Recombinant Factor VIIa for Rapid Reversal of Anticoagulant Effect in Patients with Intracranial Hemorrhage: The Israeli Experience and Review of the Literature

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Spontaneous intracerebral hemorrhage accounts for 4–5% of cases of acute stroke and is associated with a substantially worse prognosis than ischemic stroke. Spontaneous intracerebral hemorrhage is associated with a high mortality rate, almost 50%. Intracranial hemorrhages associated with oral anticoagulants can be divided into intracerebral, subdural/epidural, and subarachnoid. ICH constitutes approximately 70% of oral anticoagulant-associated intracranial hemorrhages, while subdural hematomas comprise the majority of the remainder. Subarachnoid hemorrhage is a rare complication. Both ICH and subdural hematoma can occur simultaneously in anticoagulated patients. Although infrequent, the incidence of oral anticoagulant-related intracerebral hemorrhage (OAC-ICH) is seven- to tenfold higher than in patients not taking OAC, with a mortality rate of approximately 60%. OAC-related subdural hematomas are less frequently reported than ICH and the risk is increased four- to 15-fold in patients on OAC. In about half of these anticoagulated patients with ICH the bleeding evolves slowly over 12 to 24 hours, and emergency reversal of anticoagulation is crucial. Despite accumulating knowledge, our understanding of OAC-ICH remains limited and there are currently no universally accepted guidelines for treatment.

This paper briefly reviews the epidemiology, pathophysiology, and current treatment options for OAC-related intracranial hemorrhage, including the Israeli experience.

Epidemiology

In epidemiologic studies the incidence of all strokes ranges from 200 to 500 per 100,000, and ICH accounts for 8–15% of strokes [1]. The worldwide incidence of spontaneous intracerebral hemorrhage ranges from 10 to 20 per 100,000 population/year [2], and increases with age, doubling every 10 years after age 35 [3]. Spontaneous intracerebral hemorrhage is more common in men than women, particularly those older than 55 [2,4]. The rate of occurrence is highest in Asians, intermediate in blacks, and lowest in whites, with an incidence in blacks almost twice that among whites [5,6]. The incidence of intracerebral hemorrhage in the Japanese population is similar to that among blacks [7]. The absolute rate of OAC-related intracerebral hemorrhage (OAC-ICH) is difficult to predict accurately, the reported incidence is seven- to tenfold higher than in patients not treated by OAC [8-11].

According to reported studies, OAC-ICH accounts for 10–12% of all ICH [12]. Thus, the estimated OAC-ICH occurs at a rate 2 to 9/100,000 population per year [13]. OAC are administered to treat or prevent primary and secondary venous and arterial thromboembolic complications. Atrial fibrillation, a common condition in the elderly, represents the most common long-term indication. As the number of patients with atrial fibrillation increases as a result of the aging of the population, the impact of OAC-ICH is likely to increase. Unfortunately, OAC dramatically increases the risk for ICH, worsens the severity of ICH, and significantly increases the likelihood of death when ICH occurs.

Pathophysiology

It is clear that OAC-related intracerebral hemorrhage is associated with advancing age, cerebrovascular disease, and the intensity of anticoagulation [10,14-19,20-22]. Over-anticoagulation is strongly associated with bleeding, however, most of the bleeding episodes occur when the international normalized ratio is within the therapeutic range [9,14,15,18,19,21].

The degree of INR prolongation at the time of ICH correlates with progressive hematoma enlargement after admission, functional outcome, and mortality [9,16,22]. OAC not only increases the risk of ICH, but also worsens the severity of hemorrhage when it occurs, approximately doubling its mortality [23]. The mechanism by which OAC worsens severity of ICH remains poorly understood.

OAC do not appear to promote vascular injury, inhibit vascular repair, or induce, directly or indirectly, arterial rupture. It has been postulated that oral anticoagulants (and other antithrombotic agents) are only a precipitating factor that may cause spontaneous subclinical brain hemorrhages to grow to clinical importance.

ICH = intracerebral hemorrhage
OAC = oral anticoagulant

INR = international normalized ratio
representing an unmasking of several distinct preexisting cerebral vasculopathies that cause subclinical bleeding in the absence of anticoagulation, occurring especially in the elderly population – in those individuals with hypertension and cerebrovascular disease [10,13,24]. These underlying vascular disorders might be the same for spontaneous and OAC-ICH. In this context Rosand et al. [25] studied the relationship between cerebral amyloid angiopathy and warfarin-related ICH. The authors concluded that CAA is an important cause of warfarin-associated lobar ICH in the elderly.

The prevalence of CAA is markedly age-dependent [25,26]. Pathologically it can be identified in about 35% of brains from individuals aged 85 or more, one-third of whom are affected to the severe extent associated with spontaneous intracerebral hemorrhage. Both advancing age and CAA are also important contributory factors to lobar ICH in patients taking an oral anticoagulant. CAA causes hemorrhages primarily in the lobar regions of the cerebral hemispheres. This predilection for a lobar location is likely due to the fact that CAA most commonly and severely involves the superficial vessels of the cortex (as opposed to the penetrating vessels of the basal ganglia, thalamus and brain stem typically involved by hypertensive vasculopathy in the brain) [25,26].

**In anticoagulant-related intracranial hemorrhage, a combination of activated prothrombin complex and rFVIIa might be the best therapeutic approach**

Gorter [17], for the SPIRIT (Stroke Prevention in Reversible Ischemia Trial) and EAFT (European Atrial Fibrillation Trial) investigators, reported that patients with cerebral ischemia of presumed arterial origin had a significantly higher risk of OAC-ICH. Results from SPIRIT suggested that the presence of white-matter hypodensity on computed tomography scan (leukoaraiosis) confers particular risk for post-stroke warfarin-related ICH [27,28]. Moreover, Smith et al. [28] reported that leukoaraiosis is a very strong and independent risk factor for warfarin-related ICH in survivors of ischemic stroke, including those in the commonly employed range of anticoagulation. Roob and colleagues [29] used gradient-echo magnetic resonance imaging to seek small hemosiderin deposits (indicative of asymptomatic “microbleeds”) in 280 people without clinical neurologic disease. Microbleeds were associated with advancing age, hypertension and leukoaraiosis. Hypertension was more strongly associated with deep hemispheric deposits than with lobar location. The authors conclude that MRI evidence of past microbleeds may be found even in neurologically normal elderly individuals and is related, but not restricted, to other indicators of small vessel disease.

These distinct underlying cerebral vasculopathies cause subclinical hemorrhages in the absence of anticoagulation.

ICH is a dynamic process. In the study by Flibotte and team [23], warfarin did not increase ICH volume at presentation but did raise the risk of in-hospital hematoma expansion, and this expansion appears to mediate part of warfarin’s effect on ICH mortality. An association between hematoma expansion and clinical deterioration and mortality was found in large retrospective studies [30].

**Therapeutic options**

In OAC-ICH the bleeding seems to evolve slowly, for 24 hours or more, in perhaps half the patients [31-33], compared to patients with spontaneous ICH in whom approximately 10% show progressive enlargement in the first 24 hours [34,35]. OAC-ICH often continues to enlarge after the diagnosis is made.

In one study, the expansion of hematoma was found up to the seventh day in 16% of patients without OAC compared with 54% in those on OAC [23]. An association between hematoma expansion and clinical deterioration and mortality was found in large retrospective studies [30,36]. This prolonged bleeding provides a longer time window of therapeutic opportunity compared to the relatively short time window during which most expansion is observed in hemorrhages unrelated to warfarin [23,30,32,33].

The mortality rate of OAC-ICH is very high and despite the lack of prospective data, rapid reversal of increased INR is the initial treatment of choice to prevent hematoma growth and improve the clinical outcome [9,19,23,33]. Time to INR reversal seems to be the most important determinant, a fact that should not be underestimated because even minutes may count in OAC-related ICH.

Treatment options include the use of vitamin K, fresh frozen plasma, prothrombin complex concentrates, and recombinant FVIIa.

**Vitamin K**

Vitamin K is available in several formulations that can be administered by various routes (oral, subcutaneous, intramuscular, intravenous). Subcutaneous administration of vitamin K in small doses may not correct INR as rapidly and as effectively as when administered intravenously. For rapid and complete reversal of anticoagulation, higher doses of vitamin K must be considered by the subcutaneous route. Intravenous administration of vitamin K in high doses (up to 25 mg) leads to complete INR reversal within 2 to 6 hours, however it often takes more than 24 hours to achieve an effective response to vitamin K administration, during which time the ICH may continue to enlarge.

**Fresh frozen plasma**

Fresh frozen plasma contains non-concentrated coagulation factors; hence, eight units of fresh frozen plasma are often required to immediately reverse the coagulation defect. Despite a significant fall in INR after treatment with FFP, there remained

CAA = cerebral amyloid angiopathy

FFP = fresh frozen plasma
a demonstrable coagulopathy that may have clinical relevance in the context of intracranial hemorrhage. Furthermore, the associated volume load can lead to circulatory overload, especially in patients with underlying cardiac disease. Other drawbacks of FFP in this setting include compatibility testing and thawing before transfusion. Because of the variable content of vitamin K-dependent clotting factors in FFP, and the effects of dilution, the efficacy of this approach is open to doubt.

Prothrombin-complex concentrates
Prothrombin complex concentrates are impure mixtures of vitamin K-dependent proteins. They may be produced as three-factor or four-factor concentrates. In addition to factors II, IX and X, the latter contain considerable amounts of factor VII and/or additionally protein Z and the physiologic coagulation inhibitors proteins C and S. PCC normalize the INR more rapidly than infusion of FFP or vitamin K alone and are easily administered. The use of PCC may be accompanied by adverse events including immediate allergic reactions, transmission of blood-borne viruses, heparin-induced thrombocytopenia type II due to heparin contained in the preparations, and thrombotic events – which represent the most important side effect of PCC but this risk is difficult to quantify due to varying preparations, doses, and differing patient populations in available reports. The use of PCC without vitamin K may result in re-increase of INR as the coagulation factors are metabolized, which may cause clinical deterioration.

None of these treatment regimens – vitamin K, FFP, or PCC – have been proven to be more effective than another.

Recombinant factor VIIa
Factor VIIa is a vitamin K-dependent glycoprotein that activates the extrinsic pathway of the coagulation cascade. It promotes hemostasis by complexing with tissue factor and activating factor X to factor Xa, as well as coagulation factor IX to factor IXa. Factor Xa, in complex with other factors, converts prothrombin to thrombin, which leads to the formation of a hemostatic plug by converting fibrinogen to fibrin. Recombinant FVIIa is derived from cultured baby hamster kidney cells and is almost identical to human activated factor VII. The half-life of rFVIIa is 2.3 hours after intravenous administration. Factor VIIa (rFVIIa) has been approved by the U.S. Food and Drug Administration to treat bleeding in patients with hemophilia A and B who have developed inhibitory antibodies to factor VIII (antihemophilic factor) or factor IX. It has also been reported to reduce bleeding in patients without coagulopathy.

A recently published study in patients with spontaneous intracerebral hemorrhage without OAC reported that treatment with rFVIIa within 4 hours after the onset of intracerebral hemorrhage limits the growth of the hematoma, reduces mortality, and improves functional outcome at 90 days [37].

There are only limited data on the use of rFVIIa in patients with OAC-related ICH. A review of the world literature revealed only 28 patients who were treated with rFVIIa for intracranial related OAC [Table 1]. An initial report of Sorenson and associates [38] reported six patients with OAC-related intracranial hemorrhage who were treated with rFVIIa and concluded that factor VIIa may be quite useful as adjunctive therapy. In a retrospective study, Freeman et al. [39] reported seven consecutive patients who had been on warfarin and were treated with rFVIIa (mean initial dose 62 µg/kg) for intracranial hemorrhage. The INR decreased from a mean of 2.7 (range 1.6–5.6) before administration of rFVIIa to 1.08 (range 0.6–3.5) after rFVIIa administration. Full and lasting reversal of the INR was achieved only with the combined use of vitamin K, FFP and rFVIIa. The mean time from ICH onset to treatment with factor VIIa was 6.2 hours (range 1.3–18 hours). Five of the seven patients survived and were discharged from the hospital with severe disability, and two patients died within the first week of hospitalization. The authors concluded that intravenous bolus administration of rFVIIa can rapidly lower the INR and appears to be safe for patients with warfarin-related ICH. In another retrospective study, Brody and team [40] reported 12 patients with OAC-ICH treated with FVIIa in combination with FFP. The authors concluded that FVIIa may be an effective adjunct to FFP in warfarin-related ICH, facilitating faster correction of INR and decreasing FFP requirements.

Table 1. Data from the literature

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>Age (yrs)</th>
<th>Gender</th>
<th>Type</th>
<th>Dose of rFVIIa (μg/kg)/(mg)</th>
<th>INR pre-f</th>
<th>INR post-f</th>
<th>Surgery</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorensen et al.</td>
<td>6</td>
<td>66</td>
<td>4M, 2F</td>
<td>SDH</td>
<td>10–40 µg/kg</td>
<td>1.7–6.6</td>
<td>≤ 1.5</td>
<td>Yes (6)</td>
<td>Alive</td>
</tr>
<tr>
<td>Yeshchev et al.</td>
<td>1</td>
<td>52</td>
<td>M</td>
<td>SDH</td>
<td>120 µg/kg</td>
<td>6.39</td>
<td>1.25</td>
<td>Yes</td>
<td>Died</td>
</tr>
<tr>
<td>Brody et al.</td>
<td>12</td>
<td>71</td>
<td>6M, 6F</td>
<td>ICH</td>
<td>4.8 ± 2.1 mg</td>
<td>3.7</td>
<td>0.9</td>
<td>Yes</td>
<td>5 died</td>
</tr>
<tr>
<td>Lin et al.</td>
<td>2</td>
<td>66, 53</td>
<td>M, M</td>
<td>SDH</td>
<td>1200 µg (total dose)</td>
<td>1.9–5.6</td>
<td>0.8–1</td>
<td>Yes (2)</td>
<td>Uneventful recovery</td>
</tr>
<tr>
<td>Freeman et al.</td>
<td>7</td>
<td>83, 5</td>
<td>2M, 5F</td>
<td>ICH</td>
<td>62.1 µg/kg</td>
<td>2.7</td>
<td>1.08</td>
<td>Yes</td>
<td>2 died (1st wk)</td>
</tr>
</tbody>
</table>

ICH = intracerebral hemorrhage, SDH = subdural hematoma, IVH = intraventricular hemorrhage, SAH = subarachnoid hemorrhage, PF = posterior fossa

PCC = prothrombin complex concentrates
rFVIIa = recombinant factor VIIa

PCC is prothrombin complex concentrates
rFVIIa = recombinant factor VIIa
The Israeli experience

We reviewed the clinical and laboratory features of a consecutive series of seven patients who had acute antithrombotic related intracranial hemorrhage treated with rFVIIa at several hospitals in Israel [Table 2]. The mean age was 67 (range 52–80 years) and six of the patients were men. One patient had intraparenchymal hemorrhage with intraventricular hemorrhage, two patients had intraparenchymal hemorrhage without intraventricular hemorrhage, one had subdural hematoma, two had SDH with ICH, and one had subarachnoid hemorrhage with SDH.

The Glasgow Coma Scale ranges from 3 to 14 points (mean 8.5). Six patients were treated by warfarin alone, two were on warfarin, enoxaparin and aspirin, and one patient was taking enoxaparin and aspirin. Three patients had a history of hypertension, of whom one had a history of ischemic stroke. The mean INR before administration of rFVIIa was 3.7 (range 1.1–6.39) and decreased to 0.87 after administration of rFVIIa. In six patients, the time from presentation to an INR of less than 1.3 ranged from 1 to 12 hours. The mean total dose of rFVIIa was 6 mg (range 1.2–12 mg), and all the patients but one received FFP with or without vitamin K and platelets.

All the patients underwent neurosurgical intervention, and in only one patient did CT reveal hematoma expansion. One patient developed symptomatic pulmonary emboli; no other thromboembolic events were noted in the other patients. Four patients survived, three were discharged from the hospital, and three patients died in hospital within the first week. Of the three patients who survived to discharge, one patient had severe impairment and another had an uneventful recovery.

Discussion

Based on these findings together with the data from the literature, our impression is that intravenous bolus administration of rFVIIa can rapidly lower the INR and appears to be as safe as adjunctive therapy in patients with OAC-related intracranial hemorrhage, without risk of hypervolemia or anaphylaxis.

Although rFVIIa can rapidly improve both the prothrombin time and the INR in patients on warfarin who experience bleeding complications, INR reduction should not be assumed to be an adequate means of monitoring all the effects of rFVIIa when the agent is given at pharmacological doses. High dose rFVIIa acts independently of tissue factor to enhance the generation of platelet-surface thrombin. However, it should be stressed that corrected INR under rFVIIa therapy is not an indication of a full reversal of OAC effect. While the INR is already normal due to the super-normal circulating FVIIa levels, coagulopathy may still persist due to the uncorrected deficiency of other vitamin K-dependent factors (FII, FIX, FX). Thus, a combination of PCC and rFVIIa might be the best therapeutic approach in OAC-ICH. Nonetheless, prospective controlled studies are required to confirm these preliminary findings and to determine whether rFVIIa can prevent hematoma expansion and improve neurologic outcome in patients with antithrombotic-related ICH.

Table 2. Israeli patients (demographic and clinical data)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Gender</th>
<th>Admission CT diagnosis</th>
<th>Anticoagulation + ASA</th>
<th>Glasgow Coma Score</th>
<th>History of hypertensive/ ischemic stroke</th>
<th>INR pre/post rFVIIa</th>
<th>PLT (before/after rFVIIa)</th>
<th>rFVIIa dose</th>
<th>Anti-Xa</th>
<th>Vitamin K/FFP/PLT</th>
<th>Surgery</th>
<th>Follow-up CT post-rFVIIa</th>
<th>Thromboembolic events</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>77/M</td>
<td>Rt temperoparietal, midline shift</td>
<td>Coumadin + enoxaparin, ASA</td>
<td>14</td>
<td>Hypeertension</td>
<td>1.78/0.7 (8 hr)</td>
<td>156</td>
<td>6 mg</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Partial resolution</td>
<td>–</td>
<td>Discharged</td>
</tr>
<tr>
<td>2</td>
<td>76/M</td>
<td>Rt massive temperoparietal, jvea midline shift</td>
<td>Enoxaparin &amp; coumadin</td>
<td>5</td>
<td>Hypertension</td>
<td>1.77/0.5 (3 hr)</td>
<td>235</td>
<td>7.2 mg</td>
<td>1.04, 0.91, 0.82, 0.29</td>
<td>Yes</td>
<td>Yes</td>
<td>–</td>
<td>Still in hospital</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>80/M</td>
<td>SDH + SA Rt frontal</td>
<td>Warfarin</td>
<td>14</td>
<td>Hypertension</td>
<td>4/6/1.02 (12 hr)</td>
<td>215</td>
<td>2.4 mg</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Partial resolution</td>
<td>–</td>
<td>Died in hospital</td>
</tr>
<tr>
<td>4</td>
<td>54/F</td>
<td>SDH + SA rt occipital</td>
<td>Warfarin</td>
<td>12</td>
<td>None</td>
<td>4.3/0.86 (12 hr)</td>
<td>150</td>
<td>1.2 mg</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
<td>Resolution</td>
<td>–</td>
<td>Discharged</td>
</tr>
<tr>
<td>5</td>
<td>54/M</td>
<td>SDH + temporal</td>
<td>Warfarin</td>
<td>4</td>
<td>None</td>
<td>6.2/1 (10 hr)</td>
<td>–</td>
<td>4.8 mg</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
<td>No change</td>
<td>–</td>
<td>Died after 5 days</td>
</tr>
<tr>
<td>6</td>
<td>52/M</td>
<td>SDH</td>
<td>Warfarin</td>
<td>3</td>
<td>None</td>
<td>6.39/1 (2 hr)</td>
<td>–</td>
<td>120 µg/kg</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
<td>Yes</td>
<td>–</td>
<td>Died after 4 days</td>
</tr>
<tr>
<td>7</td>
<td>78/M</td>
<td>Massive tempero-occipital</td>
<td>Enoxaparin &amp; ASA</td>
<td>7/8</td>
<td>None</td>
<td>1.11/0.78 (1 hr)</td>
<td>–</td>
<td>12 mg</td>
<td>1.18</td>
<td>–</td>
<td>Yes</td>
<td>–</td>
<td>Yes</td>
<td>Coma</td>
</tr>
</tbody>
</table>

SDH = subdural hematoma
References


