittance he was drowsy (grade 2, RLS 85) and had a severe left-sided hemiparesis. CT scan revealed a 9x3x3-cm right-sided putaminal hemorrhage (Figure 2B). The patient was treated with vitamin K (20 mg i.v.) and prothrombin complex concentrate (3,000 IU i.v.), and his PT value rose from less than 10% to 57% (decreased from less than 4.3 to 1.3 INR) within 3 hours. The following day the hematoma was surgically evacu-
FIGURE 2. Cranial computed tomographic scans of intracerebral hemorrhages during oral anticoagulant treatment in cases 1–3. Panel A: Small thalamocapsular hemorrhage (case 1). Panel B: Large putaminal hematoma with midline shift (case 2). Panels C and D: Large putaminal hemorrhage with midline shift that 2 days later shows increased size (case 3).

ated. On the fourth day, treatment with oral anticoagulants was resumed. No rebleeding occurred, but the patient was discharged with a persistent hemiparesis.

Case 3. A 67-year-old man with diabetes mellitus treated with oral anticoagulants for 3 years because of nonvalvular atrial fibrillation suddenly experienced
headache. On arrival at the hospital the patient had a severe left-sided hemiparesis, hemihypertension, and hemianopia with anosognosia (grade 1, RLS 85). CT scan revealed a 5×2.5×3-cm right-sided putaminal hemorrhage (Figure 2C). The patient was treated with vitamin K (20 mg i.v.) and fresh-frozen plasma (400 ml i.v.), and his PT value increased from 9% to 19% (decreased from 4.7 to 2.6 INR) within 2 hours. He gradually deteriorated (to grade 3), and nuchal rigidity developed on the third day. A repeat CT scan disclosed increased size of the hematoma and blood in the posterior horn of the lateral ventricle (Figure 2D). The hematoma was evacuated, and although the patient showed some recovery, he was left with severe disability.

Case 4. A 76-year-old man treated with oral anticoagulants for 3 months after coronary bypass surgery because of implanted mechanical prosthetic aortic heart valves and atrial fibrillation suddenly experienced numbness and weakness of his right arm and leg. On arrival he showed a right-sided hemiparesis and hemihypertension (grade 1, RLS 85). CT scan revealed a 4×3×3-cm left-sided hematoma in the basal ganglia. He was treated with vitamin K (10 mg i.v.) and prothrombin complex concentrate (3,000 IU i.v.), and PT increased from 14 to 98% (decreased from 3.3 to 1.0 INR) within 3 hours. Hematemesis was noted on the second day, anuria occurred on the fourth day, and he died on the fifth day. Autopsy showed the following: 1) coronary atherosclerosis and old myocardial infarcts but no thrombus formation or vegetations on the valve prosthesis; 2) cerebral microangiopathy with microaneurysms, petechial hemorrhages, a large thalamostriatal hematoma, and multiple small (mainly old) infarcts in the basal ganglia, the hemispheric white matter, and the cerebral cortex (Congo-red staining for amyloid was negative); and 3) precipitates of fibrin in renal arterioles and widespread (acute) hemorrhagic cortical infarctions in both kidneys.

Discussion

The present study shows that reversal of anticoagulation is more rapid in patients treated with prothrombin complex concentrate than in those treated with fresh-frozen plasma. Although we observed less prominent signs of progression of ICH and a nonsignificant trend for better outcome in patients treated with prothrombin complex concentrate, the design of the study (retrospective and nonrandomized) and the low number of patients preclude any conclusions on differences in clinical outcome related to the different treatments. To address this issue, a much larger study with closely balanced groups with respect to demography and size/localizations of the hemorrhages would be needed.

The more rapid reversal of anticoagulation in the group of patients treated with prothrombin complex concentrate is probably caused by the higher effective dose given (10 ml prothrombin complex concentrate is equivalent to 600 ml fresh-frozen plasma). In the subgroup receiving the smallest amount of prothrombin complex concentrate, comparable to the average dose of fresh-frozen plasma, rather limited changes in PT values are seen. The more restricted use of fresh-frozen plasma is most likely due to the concern that volumes needed for rapid reversal of anticoagulant effect (i.e., approximately 2,000–2,500 ml) could precipitate overt heart failure or pulmonary edema in these patients, in whom frequently acute electrocardiograms show left ventricular strain patterns. On the other hand, infusion of prothrombin complex concentrate involves the hazard of generalized thromboembolism triggered by activated prothrombin complexes.6,7 Extensive bilateral renal infarction, found at autopsy in one of our cases treated with prothrombin complex concentrate, might have been caused by such a mechanism. These side effects, as well as the risk of transmission of hepatitis by both types of replacement therapy,6,8 must be considered in treating anticoagulant-related ICHs. The risk of transmission of human immunodeficiency virus should today be negligible, especially for virus-inactivated prothrombin complex concentrate.

The relative risk of ICH during oral anticoagulant therapy is increased eightfold to 10-fold in patients over 50–55 years of age.9 More protracted bleeding and larger hematomas are found in patients treated with anticoagulants than in those with spontaneous ICH.1,2 Anticoagulant-related ICHs are not localized by chance, as would be expected if they were entirely caused by hemorrhagic diathesis, but occur at the same predilection sites as spontaneous ICH.10–12 This suggests similar loci minoris resistentae within the microvasculature in both groups. Segmental destructive microangiopathy is found in small penetrating arteries at these predilection sites in elderly hypertensive and normotensive individuals,12,13 supporting the view that they are bleeding sites in spontaneous ICH as well as anticoagulant-related ICH. The latter are probably due to the fact that anticoagulant treatment delays the conversion of fibrinogen to fibrin, which normally prevents rupture of necrotic resistance vessel sections until reparative fibrosis has occurred. We cannot exclude the possibility that cerebral amyloid angiopathy might have been the cause of the hemorrhage in some cases, especially in patients with a lobar hemATOMA. In our series, histopathological examination was performed in only one patient (case 4).

The annual risk of anticoagulant-related ICH is 1–1.5% per year in the elderly in our population.14 Because the risk of ICH during anticoagulant treatment is directly related to duration of therapy, it is essential that treatment periods are not longer than medically indicated. In the present study, treatment with anticoagulants had been prolonged for 8 months to 10 years (average, 4.3 years) in six of our cases after a single episode of venous thrombosis with or without pulmonary embolism or cerebral infarction without an embolic source in the heart or the cervicocranial arteries (i.e., far beyond the 3–6 months commonly recommended).7,8 These findings are in agreement with those in two previous studies of anticoagulant-related intracranial hemorrhage in which a critical review based on established criteria for oral anticoagulant therapy suggested there was no medical reason to treat one third of the patients.7,8 A more cautious use of oral anticoagulants with respect to intensity of treatment might further decrease the incidence of ICH. The average PT value at the time of ICH corresponded to an INR of 2.9 (range, 2.0–4.7) in the present study and 3.5 (range, 1.8–6.5) in another study;2 in a third study,4 a median INR of 3.7 was reported. In our study, the intensity of anticoagulation...
was unnecessarily high in seven of the 17 cases at the time of intracerebral bleeding. It has been suggested that prolongation of PT to 2–3 INR is sufficient for the prevention of thromboembolism. In a recent study, low-dose anticoagulant treatment (INR 1.5–2.7) was highly effective in preventing embolic stroke in patients with nonrheumatic atrial fibrillation. On the other hand, patients with mechanical prosthetic heart valves require more intense (and lifelong) anticoagulant therapy. Resumption of oral anticoagulants after ICH in such patients is hazardous but of utmost importance because of the imminent risk of arterial thromboembolism (case 2).

In conclusion, the present results suggest that early reversal of anticoagulation by means of prothrombin complex concentrate is advantageous to fresh-frozen plasma in patients with intracerebral hemorrhage. Other means of importance in reducing the devastating complication of anticoagulant-related ICH include differentiated intensity levels of anticoagulation according to underlying disorder, careful control of treatment, and attention to treatment duration according to accepted medical guidelines.

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