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Received, February 10, 2006.
Accepted, June 7, 2006.

DYNAMICS OF INTRAVENTRICULAR HEMORRHAGE IN PATIENTS WITH SPONTANEOUS INTRACEREBRAL HEMORRHAGE: RISK FACTORS, CLINICAL IMPACT, AND EFFECT OF HEMOSTATIC THERAPY WITH RECOMBINANT ACTIVATED FACTOR VII

OBJECTIVE: To evaluate predictors of intraventricular hemorrhage (IVH) and IVH growth, impact of IVH growth on outcome, and impact of recombinant activated factor VII (rFVIIa) in patients with intracerebral hemorrhage (ICH).

METHODS: We analyzed 374 patients out of 399 who were randomized to rFVIIa (40, 80, or 160 μg/kg) or placebo for ICH (diagnosed within 3 h of symptoms). Risk factors for IVH growth (>2 ml increase in IVH volume at 24 h), and death or severe disability (modified Rankin scale score 4–6) at 3 months were identified (logistic regression).

RESULTS: IVH was present in 38% (n = 141) of patients at baseline and 45% (n = 169) by 24 hours. IVH growth, by 24 hours, occurred in 17 and 10% of placebo- and rFVIIa-treated patients, respectively ($P = 0.037$). Risk factors for IVH growth included baseline mean arterial pressure greater than 120 mmHg, larger baseline ICH volume, IVH present at baseline, shorter time from symptom onset to baseline computed tomographic scan, and treatment (rFVIIa versus placebo) (all, $P \leq 0.037$). Predictors of death or severe disability included older age, lower baseline Glasgow Coma Score, larger baseline ICH volume, IVH growth greater than 2 ml, IVH present at baseline or 24 hours, and treatment (rFVIIa versus placebo) (all, $P \leq 0.0405$).

CONCLUSION: Presence of IVH at any time and early IVH growth worsen clinical outcome and increase mortality. Elevated mean arterial pressure at baseline may be a modifiable risk factor for IVH growth. Beneficial effects of rFVIIa on ICH outcome may be mediated, at least in part, by reducing IVH growth.

KEY WORDS: Hemorrhage growth, Hemostatic treatment, Intracerebral hemorrhage, Intraventricular hemorrhage, Recombinant activated factor VII

Neurosurgery 59:767-774, 2006 DOI: 10.1227/01.NEU.0000232837.34992.32 www.neurosurgery-online.com

Intracerebral hemorrhage (ICH) is the deadliest form of stroke; more than one-third of patients experiencing ICH die within 1 month after symptom onset, and only 20% of patients regain functional independence. The outlook is particularly poor for patients who, in addition, have intraventricular hemorrhage (IVH). Studies have reported that 30 to 50% of patients with spontaneous ICH experience additional IVH (12, 25, 26), and Tuhrim et al. (26) reported that the 30-day mortality rate for patients with IVH was nearly five times higher than those with ICH alone. Intraventricular blood volume was significantly associated with higher mortality at Day 30. Location of parenchymal origin of ICH, distribution of ventricular blood, and IVH volumes have been reported to be predictors of outcome in patients with spontaneous ICH and intraventricular extension (5, 10, 27). IVH is an important predictor of 30-day mortality (9). The development of IVH, therefore, seems to be an important factor in the clinical outcome of ICH patients.

Intuitively, it makes sense that IVH impacts on clinical outcome based on several possible mechanisms. The ventricular system can provide an outlet for ICH expansion with perhaps

less resistance than brain parenchyma, and IVH volume can independently exert mass effect on the surrounding brain tissue (3). In addition, obstruction of the cerebrospinal fluid (CSF) can result in obstructive hydrocephalus, which can raise intracranial pressure and result in global impairment. Last, the presence of blood in the CSF may represent a global injury to the brain, whereas the original ICH may only result in a focal deficit.

Most studies that have investigated the influence of IVH on clinical outcome and mortality have focused on the effect of IVH at one particular time point (26). However, ICH and IVH are not static events, but rather part of a dynamic process. Brott et al. (3) demonstrated that nearly 40% of patients with an ICH develop an increase in hematoma size within 24 hours, which has been validated in three Japanese studies (7, 8, 11). These results have been further elaborated by Davis et al. (4), who, in a quantitative assessment of ICH, showed that 72.9% of patients demonstrate increased hematoma after the baseline computed tomographic (CT) scan. Tuhrim et al. have also found the total volume of ICH on admission to be correlated with the size of IVH.

Surgical approaches have targeted a reduction of blood volume at early and very early time points (16–18), but could not demonstrate an effect on mortality or outcome. Hemostatic agents have been studied to attempt to reduce parenchymal hematoma growth (13, 22). We recently demonstrated that recombinant activated factor VII (rFVIIa) reduces hematoma growth, decreases mortality, and improves clinical outcome when administered within 4 hours of symptom onset of ICH. Treatment with rFVIIa not only reduced parenchymal hemorrhage size, but also total volume increase, which included the parenchymal and intraventricular blood as well as edema volume (13).

Although it is well established that parenchymal ICH can acutely increase in size, to our knowledge, no studies have focused specifically on the dynamics and clinical impact of early IVH growth in isolation. In this report we aimed to 1) identify factors that influence the dynamics of IVH growth during the acute stage of hemorrhage; 2) analyze the isolated effect of IVH growth on overall mortality and morbidity; and 3) determine the impact of rFVIIa treatment on early IVH growth.

METHODS

This study represents a planned secondary analysis of data from a multicenter, randomized, placebo-controlled trial on the effectiveness of rFVIIa in spontaneous ICH (13). Patients were included with spontaneous ICH documented by CT scan within 3 hours of onset of symptoms, with exclusion of patients with a Glasgow Coma Score (GCS) of 5 or less; planned surgical hematoma evacuation; secondary ICH related to aneurysm, arteriovenous malformation, trauma, or other causes; known use of oral anticoagulant; known thrombocytopenia; history of coagulopathy, acute sepsis, crush injury, or disseminated intravascular coagulation; pregnancy; preexisting disability modified Rankin scale (mRS) score greater than 2; and symptomatic thrombotic or vaso-occlusive disease (i.e., angina, claudication, deep vein thrombosis, or cerebral or myocardial infarction) within 30 days before the onset ICH. The trial was approved by local institutional review boards and by local and national ethics boards as applicable (13). In this trial, 399 patients were randomized to receive rFVIIa (40, 80, or 160 μg/kg) or placebo administered within 4 hours of ICH symptom onset. CT scans were performed at baseline (admission) and at 24 and 72 hours after treatment. ICH and IVH volumes were calculated using standard planimetric techniques and analyzed by two independent neuroradiologists. These changes in hemorrhage were carefully assessed using planimetric methods in which the inter-reader correlation coefficient for the determination of ICH volume was 0.9596, and the determination of IVH was 0.9468, with an average difference of 0.3 ml between readers, and have been recently published (28).

Clinical assessments in this analysis were performed at baseline, 24 hours, and 90 days. Neurological deficit was assessed using the National Institute of Health Stroke Scale and level of consciousness using the GCS, whereas functional status was assessed using the mRS, GCS, and the Barthel Index. Clinical outcome at Day 90 was defined with mRS dichotomized into favorable (mRS, 0–3) and poor (mRS, 4–6).

The analyses were restricted to the baseline and 24-hour CT scan because a treatment effect is only expected within that time window because of the 2.6-hour half-life of rFVIIa. The three rFVIIa dose groups with and without initial presence of IVH were not appreciably different in sex, age, or baseline ICH volumes, and the frequency of IVH was low. Therefore, for purposes of this IVH analysis, we pooled patients from all three rFVIIa dose groups and compared them with the placebo group. We defined presence of IVH as any blood in any part of the ventricular system. The definition of IVH growth was an increase in IVH volume of 2 ml or greater between the baseline and 24-hour CT scans, which represents six times the inter-reader variability. Multivariate analyses were performed including and excluding patients with external ventricular drainage (EVD), whether placed simply for intracranial pressure monitoring or for treatment of obstructive hydrocephalus, to assess the impact of EVD on outcomes.

Statistical Analyses

Analyses were performed to identify factors predictive of presence of IVH; increase in IVH in the first 24 hours of the study; poor clinical outcome (mRS, 4–6); and mortality. In each case, a logistic regression model was applied. Covariates were analyzed individually (univariate analysis) to find possible significant predictors for the outcome under evaluation. The covariates found to be significant at P values less than 0.25 in these univariate analyses were then included in a multivariate model. This multivariate model was reduced by successively removing the least significant covariate from the model.

All covariates with *P* values less than 0.10 were kept in the final model.

The covariates examined were time from symptom onset to baseline CT, time from symptom onset to dosing, time from baseline CT to dosing, ICH volume at baseline, GCS score at baseline, age, body temperature, systolic blood pressure, diastolic blood pressure, mean arterial pressure (MAP), presence of IVH increase, size of IVH increase, IVH present at baseline, IVH present at any time point, IVH volume at baseline, body mass index (>25 versus ≤25), history of diabetes or hypertension, Asian versus non-Asian, fibrinogen level, platelet count, sex, location of hemorrhage (basal ganglia, thalamic, other), and treatment (any dose rFVIIa versus placebo). Missing CT scan values were replaced by the closest available CT scan, not including the baseline, where possible.

RESULTS

Three hundred seventy-four patients out of the 399 in the original study were included in this analysis. Twenty-five patients were excluded because of missing values because of death (n = 7), incomplete CT images (n = 4), hematoma evacuation before the 24-hour scan (n = 9), or because of logistical reasons (n = 5). For the remaining 374 patients included in this study, 41 (11%) had 24-hour CT scans performed outside the protocol time window (± 3 hr) and had a nonbaseline CT scan used in the current analyses. An EVD was placed within 24 hours in 7.6% (13 out of 170) of the IVH patients.

IVH Presence

Of the 374 patients, 170 (45%) had IVH at baseline or at 24 hours (*Table 1*). The proportion of patients with IVH present at baseline or 24-hours was 50% in placebo and 44% in the rFVIIa treated patients. An increase in IVH of more than 2 ml comparing baseline and 24-hour volume was seen in 17% of placebo patients and 10% of rFVIIa patients ($P = 0.037$, in multivariate analysis reported later).

Table 2 summarizes baseline characteristics of patients according to whether they presented with or developed IVH within 24 hours. Risk factors for the presence of IVH identified by logistic regression were an increase of age, baseline ICH volume, MAP values greater than 120 mmHg, and thalamic location of parenchymal blood (*Table 3*).

TABLE 2. Baseline characteristics of patients with presence (at baseline or 24 hr) or absence of intraventricular hemorrhage[a]

	IVH (n = 170)	No IVH (n = 204)
Age, yr (SD)	68.8 (11)	63.7 (13)
Race, no. (%)		
Non-Asian	146 (86)	170 (83)
Asian	24 (14)	34 (17)
Sex, no. (%)		
Male	100 (59)	129 (63)
Female	70 (41)	75 (37)
Baseline GCS	14	15
BMI, no. (%)		
>25	76 (48)	69 (37)
≤25	83 (52)	119 (63)
Body temperature, °C (SD)	36.4 (0.6)	36.4 (0.56)
Risk factors, n (%)		
Diabetes	29 (17)	27 (13)
Hypertension	139 (82)	155 (76)
MAP ≤ 120 mmHg (SD)	78 (46)	106 (53)
MAP > 120 mmHg (SD)	91 (54)	94 (47)
SBP ≤ 170 mmHg (SD)	71 (42)	101 (50)
SBP > 170 mmHg (SD)	98 (58)	102 (50)

[a] IVH, intraventricular hemorrhage; SD, standard deviation; GCS, Glasgow Coma Score; BMI, body mass index; MAP, mean arterial pressure; SBP, systolic blood pressure.

IVH Dynamics

In 12% (44 out of 374) of patients, there was an increase of more than 2 ml in volume between baseline and 24 hours (*Table 1*). Multivariate analyses revealed the following independent predictors for IVH growth: MAP higher than 120 mmHg ($P = 0.0078$), ICH volume at baseline ($P < 0.0001$), IVH

TABLE 1. Summary of intraventricular hemorrhage by visit and treatment, intention-to-treat population[a]

	Placebo	rFVIIa (μg/kg)				Total
		40	80	160	Combined	
No. of patients	92	99	87	96	282	374
Readers averaged						
IVH present at baseline, no. (%)	40 (43)	31 (31)	32 (37)	38 (40)	101 (36)	141 (38)
IVH present at 24 hr, no. (%)	45 (49)	38 (38)	39 (45)	47 (49)	124 (44)	169 (45)
IVH present at baseline or 24 hr, no. (%)	46 (50)	38 (38)	39 (45)	47 (49)	124 (44)	170 (45)
Increase between baseline and 24 hr > 2 ml, no. (%)	16 (17)	9 (9)	10 (11)	9 (9)	28 (10)	44 (12)

[a] rFVIIa, recombinant activated factor VII; IVH, intraventricular hemorrhage.

TABLE 3. Analysis of predictors of presence of intraventricular hemorrhage (at baseline or 24 hr)[a]

	OR	95% CI	*P* value
Age[b]	1.19	1.06; 1.34	0.0043
ICH volume at baseline[c]	1.04	1.03; 1.06	<0.0001
MAP > 120 mmHg	2.11	1.21; 3.66	0.0080
Location			
Basal ganglia	1[d]		
Thalamic	2.64	1.39; 5.03	0.0031
Other	1.02	0.49; 2.10	0.9578

[a] OR, odds ratio; CI, confidence interval; ICH, intracerebral hemorrhage; MAP, mean arterial pressure.
[b] Per 5 year.
[c] Per 1 ml.
[d] Reference point for other OR calculations.

present at baseline ($P = 0.0002$), and time from symptom onset to baseline CT scan ($P = 0.0045$). The time interval from symptom onset to baseline CT scan was similar (114.5 min [standard deviation, 37.8]; placebo 111.4 min [standard deviation, 32.6]). In addition, a significant treatment effect was demonstrated ($P = 0.0370$) (*Table 4*). A comparison of analyses including and excluding those patients with an EVD revealed similar results.

Figure 1 displays the relationship between increase of parenchymal blood and change of intraventricular blood volume for those patients who had IVH growth. The graph reflects that, for each additional 10 ml of intraparenchymal blood, there is an increase of IVH volume of approximately 2.3 ml ($P = 0.02$).

Impact of IVH Growth on Outcome

To analyze the impact of IVH growth on outcome, we compared patients who had no IVH or no IVH growth (n = 330) with patients who had IVH growth (n = 44). Poor clinical outcome (mRS, 4–6) was significantly different at Day 90, occurring in 93% of patients with IVH growth and 50% of patients without IVH growth ($P = 0.04$) (*Fig. 2*). Mortality was also significantly different between these two groups: 59 and 14% ($P < 0.0001$). These analyses were adjusted for other significant predictors found in the logistic regression analyses. For poor outcome, we found the following covariates significant: age ($P < 0.0001$), baseline GCS ($P < 0.0001$), ICH volume at baseline ($P = 0.0007$), IVH increase greater than 2 ml ($P = 0.0405$), IVH present at baseline or 24 hours ($P = 0.0014$), and treatment with placebo ($P = 0.0327$) (*Table 5*). Predictors of mortality were age ($P = 0.0194$), baseline GCS ($P < 0.0001$), history of hypertension ($P = 0.0004$), baseline ICH volume ($P = 0.0003$), and IVH increase greater than 2 ml ($P < 0.0001$) (*Table 6*).

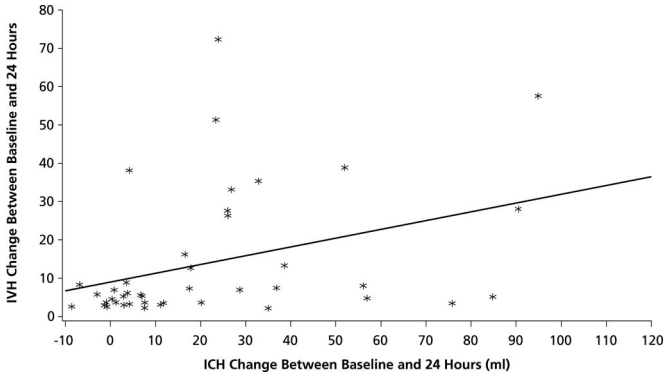

FIGURE 1. *Graph showing the dynamics of intraventricular and parenchymal hemorrhage, as well as the best linear fit of IVH change to ICH change (baseline to 24-hr CT scan).*

DISCUSSION

The results of the analysis reported here confirm the previous observations that as many as half of the patients with spontaneous ICH develop IVH within 24 hours of symptom onset, a finding associated with increased morbidity and worse clinical outcomes (*Fig. 2*) (3, 15, 25–27). In the current analyses, increase of age, additional milliliters of ICH volume, and baseline MAP greater than 120 mmHg increased the likelihood of IVH being present on the baseline or 24-hour CT scan study. This confirms previous data demonstrating that ICH volume predicts IVH occurrence (2, 10, 24, 26). To our knowledge, this is the first study that prospectively demonstrated the predictive value of elevated blood pressure at baseline on an increased probability of growth of intraventricular blood associated with poor outcome. Leira et al. (12) found early neurological deterioration to be associated with IVH and highest systolic blood pressure at

TABLE 4. Predictors of intraventricular hemorrhage growth[a]

	OR	95% CI	*P* value
MAP > 120 mmHg	3.09	1.35; 7.09	0.0078
ICH volume at baseline[b]	1.04	1.03; 1.06	<0.0001
IVH present at baseline	4.32	1.99; 9.38	0.0002
Time from symptom onset to baseline CT[c]	0.84	0.75; 0.95	0.0045
Treatment[d]	2.28	1.05; 4.96	0.0370

[a] OR, odds ratio; CI, confidence interval; MAP, mean arterial pressure; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; CT, computed tomography.
[b] Per 1 ml.
[c] Per 30 minutes.
[d] Placebo versus recombinant activated factor VII.

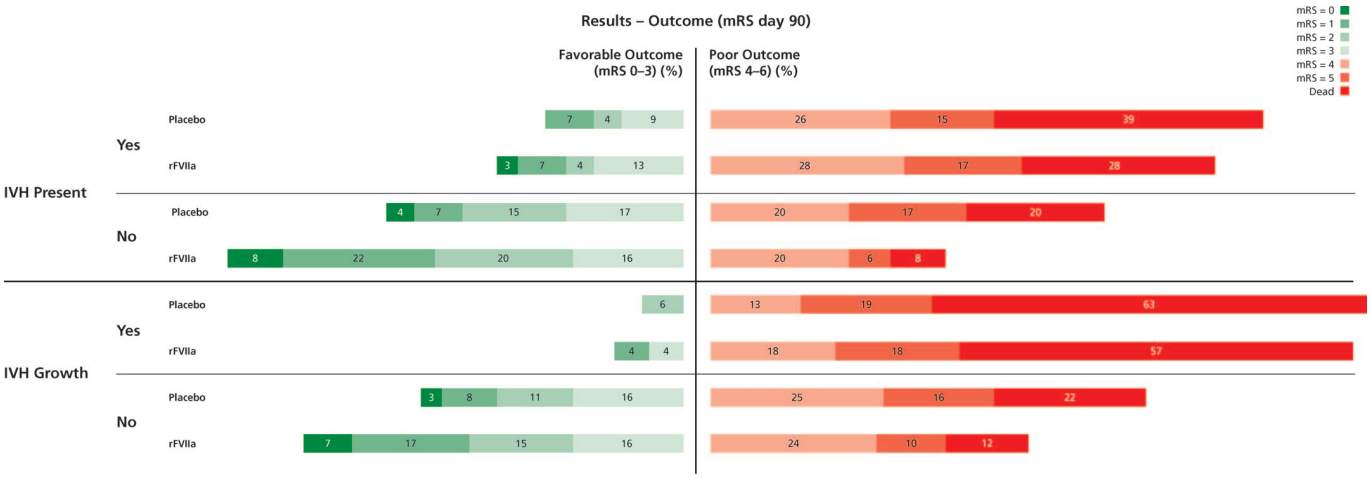

FIGURE 2. *Graph showing each subgroup, IVH presence and IVH growth, by treatment group presented as a distribution of the percentage of their mRS.* mRS, *modified Rankin scores;* IVH, *intraventricular hemorrhage;* rFVIIa, *recombinant activated factor VII;* IVH present yes, *IVH present at baseline or at 24 hours;* IVH present no, *no IVH at any time point;* IVH growth yes, *volume increase of more than 2 ml between baseline and 24 hours;* IVH growth no, *all patients with no increase.*

TABLE 5. Predictors of poor outcome[a]

	OR	95% CI	*P* value
Age[b]	1.59	1.39; 1.81	<0.0001
Baseline GCS	0.71	0.60; 0.83	<0.0001
ICH volume at baseline[c]	1.03	1.01; 1.05	0.0007
IVH increase > 2 ml	4.21	1.06; 16.63	0.0405
IVH present at baseline or 24 hr	2.53	1.43; 4.47	0.0014
Treatment[d]	2.02	1.06; 3.86	0.0327

[a] OR, odds ratio; CI, confidence interval; GCS, Glasgow Coma Score; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage.
[b] Per 5 year.
[c] Per 1 ml.
[d] Placebo versus recombinant activated factor VII.

TABLE 6. Predictors of mortality[a]

	OR	95% CI	*P* value
Age[b]	1.18	1.03; 1.37	0.0194
Baseline GCS	0.71	0.62; 0.82	<0.0001
History of hypertension	3.61	1.77; 7.35	0.0004
ICH volume at baseline[c]	1.02	1.01; 1.04	0.0003
IVH increase > 2 ml	6.09	2.68; 13.86	<0.0001

[a] OR, odds ratio; CI, confidence interval; GCS, Glasgow Coma Score; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage.
[b] Per 5 year.
[c] Per 1 ml.

48 hours. In particular, the influence of elevated MAP at baseline has an important impact on current treatment strategies because it is a modifiable risk factor. The American Heart Association guidelines recommend treatment of elevated MAP if greater than 130 mmHg (1). Qureshi et al. (23) found growth of ICH to be only 9% when they maintained blood pressure even lower (systolic blood pressure below 160 mmHg and diastolic blood pressure below 90 mmHg). These results support the need for further studies on blood pressure treatment in ICH.

In addition, ICH location was a significant predictor of IVH risk; we found that thalamic ICH location nearly tripled the risk of IVH (*Table 3*). These findings support current hypotheses on the mechanism of secondary IVH in patients with spontaneous ICH and its impact on outcomes. Brott et al. (3) speculated that hemorrhages originating in the periventricular regions are more likely to expand toward the nearby ventricle because the fluid spaces are more compressible than the surrounding brain parenchyma as CSF redistributes extracranially. This is supported by the results from Young et al. (27), who found that thalamic hemorrhages, with their proximity to the ventricles, were associated with larger IVH volume and worse outcomes; and Tuhrim et al. (26) who showed a close correlation between volume of baseline parenchymal and intraventricular blood and outcome. Similarly, Diringer et al. (5) found that deep hemorrhages were associated with increased incidence of obstructive hydrocephalus, which results in raised intracranial pressure above the direct effects attributed to the hemorrhage volume.

IVH growth was significantly associated with increased mortality and poorer clinical outcome. Furthermore, outcome was not only worse in those patients who developed an IVH (compared with those who did not have IVH at any time point), but it was significantly worse when patients with IVH had intraventricular blood volume growth.

The correlation between IVH and increased morbidity is not clearly understood. Certainly, blockage of CSF outflow with obstructive hydrocephalus and the subsequent increase of intracranial pressure (and, therefore, reduction in cerebral

perfusion pressure) plays an important prognostic role. Hydrocephalus was shown to be an independent predictor of outcome in spontaneous ICH (5). The concept is further supported by the observation that IVH volume may be associated with a commensurate decrease in global cerebral blood flow (14). Interestingly, in other studies, outcome did not differ in those patients treated with a ventriculostomy or EVD (5, 27). This may support the hypothesis that the enhanced morbidity associated with IVH is attributable, at least in part, to the pressure exerted by the clot on periventricular structures (26). This emphasizes the possible impact of a treatment that prevents IVH or limits further IVH expansion.

To our knowledge, this is the first evaluation on the dynamics of IVH in a large prospective trial. Our data suggest that 12% of patients who develop an IVH will show a further increase of intraventricular blood. In fact, our analyses may underestimate the extent of IVH expansion because we chose a conservative threshold of 2 ml increase. The risk of IVH growth was tripled by a MAP above 120 mmHg, quadrupled by the presence of IVH at baseline (*Table 4*), and increased with every ml of ICH volume at baseline.

Even more important, the risk of further increases in IVH volume was reduced when patients received rFVIIa. A greater percentage of rFVIIa-treated patients had a favorable functional outcome (mRS, 0–3) across all groups (*Fig. 2*), although these results did not reach statistical significance. This is in agreement with the results of the primary analysis of this study, which found that rFVIIa treatment significantly reduced 90-day mortality and reduced the percentage of patients with a poor clinical outcome (13). These results, therefore, suggest that the clinical effect of rFVIIa on functional outcome in patients with ICH may be, at least in part, caused by its effects on both ICH and IVH expansion.

Previous studies tried to accelerate intraventricular clot resolution (either by EVD to treat obstructive hydrocephalus or in combination with intraventricular thrombolysis). We did not prospectively obtain information on the distribution of intraventricular blood or the occurrence of obstructive hydrocephalus. Thirteen out of 170 patients with IVH were treated with an EVD. Comparison of the different analyses with and without patients who had received an EVD revealed that this did not influence the overall results on treatment effect, mortality, or outcome. However, this comparison was limited by the numbers of patients in the EVD group. These observations are consistent with other studies that did not observe a beneficial effect of ventricular drainage in patients with spontaneous ICH (5, 27). Principally, the results of this current analysis represent a potential new therapeutic approach to the treatment of ICH.

Intraventricular thrombolysis in primary IVH unrelated to ICH does lead to an improvement of 30-day survival (19). Intraventricular thrombolysis has been shown to speed up clot resolution in patients with secondary IVH after subarachnoid hemorrhage and after spontaneous ICH (6, 21). However, intraventricular thrombolysis may be associated with an increased risk of symptomatic bleeding (20). In contrast, the current study used a hemostatic agent in essence as "prophylaxis" for intraparenchymal expansion and intraventricular extension of parenchymal blood.

The results of this study should be considered in the light of a number of limitations. First, this planned secondary analysis was not powered to detect effects of rFVIIa treatment on IVH volume changes and outcome. However, the trend of a lower mortality and better outcome was consistently observed in the active treatment groups whether IVH was present at baseline or not (*Fig. 2*). Second, CT scan data were missing for 25 (6.3%) patients. However, because the missing data were approximately evenly distributed between the four treatment groups, it is unlikely that these omissions would have significantly impacted the results of the analyses.

CONCLUSIONS

The results of these analyses provide further confirmation that the presence of IVH within the first few days after ICH is associated with increased mortality and an overall worse clinical outcome. In addition, an increase in IVH over the first 24 hours after the symptom onset of ICH seems to be associated with a particularly poor prognosis. The risk of IVH is particularly high in patients with thalamic hemorrhages, in which the ICH is in close proximity to the ventricular system. Similarly, the risk of IVH increase is particularly high in patients who present with IVH on the initial CT scan. Treatment with rFVIIa reduced the risk of increase in IVH (above a 2 ml threshold) compared with placebo and appeared to reduce the risk of poor clinical outcome and death. These data suggest that rFVIIa therapy may reduce morbidity and mortality associated with ICH, at least in part through its impact on limiting IVH growth in the early period after ICH. Further studies involving expanded sample sizes are warranted to confirm the impact of rFVIIa on IVH secondary to ICH and to further explore IVH dynamics and the effects of obstructive hydrocephalus and EVD treatment on outcomes.

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Acknowledgments

We thank Nikolai Brun, M.D., Ph.D. (Novo Nordisk A/S), for his valuable advice and guidance.

COMMENTS

This excellent multicenter investigation demonstrated that intracerebral hemorrhage (ICH) and intraventricular hemorrhage (IVH) are parts of a dynamic process, with half of patients developing IVH within 24 hours of symptom onset and 12% of these hemorrhages enlarging. Risk factors for IVH growth included hypertension, larger initial ICH volume, IVH at baseline, and shorter time intervals from symptom onset to the time of the computed tomographic scan. IVH was associated with increased morbidity and worse outcomes. In contrast to the unfavorable results reported in the Surgical Trial in Intracerebral Hemorrhage with surgical evacuation and similarly disappointing results with intraventricular thrombolysis for IVH, this study identifies an intervention that might be beneficial. Recombinant factor VIIa (rFVIIa) prevented or limited IVH expansion in this study and improved chances for good outcomes. Furthermore, it may be safer and easier to intervene pharmacologically in these patients than with surgical evacuation or direct intraventricular manipulations. However, some of the favorable results observed with rFVIIa were not statistically significant in this report, and further study is needed.

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This is a well-conducted study and part of a series of ongoing studies funded by the drug company. rFVIIa has certainly generated a fair amount of interest and potential use with ICH. The authors address the issue of hemorrhage location and outcome. However, this may be inextricably linked to the higher mortality seen with IVH/hypertensive hemorrhage patients. Specifically, patients with thalamic hemorrhages are typically in worse clinical condition, and these patients have a higher incidence of IVH. The authors did perform a separate analysis in which location, defined as thalamic, basoganglion, or other, was evaluated as a covariate. The effect of location could not be separated from the effect of presence of IVH, presumably because of the high correlation between thalamic location and the presence of IVH (*Table 3*). The authors attempted a subgroup analysis, but this was not feasible due to the small sample size.

In the patient study, 13 out of 170 (7. 6%) patients received external ventricular drainage in the first 24 hours. The numbers are too small to generate any meaningful statistics regarding whether or not this therapy is beneficial in the management of patients with IVH and parenchymal hemorrhage. This has been a long debated issue and we remain without a clear cut answer. However, the overall findings of

these authors are of great interest in the utilization of rFVIIa. The authors are to be commended for their continued work in this area.

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Administration of a high dose of rFVIIa results in faster and higher thrombin generation when tissue factor is exposed at sites of injury, and binding of rFVIIa to the phospholipid membrane of activated platelets activates FX and FIX, heightening the coagulation response even in the absence of tissue factor. Also, fibrin clots formed in the presence of high rFIIVa and thrombin concentrations are stronger and more resistent to fibrinolytic degration. So, by several mechanisms, rFVIIa can significantly boost coagulation, probably better than any other agent presently available. Only approved, at present, in the United States and Canada for use preventing and treating bleeding episodes in hemophilic patients with inhibitors to coagulation factors VIII or IX, it has been used "off-label" in a wide range of high-risk bleeding crises, such as ICH, severe trauma, and postpartum hemorrhage. Its use after ICH already has important scientific support. In a Phase IIb, international, multicenter, randomized placebo-controlled trial examining 399 patients with primary ICH, rFVIIa administration within 4 hours of spontaneous, primary ICH reduced hematoma growth and improved 90-day clinical outcomes, despite a small increase in the frequency of thromboembolic complications (1). The study reported here, the findings of a planned secondary analysis of patients enrolled in the aforementioned trial, confirms that IVH accompanying ICH is associated with worse outcome, but also indicates that prognosis is especially poor for patients with IVH growth within 24 hours of ictus. IVH growth, by 24 hours, occurred in 17% of patients in the placebo-treated group and 10% of the patients treated with rFVIIa ($P = 0.037$). Although this is important information, we cannot yet conclude that prevention of the IVH growth, as opposed to growth of the underlying ICH growth (or even, more probably, a combination of the two), was primarily responsible for the worse outcome. That seven of the eight authors receive financial compensation from the company that manufactures this hemostatic agent and sponsors this research requires mention, but can't diminish the importance of this work. Neurosurgeons need to know about rFVIIa and, indeed, many of us have already used it during a clinical crisis, despite corroborated proof of efficacy or its extraordinary cost. Fortunately, more evidence is on its way for the use of rFVIIa in the setting of spontaneous ICH.

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Steiner et al. present a planned secondary analysis of a previous randomized trial of patients who were administered rFVIIa after spontaneous ICH. The analysis focuses on the kinetics and contribution of IVH in association with the ICH to ultimate outcome. Of the 399 patients enrolled in the original trial, 374 had adequate imaging and clinical data to satisfy inclusion for the current analysis. One hundred and forty-one patients had IVH at baseline, defined as the presence of blood in any portion of the ventricular system. This number increased to 169 patients within 24 hours of admission. Among these patients, 17% of those who were administered placebo showed IVH volume increase, whereas only 10% of those treated with rFVIIa experienced IVH enlargement. Multivariate analysis yielded several factors associated with IVH growth, including mean arterial blood pressure greater than 120 mmHg, larger baseline ICH volume, and the presence of IVH at admission. Risk factors for death or severe disability included advanced age, poor neurological grade, larger ICH volume upon admission, growth of IVH greater than 2 ml in the first 24 hours, and the presence of IVH at admission.

The authors attempt to separate the effect of the IVH growth on outcome independent of other factors by comparing patients who had either no IVH or no growth of IVH to patients who had IVH growth. They found a statistically significant predominance of poor outcome and death in patients who had IVH growth versus those who did not.

Of note, only a small minority of patients with IVH (7.6%) received an external ventricular drain, which may reflect a selection bias to exclude patients with Glasgow Coma Scale scores less than 5. Furthermore, the original trial was designed to evaluate the effect of rFVIIa at different doses on ICH and was not powered to examine the dose response of IVH. All four dose cohorts were, therefore, pooled to determine the effect of rFVIIa on IVH. Lastly, outcome was assigned to either favorable or unfavorable groups based on modified Rankin score. Because the original trial included Grade 3 (moderate disability) patients in the favorable category, the authors preserved this methodology.

This article reaffirms the intensively morbid nature of ICH and the fact that it is made worse by the presence of IVH. Historically, medical and surgical treatment options have had only a modest impact on the natural history of the disease and long-term outcome. The results of this analysis add to our understanding of the kinetics of IVH in association with ICH. rFVIIa is a potent hemostatic agent that has now demonstrated an ability to stabilize both ICH and IVH growth. Perhaps a combined therapy using rFVIIa with intraventricular administration of tissue plasminogen activator, a potent thrombolytic, may strike the right balance between thrombosis and thrombolysis to minimize tissue damage and secondary injury. These factors are often the difference between a favorable functional outcome and neurological devastation or death.

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