

 Agence française de sécurité sanitaire des produits de santé	DENOMINATION COMMUNE INTERNATIONALE : Facteur VIIa de coagulation recombinant	
	NOM COMMERCIAL : Novoseven®	
 HAUTE AUTORITÉ DE SANTÉ	LABORATOIRE EXPLOITANT OU TITULAIRE DE L'AMM :NOVO NORDISK	
	Version : 1 Date : avril 2008 Date de révision : février 2010 Historique des modifications :	Condition de prescription : prescription médicale restreinte

III. Situations non acceptables

Hémorragie intracrânienne avec engagement du pronostic vital

Les hémorragies intracrâniennes (15 % des accidents vasculaires cérébraux, dont la prévalence est de 4 à 6/1000 habitants) peuvent être d'origine traumatique ou apparemment spontanée. Ces dernières sont dues soit à l'artériolosclérose (souvent d'origine hypertensive), soit à l'amylose vasculaire cérébrale. Elles peuvent siéger dans les espaces extra-dural, sous dural, lepto-méningé ou dans le parenchyme cérébral.

Des études randomisées en double-aveugle ne montrent aucune modification significative du taux de mortalité à 90 jours (après ajustement des diverses variables) pour une dose de Novoseven® de 80 µg/kg. Un effet significatif apparaît pour la plus forte dose (160 µg/kg). L'analyse en régression logistique suggère une courbe de risque en forme de U avec un risque thromboembolique plus grand aux doses faibles et fortes.

Une étude internationale de phase III (FAST), multicentrique, en double-aveugle étudiant les doses de 20 et 80 µg/kg versus placebo chez 821 patients a été publiée en 2008. Le critère principal étudié est la mortalité ou l'incapacité sévère à 90 jours.

Les résultats de cette étude montrent une réduction significative des saignements intracrâniens dans le groupe traité par rapport au groupe placebo et une amélioration fonctionnelle et neurologique 15 jours après l'hémorragie mais aucune amélioration n'est observée sur la mortalité et le handicap au terme de l'étude, c'est-à-dire 90 jours après la survenue de l'hémorragie, ce dernier point étant l'objectif principal de l'étude.

Par ailleurs, un risque thrombo-embolique (infarctus du myocarde et infarctus cérébral) a été observé dans le groupe « 80µg/kg » et plus particulièrement chez les personnes âgées.

Cette situation est qualifiée « non acceptable » en raison d'une balance bénéfico-risque défavorable.

Notons que le rapport bénéfico-risque est également défavorable chez les patients recevant des anti-vitamine K et traités par Novoseven® pour accident hémorragique intracrânien. Dans cette situation, l'alternative thérapeutique est le PPSB (concentré de complexes prothrombiniques).

Effet de Novoseven® dans le traitement des hémorragies intracrâniennes

Auteur	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
Mayer (2008)	Etude Fast (phase III) Randomisée, double-aveugle versus placebo N = 841 . n = 268 : placebo . n = 276 : 20 µg/kg rFVIIa . n = 297 : 80 µg/kg rFVIIa	- 20 µg/kg - 80 µg/kg	90 jours	- principal : Mortalité ou incapacité sévère à J90 post-hémorragie intracérébrale selon l'échelle de RANKIN (handicap ou mortalité)	<u>24 h post-hémorragie intracérébrale:</u> ↑ volume de l'hématome intracérébral : . placebo : + 26% . 20 µg/kg : + 18 % NS (p = 0.09) . 80 µg/kg : + 11% S (p < 0.001) ↓ volume de l'hématome : . 20 µg/kg : 2.6 ml NS (p = 0.08) . 80 µg/kg : 3.8 ml S (p = 0.009) <u>A 90 j :</u> Critère principal : NS Effets indésirables : similaires dans les 3 groupes Evénements thromboemboliques artériels: S (p = 0.04) - gpe 80 µg/kg : 9% - placebo : 4%
Mayer (2006)	Randomisée, double - aveugle contre placebo, étude de dose phase II N = 40 patients (>18 ans) ayant une hémorragie intracérébrale	FVIIa : - 5 µg/kg (n = 8) - 20 µg/kg (n = 8) - 40 µg/kg (n = 8) - 80 µg/kg (n = 8) - placebo (n = 8)	90 jours	- % des effets indésirables - volume moyen de l'œdème cérébral 24 et 72 h post-administration	- % d'évènements indésirables : NS .20 µg/kg : 1 cas de thrombose veineuse profonde dans les 72h post -administration et 1 cas d'embolie pulmonaire .40 µg /kg : 1 cas d'embolie pulmonaire - mortalité moyenne : 20 % (13 % placebo et 22 % groupes traités) - volume moyen de l'œdème cérébral : NS
Mayer (2005)	Randomisée, double-aveugle, contre placebo, groupes parallèles phase IIb N = 399 patients (> 18 ans) ayant une hémorragie cérébrale	FVIIa : - 40 µg/kg (n = 108) - 80 µg/kg (n = 92) - 160 µg/kg (n = 103) - placebo (n = 96)	90 jours	- taille de l'hématome 24 h et 72 h après traitement - tolérance	- croissance moyenne de l'hématome 24 h post-administration : . placebo : 29 % . 40 µg/kg : 16 % . 80 µg/ kg : 14 % . 160 µg/kg : 11 % - groupes traités par rapport au placebo : p = 0.01 - 72 h après traitement : p = 0.003 . Les différences sont plus marquées lorsque les doses augmentent. - mortalité à 90 jours : . 29 % placebo . 18 % pour les 3 groupes traités p = 0.02 : S - % d'évènements thromboemboliques NS 7 % groupes traités et 2 % groupe placebo
Mayer (2005)	Randomisée, double-aveugle, contre placebo, étude de dose phase II N = 48 patients (> 18 ans) ayant une hémorragie intracérébrale	FVIIa : - 10 µg/kg (n = 6) - 20 µg/kg (n = 6) - 40 µg/kg (n = 6) - 80 µg/kg (n = 6) - 120 µg/kg (n = 6) - 160 µg/kg (n = 6) - placebo (n = 12)	90 jours	- % des effets indésirables - évaluation de la taille de l'hématome à 24 et 72 h post-administration	- % d'évènements indésirables : NS . 1 cas d'évènement thromboembolique dans le groupe 20 µg/kg et . 1 cas dans le groupe placebo - 72 h post -administration : croissance moyenne de l'hématome : NS mais à l'inclusion différences importantes entre les groupes et nombre de patients insuffisant dans chaque groupe.

Bibliographie

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- 2- Mayer SA, Brun NC, Broderick J, Davis SM, Diringer MN, Skolnick BE, Steiner T; United States NovoSeven ICH Trial Investigators. Recombinant activated factor VII for acute intracerebral hemorrhage: US phase IIA trial. *Neurocrit Care*. 2006;4(3):206-14
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Résumés-abstracts

Recombinant activated factor VII for acute intracerebral hemorrhage: US phase IIA trial.

Mayer SA, Brun NC, Broderick J, Davis SM, Diringer MN, Skolnick BE, Steiner T; United States NovoSeven ICH Trial Investigators. *Neurocrit Care*. 2006;4(3):206-14

BACKGROUND AND PURPOSE: Ultra-early hemostatic therapy may improve outcome after intracerebral hemorrhage (ICH) by preventing rebleeding and hematoma expansion. We conducted this trial to evaluate the safety of activated recombinant factor VII (rFVIIa; NovoSeven) for preventing early hematoma growth in acute ICH. **METHODS:** In this multicenter, randomized, double-blind, placebo-controlled, dose-escalation trial, 40 patients diagnosed with ICH by computed tomography within 3 hours of onset were treated with placebo or 5, 20, 40, or 80 microg/kg of rFVIIa (n = 8 per group). Patients with any history of thromboembolic or vaso-occlusive disease were excluded. The primary endpoint was the frequency of adverse events (AEs). **RESULTS:** Mean age was 65 years (range 34 - 91) and the median admission Glasgow Coma Scale score was 14.5 (range 6 to 15). Mean ICH volume was 17 +/- 19 mL; nearly three-quarters were located in the basal ganglia (n = 29). The mean interval from onset to treatment was 178 +/- 41 minutes. Thirty-three patients experienced 186 AEs, which occurred with similar frequency in the five groups. There were 10 thromboembolic AEs, including one case of deep vein thrombosis (20 microg g/kg group); one case of cerebral infarction (placebo); two cases of pulmonary embolism (20 and 40 microg g/kg groups); and six instances of ischemic ECG changes or cardiac enzyme elevation (placebo [n = 2], 20 microg g/kg [n = 1], 40 microg g/kg [n = 1], and 80 microg g/kg [n = 2] groups). No consumption coagulopathy or dose-related increase in edema-to-ICH volume ratio occurred. **CONCLUSIONS:** Ultra-early rFVIIa treatment for ICH was associated with a reasonable safety profile in this preliminary study across a wide range of dosages. Further research is warranted to investigate the safety and potential efficacy of rFVIIa for minimizing ICH growth.

Recombinant activated factor VII for acute intracerebral hemorrhage

Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T. Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators. *N Engl J Med*. 2005 Feb 24;352(8):777-85

BACKGROUND: Intracerebral hemorrhage is the least treatable form of stroke and is associated with high mortality. Among patients who undergo computed tomography (CT) within three hours after the onset of intracerebral hemorrhage, one third have an increase in the volume of the hematoma related to subsequent bleeding. We sought to determine whether recombinant activated factor VII (rFVIIa) can reduce hematoma growth after intracerebral hemorrhage. **METHODS:** We randomly assigned 399 patients with intracerebral hemorrhage diagnosed by CT within three hours after onset to receive placebo (96 patients) or 40 microg of rFVIIa per kilogram of body weight (108 patients), 80 microg per kilogram (92 patients), or 160 microg per kilogram (103 patients) within one hour after the baseline scan. The primary outcome measure was the percent change in the volume of the intracerebral hemorrhage at 24 hours. Clinical outcomes were assessed at 90 days. **RESULTS:** Hematoma volume increased more in the placebo group than in the rFVIIa groups. The mean increase was 29 percent in the placebo group, as compared with 16 percent, 14 percent, and 11 percent in the groups given 40 microg, 80 microg, and 160 microg of rFVIIa per kilogram, respectively (P=0.01 for the comparison of the three rFVIIa groups with the placebo group). Growth in the volume of intracerebral hemorrhage was reduced by 3.3 ml, 4.5 ml, and 5.8 ml in the three treatment groups, as compared with that in the placebo group (P=0.01). Sixty-nine percent of placebo-treated patients died or were severely disabled (as defined by a modified Rankin Scale score of 4 to 6), as compared with 55 percent, 49 percent, and 54 percent of the patients who were given 40, 80, and 160 microg of rFVIIa, respectively (P=0.004 for the comparison of the three rFVIIa groups with the placebo

group). Mortality at 90 days was 29 percent for patients who received placebo, as compared with 18 percent in the three rFVIIa groups combined (P=0.02). Serious thromboembolic adverse events, mainly myocardial or cerebral infarction, occurred in 7 percent of rFVIIa-treated patients, as compared with 2 percent of those given placebo (P=0.12). **CONCLUSIONS:** Treatment with rFVIIa within four hours after the onset of intracerebral hemorrhage limits the growth of the hematoma, reduces mortality, and improves functional outcomes at 90 days, despite a small increase in the frequency of thromboembolic adverse events. Copyright 2005 Massachusetts Medical Society.

Safety and feasibility of recombinant factor VIIa for acute intracerebral hemorrhage.

Mayer SA, Brun NC, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T; Europe/AustralAsia NovoSeven ICH Trial Investigators. *Stroke*. 2005 Jan;36(1):74-9.

BACKGROUND AND PURPOSE: Hematoma growth occurs in 38% of intracerebral hemorrhage (ICH) patients scanned by computed tomography (CT) within 3 hours of onset. Activated recombinant factor VII (rFVIIa) promotes hemostasis at sites of vascular injury and may minimize hematoma growth after ICH. **METHODS:** In this randomized, double-blind, placebo-controlled, dose-escalation trial, 48 subjects with ICH diagnosed within 3 hours of onset were treated with placebo (n=12) or rFVIIa (10, 20, 40, 80, 120, or 160 microg/kg; n=6 per group). The primary endpoint was the frequency of adverse events (AEs). Safety assessments included serial electrocardiography (ECG), troponin I and coagulation testing, lower extremity Doppler ultrasonography, and calculation of edema:ICH volume ratios. **RESULTS:** Mean age was 61 years (range, 30 to 93) and 57% were male. At admission, mean National Institutes of Health Stroke Scale (NIHSS) score was 14 (range, 1 to 26), median Glasgow Coma Scale score was 14 (range, 6 to 15), and mean ICH volume was 21 mL (range, 1 to 151). Mean time from onset to treatment was 181 minutes (range, 120 to 265). Twelve serious AEs occurred, including 5 deaths (mortality 11%). Six AEs were considered possibly treatment-related, including rash, vomiting, fever, ECG T-wave inversion, and 2 cases of deep vein thrombosis (placebo and 20-microg/kg groups). No myocardial ischemia, consumption coagulopathy, or dose-related increase in edema:ICH volume occurred. **CONCLUSIONS:** This small phase II trial evaluated a wide range of rFVIIa doses in acute ICH and raised no major safety concerns. Larger studies are justified to determine whether rFVIIa can safely and effectively limit ICH growth.

Ultra-early hemostatic therapy for acute intracerebral hemorrhage.

Mayer SA, Rincon F. *Semin Hematol*. 2006 Jan;43(1 Suppl 1):S70-6.

Intracerebral hemorrhage (ICH) is the least treatable form of stroke, and causes high mortality, severe disability, and a staggering economic burden. ICH accounts for 15% of stroke cases in the United States and Europe, and up to 30% in Asian populations. Computed tomography-based studies suggest that ICH growth within the first few hours of onset is common, and the principal cause of early neurological deterioration. Hematoma volume is also a well-established predictor of 30-day mortality. Intervention with ultra-early hemostatic therapy could minimize or prevent this early dynamic bleeding process, and might improve outcome. Recombinant activated factor VII (rFVIIa; NovoSeven, Novo Nordisk, Bagsvaerd, Denmark) is approved for the treatment of bleeding in patients with hemophilia and inhibitors, but it may also promote hemostasis in patients with normal coagulation by acting locally at the bleeding site without activation of systemic coagulation. In a randomized, double-blind, placebo-controlled trial of 399 ICH patients treated with a single dose of 40, 80, or 160 microg/kg of rFVIIa or placebo within 4 hours of onset, subsequent hematoma growth was reduced by approximately 50% with rFVIIa. This was associated with a significant reduction (38%) in mortality, and improved functional outcomes among survivors. A phase III trial comparing 20 and 80 microg/kg rFVIIa with placebo is now in progress to confirm these results.

Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage.

Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T; FAST Trial Investigators. *N Engl J Med*. 2008 May 15;358(20):2127-37

BACKGROUND: Intracerebral hemorrhage is the least treatable form of stroke. We performed this phase 3 trial to confirm a previous study in which recombinant activated factor VII (rFVIIa) reduced growth of the hematoma and improved survival and functional outcomes. **METHODS:** We randomly assigned 841 patients with intracerebral hemorrhage to receive placebo (268 patients), 20 microg of rFVIIa per kilogram of body weight (276 patients), or 80 microg of rFVIIa per kilogram (297 patients) within 4 hours after the onset of stroke. The primary end point was poor outcome, defined as severe disability or death according to the modified Rankin scale 90 days after the stroke. **RESULTS:** Treatment with 80 microg of rFVIIa per kilogram resulted in a significant reduction in growth in volume of the hemorrhage. The mean estimated increase in volume of the intracerebral hemorrhage at 24 hours was 26% in the placebo group, as compared with 18% in the group receiving 20 microg of rFVIIa per kilogram (P=0.09) and 11% in the group receiving 80 microg (P<0.001). The growth in volume of intracerebral hemorrhage was reduced by 2.6 ml (95% confidence interval [CI], -0.3 to 5.5; P=0.08) in the group receiving 20 microg of rFVIIa per kilogram and by 3.8 ml (95% CI, 0.9 to 6.7; P=0.009) in the group receiving 80 microg, as compared with the placebo group. Despite this reduction in bleeding, there was no significant difference among the three groups in the proportion of patients with poor clinical outcome (24% in the placebo group, 26% in the group receiving 20 microg of rFVIIa per kilogram, and 29% in the group receiving 80 microg). The overall frequency of thromboembolic serious adverse events was similar in the three groups; however, arterial events were more frequent in the group receiving 80 microg of rFVIIa than in the placebo group (9% vs. 4%, P=0.04). **CONCLUSIONS:** Hemostatic therapy with rFVIIa reduced growth of the hematoma but did not improve survival or functional outcome after intracerebral hemorrhage.