

Recombinant activated factor VII as treatment for intractable haemorrhage

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العامل السابع المنشط المأشوب لعلاج حالات النزف المستعصية

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الخلاصة: تهدف هذه الدراسة إلى تحديد نتائج معالجة المرضى بالعامل السابع المنشط المأشوب من أجل تعزيز وقف النزف في حالات النزف المستعصية المرتبطة بإصابات الرضوح أو بأسباب أخرى. وجرى مراجعة استيعادية للسجلات الطبية لـ 44 مريضاً على التوالي ممن عولجوا بالعامل السابع المنشط المأشوب للتعرف على استخدام منتج الدم قبل المعالجة وبعدها. وبدا واضحاً أن هناك انخفاضاً يُعتد به إحصائياً في نقل منتجات الدم لدى 23 مريضاً مصابين برضوح و21 مريضاً يعانون من أسباب أخرى للنزف ممن بقوا على قيد الحياة لمدة تزيد على 4 ساعات بعد تسريب العامل السابع المنشط المأشوب. وعلى الرغم من وفاة 10 مرضى من 13 مريضاً مصابين برضوح و12 مريضاً من 21 مريضاً يعانون من أسباب أخرى، في فترة تتراوح بين يومين و50 يوماً بعد تسريب العامل السابع المنشط المأشوب، فقد كانت هذه الوفيات ترجع إلى أسباب أخرى غير النزف. وارتبط الاستخدام المبكر للعامل السابع المنشط المأشوب بانخفاض الوفيات في الخمسين يوماً في المرضى المصابين برضوح شديدة ويحتاجون إلى نقل كميات كبيرة من الدم، لكنه لم يرتبط بزيادة خطر حدوث الجلطات.

ABSTRACT The objective of this study was to determine the outcome of patients treated with recombinant activated factor VII (rFVIIa) to promote haemostasis in intractable bleeding associated with trauma injury or other causes. The medical records of 44 consecutive patients treated with rFVIIa were retrospectively reviewed for blood product use before and after treatment. A statistically significant decrease in blood product transfusion was evident in 23 trauma patients and 21 patients with other causes of bleeding who survived more than 4 hours after rFVIIa infusion. Although 10/23 trauma patients and 12/21 other causes patients died, between 2 and 50 days after rFVIIa infusion, these deaths were due to causes other than haemorrhage. The early use of rFVIIa was associated with decreased 50-day mortality in patients with severe trauma requiring massive transfusion, but was not associated with increased risk of severe thrombotic events.

Le facteur VII activé recombinant comme traitement de l'hémorragie incoercible

RÉSUMÉ La présente étude avait comme objectif d'évaluer l'issue thérapeutique chez les patients traités par facteur VII activé recombinant (rFVIIa), qui favorise l'hémostase en cas d'hémorragie incoercible due à un traumatisme ou à d'autres causes. Les dossiers médicaux de 44 patients consécutifs ayant reçu ce traitement ont fait l'objet d'un examen rétrospectif visant à identifier l'utilisation de produits sanguins avant et après le traitement. Chez les 23 patients dont l'hémorragie était d'origine traumatique et les 21 patients pour qui elle avait d'autres causes, qui ont survécu plus de 4 heures après l'administration du facteur VII, on a constaté une diminution statistiquement significative de la transfusion de produits sanguins. Dix des vingt-trois patients ayant subi un traumatisme sont décédés, de même que douze des vingt et un patients souffrant d'une hémorragie liée à d'autres causes. Ces décès, survenus entre 2 et 50 jours après l'administration du facteur VII étaient cependant dus à d'autres causes que l'hémorragie. L'administration précoce du facteur rFVIIa était associée à une baisse de la mortalité dans les 50 jours chez les patients souffrant de traumatisme grave qui avaient besoin d'une transfusion massive, mais elle n'était pas liée à un risque accru d'événements thrombotiques sévères.

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Introduction

Recombinant activated factor VII (rFVIIa) is a pro-haemostatic agent that is licensed in the United States for control of bleeding in patients with haemophilia with inhibitors to factor VIII concentrate. Additionally, it is licensed in Europe for patients with Glanzmann thrombasthenia who are refractory to platelet transfusions. In the only published randomized controlled trial evaluating rFVIIa in trauma patients, its use in patients with blunt traumatic injury was associated with reduced red blood cell (RBC) usage and acute respiratory distress syndrome without an increase in adverse thrombotic events [1].

Recombinant factor VIIa (rFVIIa), originally developed for the treatment of acquired inhibitors associated with haemophilia [2,3], has been successfully used for bleeding due to acquired or congenital thrombocytopenia [4,5] extensive trauma and a variety of surgical procedures, including anecdotal reports of use in cardiac surgery patients [6,7]. It reverses the effect of warfarin in healthy volunteers [8], and corrects the prothrombin time in patients with hepatic failure [9]. Most critically ill patients with trauma suffer profound coagulopathy. Coagulation abnormalities in these patients have been attributed to multiple factors including disseminated intravascular coagulation, excessive fibrinolysis due to release of tissue plasminogen activator, dilutional coagulopathy from fluid replacement and massive blood product transfusion, dysfunctional platelets and metabolic abnormalities including acidosis and hypothermia [10–16]. Although the mechanism of action of rFVIIa remains unclear, many investigators have suggested that it binds to the surface of activated platelets and directly activates factor X, thus bypassing the early steps of the coagulation cascade. Activated factor X then combines with activated factor V on the platelet surface, leading to rapid conversion of prothrombin

to thrombin [17,18]. Haemostasis is promoted through high concentrations of thrombin generated near activated platelets at the site of vascular injury. Based on its mechanism of action, rFVIIa may be effective in controlling haemorrhage due to trauma, surgery and other causes.

The present report is a retrospective review of 44 consecutive patients treated with rFVIIa for intractable haemorrhage. The need for transfusion of blood products both before and after treatment and the mortality rate at 4 hours and 50 days were assessed.

Methods

Patients

The medical records were examined for 44 consecutive patients treated with rFVIIa between November 2007 and May 2011 at Alnoor specialist hospital, Mecca, Saudi Arabia. The patients were divided into 2 groups: 23 patients had suffered trauma and 21 patients had bleeding from other causes.

Administration of rFVIIa

Commercially available rFVIIa (NovoSeven, Novo Nordisk) was used in all patients. There were no predetermined criteria for administration. In most patients, treatment was given after extensive blood product support had failed to control haemorrhage, and the decision to treat was made jointly by the surgeon, haematologist and blood bank pathologist. rFVIIa was administered as a bolus dose of 90 µg/kg.

Endpoints and assessment of risk

The total number of blood products given before and up to 24 hours after rFVIIa administration, or until death, whichever came first, was quantified. Also, given the short half-life of rFVIIa, this time frame did not allow for an accurate determination of efficacy. The number of patients surviving at 4 hours

and 50 days after the administration of rFVIIa was compared. Fifty days, or death, was chosen as an endpoint. To determine the risk factors for poor outcome, patients were assessed for age, sex, comorbid conditions, haemoglobin, platelet count, arterial blood gas results and coagulation parameters. Laboratory parameters were not available for some patients.

Statistical analysis

Frequency tables (number, percentage) were mainly calculated for all the measurements. Comparability tests were measured among patients of the study using the chi-squared test for categorical variables such as sex and Student *t*-test for continuous variables such as age groups. Significance was detected at *P*-value < 0.05

Results

Patient demographics

There were 44 patients surveyed, of whom 30 (68%) were men. The mean age was 34.7 (SD 15.1) years, range 9–72 years. The patients were divided into 2 groups: 23 (52%) patients who had trauma injury and 21 (48%) patients who had bleeding from other causes. There were more males than females in the trauma injury group (20 males and 3 females), whereas the sex ratio was similar in the other bleeding problems group (10 males and 11 females) (Table 1). The median age of the trauma injury patients was lower (29 years, range 9–72 years) compared with patients with other bleeding problems (41 years, range 22–62 years). The mean period of stay in the intensive care unit (ICU) was 10 days overall (range 0.5–50 days): 9 days (range 0.5–40 days) for patients with trauma injury and 12 days (range 1–50 days) for those with other bleeding problems. The mean Acute Physiology and Chronic Health Evaluation II (APACHE II) score was 48.4 (range 18.2–79.9) for trauma injury and 52.5

Table 1 Baseline characteristics of the study patients

Variable	Total group		Trauma injury group		Other causes of bleeding group		P-value
	No.	%	No.	%	No.	%	
Total	44	100	23	52	21	48	
Sex							
Male	30	68	20	45	10	23	0.005
Female	14	32	3	7	11	25	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	
Age (years)	34.7 (15.1)	9.0–72	29.0 (15.3)	9.0–72	41.0 (12.4)	22.0–62.0	0.007
ICU length of stay (days)	10.0 (1.7)	0.5–50	9.0 (1.7)	0.5–40	12.0 (3.1)	1.0–50.0	0.344
APACHE II score	50.4 (2.5)	18.2–80.5	48.4 (3.2)	18.2–79.9	52.5 (3.8)	29.1–80.5	0.412

SD = standard deviation; ICU = intensive care unit; APACHE = Acute Physiology and Chronic Health Evaluation.

(range 29.1–80.5) for other bleeding problems.

Laboratory results before treatment with rFVIIa

There were no significant differences in the mean (SD) of the international normalized ratios before treatment: 1.70 (SD 0.74) for the whole sample, 1.77 (SD 0.62) for trauma patients and 1.61 (SD 0.86) for the other causes group ($P = 0.479$) (Table 2). The mean of partial thromboplastin times before treatment were 61.2 (SD 24.8) for the whole sample, 68.0 (SD 27.4) for trauma patients and 53.8 (SD 19.7) for the other causes group, and these differences were also not significant.

Haematological profile of patients before and after treatment

Trauma patients

The ISS for trauma patients was 23 (SD 2.8) (range 3–50) and the results of their pre- and post-treatment

blood product use are listed in Table 3. Before the administration of rFVIIa, patients received on average around 10 U of packed RBC (range 2–26), 8 U of platelets (range 0–25), 15 U of fresh-frozen plasma (range 4–41) and 4 U of cryoprecipitate (range 0–32). Post-rFVIIa-treatment, an average of less than 3 U of packed RBC (range 0–6), 4 U of platelets (range 0–28), 3 U of fresh-frozen plasma (range 0–15) and 1 U of cryoprecipitate (range 0–6) were transfused. Haemoglobin at pre-rFVIIa-administration was 9.4 g/L (range 5.7–15.1 g/L) and post-rFVIIa-administration become 10.2 g/L (range 3.9–14.7 g/L) with no significance difference ($P = 0.242$). Except for cryoprecipitate ($P = 0.055$), the difference between the pre- and post-transfusion requirements was significantly lower for all blood products: packed RBC ($P < 0.001$), platelets ($P = 0.046$) and fresh-frozen plasma ($P < 0.001$).

Other causes of bleeding patients

Among the patients with other causes of bleeding the results of their pre- and post-treatment blood product use are listed in Table 3. Before and after the administration of rFVIIa, patients received an average of around 11 U of packed RBC (range 3–22), 10 U of platelets (range 0–34), 15 U of fresh-frozen plasma (range 0–41) and 7 U of cryoprecipitate (range 0–31). Post-rFVIIa-treatment, an average of 3 U of packed RBC (range 0–10), 6 U of platelets (range 0–46), 6 U of fresh-frozen plasma (range 0–55) and 4 U of cryoprecipitate (range 0–37) were transfused. Haemoglobin was measured pre-rFVIIa-administration was 8.5 g/L (range 5.2–14.6 g/L) and post rFVIIa-administration become 9.5 g/L (range 5.7–13.5 g/L) with no significant difference ($P = 0.148$). The difference between the pre- and post-transfusion requirement was significantly lower for packed RBC ($P <$

Table 2 Laboratory results of the 2 groups of patients before treatment with recombinant activated factor VII (rFVIIa)

Patient group	International normalized ratio		Partial thromboplastin time (s)	
	Mean (SD)	Range	Mean (SD)	Range
Total group ($n = 44$)	1.70 (0.74)	0.8–4	61.2 (24.8)	25.7–120
Trauma group ($n = 23$)	1.77 (0.62)	0.8–3	68.0 (27.4)	29.6–120
Other bleeding problems group ($n = 21$)	1.61 (0.86)	1.0–4	53.8 (19.7)	25.7–92.6
P-value	0.479		0.053	

SD = standard deviation.

Table 3 Haemoglobin level and units of products received by the 2 groups of patients before and after treatment with recombinant activated factor VII (rFVIIa)

Patient group/ haematological variables	Pre-rFVIIa		Post-rFVIIa		P-value
	Mean (SD)	Range	Mean (SD)	Range	
Trauma group (n = 23)					
Haemoglobin level (g/L)	9.4 (17.1)	5.7-15.1	10.2 (2.2)	3.9-14.7	0.242
Packed RBC received (units)	10.1 (25.2)	2-26	2.5 (1.5)	0-6	< 0.001
Platelets received (units)	8.0 (28.4)	0-25	4.0 (6.1)	0-28	0.046
Fresh-frozen plasma received (units)	15.1 (32.8)	4-41	3.1 (3.6)	0-15	< 0.001
Cryoprecipitate received (units)	4.5 (23.0)	0-32	0.9 (2.1)	0-6	0.055
Other causes of bleeding group (n = 21)					
Haemoglobin level (g/L)	8.5 (0.5)	5.2-14.6	9.5 (0.5)	5.7-13.5	0.148
Packed RBC received (units)	11.0 (1.3)	3-22	2.9 (0.6)	0-10	< 0.001
Platelets received (units)	10.5 (2.1)	0-34	6.3 (2.5)	0-46	0.212
Fresh-frozen plasma received (units)	15.8 (2.3)	0-41	6.5 (2.7)	0-55	0.013
Cryoprecipitate received (units)	7.4 (1.70)	0-31	4.0 (2.2)	0-37	0.234

SD = standard deviation; RBC = red blood cells.

0.001) and fresh frozen plasma ($P = 0.013$) but not for platelets ($P = 0.212$) and cryoprecipitate ($P = 0.234$).

Outcome

Out of the 44 patients 22 patients survived and were eventually discharged home. The remaining 22 patients died; 5 of them died within the first day after rFVIIa treatment while the others 17 patients died between 2 and 50 days from a variety of causes including multiorgan failure and infections. In trauma patients 13 (30%) survived while 10 (23%) died and in other causes of bleeding patients 9 (20%) survived while 12 (27%) died, with no statistically significant difference between the groups ($P = 0.365$).

Discussion

This retrospective case series suggests that rFVIIa was effective in promoting haemostasis even when given as a last life-saving measure in poor prognosis patients with massive transfusion-refractory haemorrhage, and that use of rFVIIa may have decreased the mortality in patients severe traumatic injuries who received massive transfusions. Our approach to the administration of rFVIIa is supported by consensus statements and

review articles that describe the optimal use of rFVIIa [19,20]. These guidelines recommend rFVIIa for patients with life-threatening haemorrhage who are in a hypocoagulable state from severe trauma after metabolic acidosis and hypocalcaemia are corrected. In addition, these guidelines recommend rFVIIa for patients with adequate concentrations of platelets, fibrinogen and coagulation factors. Our findings differ from those of a randomized controlled trial by Boffard et al., who reported that rFVIIa usage did not significantly improve survival in patients with penetrating or blunt injuries [1]. Increased injury severity and indicators of admission hypoperfusion may account for these differences.

A statistically significant decrease in blood product transfusion was evident in patients with trauma or with other causes of bleeding who survived more than 4 hours after rFVIIa infusion. Although 10/23 trauma patients and 12/21 other causes patients died, between 2 and 50 days after rFVIIa infusion, these deaths were due to causes other than haemorrhage. The trauma patients and those with other causes of bleeding who survived received an average of 10 and 11 U of RBC respectively in the peri-rFVIIa period, but after

rFVIIa infusion the averages were 2.5 and 2.8 U respectively.

There were 4 trauma patients who died within 4 hours who had suffered from major blood-vessel injury, blunt abdominal trauma or fall from height. These patients were unstable upon arrival to the emergency room with haemoglobin in the range of 7.7-13.7 g/dL. Excessive haemorrhage requiring massive transfusion can lead to hypothermia, disseminated intravascular coagulation, excessive fibrinolysis, dilutional coagulopathy, and metabolic acidosis, which may further exacerbate bleeding and morbidity [12-15].

Despite similar ISS in the trauma injury patients studied by Boffard et al. and our patients, the ISS underestimates the severity of injury in trauma patients with penetrating injuries [21]. The mortality reported in the Boffard trial was 26% compared with 50% in this report, which may also indicate more severe injuries in our patient population. Improvement in mortality rates may only occur when rFVIIa is given to patients who are significantly coagulopathic or severely injured. The physiology of haemostasis in patients with trauma injuries is a dynamic process. Most patients with mild to moderate trauma injuries are hypercoagulable, but

those with severe trauma are frequently hypocoagulable at admission [22–24].

A retrospective report, based on a similar cohort in trauma patients requiring massive transfusion, revealed that early administration of rFVIIa decreased RBC use by 23% [25]. This concept of timing of rFVIIa administration and effect on outcome may be illustrated in a comparison of the two previously published randomized controlled trials [1,26]. In the Mayer intracerebral haemorrhagic stroke trial, when rFVIIa was administered at a mean of 2 hours from the onset of symptoms, there was a mortality benefit compared with those who did not receive rFVIIa (18% versus 29%, respectively). This trial included patients with haemorrhagic stroke and not traumatic brain injury, which limits the application of its results to patients with traumatic injury. In the Boffard trauma trial, when rFVIIa was given at a median of 4 hours from admission, mortality was unchanged. The differences in mortality outcomes between our retrospective review and the Boffard et al. trial may have been affected by the time to administration of rFVIIa. In our study, there was decreased mortality when rFVIIa was given at a median of 4 hours from admission. Thus, in patients of more severely injured patients who received the drug sooner, better mortality outcomes were seen. The timing of rFVIIa use may be essential regarding its efficacy.

Generally, our practice is to use rFVIIa, cryoprecipitate, fresh-frozen

plasma, and, when available, packed RBC and apheresis platelets, early in the resuscitation for patients with severe traumatic injuries [27,28] and independently associated with increased 48-hour and 50-day survival and decreased mortality in these patients.

These results support the concept of haemostatic or damage control resuscitation, which emphasizes the early and increased use of multiple haemostatic agents to aggressively treat the coagulopathy of trauma in patients with life-threatening traumatic injuries [19,29–33]. This was also shown in the randomized controlled trial of penetrating trauma patients by Boffard et al. [1]

The small sample size in our analysis did not allow for adequate power to make adequate comparisons of adverse events. There are now 8 randomized controlled trials in surgical patients, none of which show an increased in the thrombotic complication rate with rFVIIa [1,26,33–39].

The optimal dose of rFVIIa for these patients is unknown. However, in considering the data from the aforementioned studies, it would appear that higher initial doses, or additional doses, might improve outcome. It is also tempting to speculate that earlier treatment with rFVIIa may have prevented rapid clinical deterioration and complications associated with massive blood product transfusion in this series of patients. This question would best be addressed in controlled studies using standard dosing

protocols and well-defined criteria for intractable haemorrhage. Although rFVIIa is expensive, it would appear to be cost effective when compared with the combined cost of large amount of blood products. Previous clinical experience with rFVIIa supports a good safety profile in patients with haemophilia and trauma. Less than 1% of patients receiving rFVIIa had thrombosis and thrombosis-related complications [17,40].

Extension of life for patients who eventually died is important since this may allow the critical care team additional time to intervene and support the critically ill patient, improving the overall mortality in these patients. Recombinant FVIIa may not improve survival, however, if used too late in the resuscitation when the patient is in a state of irreversible shock [19,41].

Conclusions

This retrospective study suggests that rFVIIa can play a beneficial role as an adjunctive haemostatic agent in patients after extensive trauma with a very poor prognosis associated with refractory bleeding, coagulopathy, acidosis, hypothermia following conventional resuscitation and who experience bleeding that cannot be controlled by conventional therapies. Use of rFVIIa resulted in better than expected survival rates according to those suggested by the APACHE II score.

References

- Boffard KD et al.; NovoSeven Trauma Study Group. Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. *Journal of Trauma*, 2005, 59:8–15.
- Hedner U, Kisiel W. Use of human factor VIIa in the treatment of two hemophilia A patients with high-titer inhibitors. *Journal of Clinical Investigation*, 1983, 71:1836–1841.
- Lusher JM. Recombinant factor VIIa (NovoSeven) in the treatment of internal bleeding in patients with factor VIII and IX inhibitors. *Haemostasis*, 1996, 26(Suppl. 1):124–130.
- Monroe DM et al. The factor VII-platelet interplay: effectiveness of recombinant factor VIIa in the treatment of bleeding in severe thrombocytopenia. *Seminars in Thrombosis and Hemostasis*, 2000, 26:373–377.
- Poon MC et al. Recombinant factor VIIa is effective for bleeding and surgery in patients with Glanzmann thrombasthenia. *Blood*, 1999, 94:3951–3953.
- White B et al. Successful use of recombinant FVIIa (Novoseven) in the management of intractable postsurgical intra-abdominal haemorrhage. *British Journal of Haematology*, 1999, 107:677–678.
- Martinowitz U et al. Recombinant activated factor VII for adjunctive hemorrhage control in trauma. *Journal of Trauma*, 2001, 51:431–438, discussion 438–439.
- Erhardttsen E et al. The effect of recombinant factor VIIa (NovoSeven) in healthy volunteers receiving acenocoumarol to an

- International Normalized Ratio above 2.0. *Blood Coagulation and Fibrinolysis*, 1998, 9:741-748.
9. Bernstein DE et al. Recombinant factor VIIa corrects prothrombin time in cirrhotic patients: a preliminary study. *Gastroenterology*, 1997, 113:1930-1937.
 10. Reiss RF. Hemostatic defects in massive transfusion: rapid diagnosis and management. *American Journal of Critical Care*, 2000, 9:158-165.
 11. Gubler KD et al. The impact of hypothermia on dilutional coagulopathy. *Journal of Trauma*, 1994, 36:847-851.
 12. Krause KR et al. Hypothermia-induced coagulopathy during hemorrhagic shock. *American Surgeon*, 2000, 66:348-354.
 13. Rohrer MJ, Natale AM. Effect of hypothermia on the coagulation cascade. *Critical Care Medicine*, 1992, 20:1402-1405.
 14. Ferrara A et al. Hypothermia and acidosis worsen coagulopathy in the patient requiring massive transfusion. *American Journal of Surgery*, 1990, 160:515-518.
 15. Gando S et al. Significant correlations between tissue factor and thrombin markers in trauma and septic patients with disseminated intravascular coagulation. *Thrombosis and Haemostasis*, 1998, 79:1111-1115.
 16. Meng ZH et al. The effect of temperature and pH on the activity of factor VIIa: implications for the efficacy of high-dose factor VIIa in hypothermic and acidotic patients. *Journal of Trauma*, 2003, 55:886-891.
 17. Hoffman M, Monroe DM 3rd, Roberts HR. Activated factor VII activates factors IX and X on the surface of activated platelets: thoughts on the mechanism of action of high-dose activated factor VII. *Blood Coagulation & Fibrinolysis*, 1998, 9(Suppl. 1):S61-S65.
 18. Roberts HR. Clinical experience with activated factor VII: focus on safety aspects. *Blood Coagulation & Fibrinolysis*, 1998, 9(Suppl. 1):S115-S118.
 19. Martinowitz U, Michaelson M; Israeli Multidisciplinary rFVIIa Task Force. Guidelines for the use of recombinant activated factor VII (rFVIIa) in uncontrolled bleeding: a report by the Israeli Multidisciplinary rFVIIa Task Force. *Journal of Thrombosis and Haemostasis*, 2005, 3:640-648.
 20. Holcomb JB. Use of recombinant activated factor VII to treat the acquired coagulopathy of trauma. *Journal of Trauma*, 2005, 58:1298-1303.
 21. Abbreviated injury scale, military edition. Chicago, Illinois, Association for the Advancement of Automotive Medicine, 2005.
 22. Brohi K et al. Acute traumatic coagulopathy. *Journal of Trauma*, 2003, 54:1127-1130.
 23. Kaufmann CR et al. Usefulness of thrombelastography in assessment of trauma patient coagulation. *Journal of Trauma*, 1997, 42:716-720.
 24. Schreiber MA et al. Early predictors of massive transfusion in combat casualties. *Journal of the American College of Surgeons*, 2007, 205:541-545.
 25. Perkins JGSM et al. Early versus late recombinant factor VIIa in combat trauma patients requiring massive transfusion. *Journal of Trauma*, 2007, 62:1095-1099.
 26. Mayer SA et al.; Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators. Recombinant activated factor VII for acute intracerebral hemorrhage. *New England Journal of Medicine*, 2005, 352:777-785.
 27. Lavee J et al. The effect of transfusion of fresh whole blood versus platelet concentrates after cardiac operations. A scanning electron microscope study of platelet aggregation on extracellular matrix. *Journal of Thoracic and Cardiovascular Surgery*, 1989, 97:204-212.
 28. Manno CS et al. Comparison of the hemostatic effects of fresh whole blood, stored whole blood, and components after open heart surgery in children. *Blood*, 1991, 77:930-936.
 29. Malone DL, Hess JR, Fingerhut A. Massive transfusion practices around the globe and a suggestion for a common massive transfusion protocol. *Journal of Trauma*, 2006, 60(Suppl.):S91-S96.
 30. Hess JR, Holcomb JB, Hoyt DB. Damage control resuscitation: the need for specific blood products to treat the coagulopathy of trauma. *Transfusion*, 2006, 46:685-686.
 31. McMullin NR, Hess JR, Sondeen J. Hemostatic resuscitation. In: Vincent J, ed. Yearbook of intensive care and emergency medicine. New York, Springer, 2006:265-278.
 32. McLaughlin DF et al. A predictive model for massive transfusion in combat casualty patients. *Journal of Trauma*, 2008, 64(Suppl.):S57-S63.
 33. Ho AM, Karmakar MK, Dion PW. Are we giving enough coagulation factors during major trauma resuscitation? *American Journal of Surgery*, 2005, 190:479-484.
 34. Shao YF et al. Safety and hemostatic effect of recombinant activated factor VII in cirrhotic patients undergoing partial hepatectomy: a multicenter, randomized, double-blind, placebo-controlled trial. *American Journal of Surgery*, 2006, 191:245-249.
 35. Ekert H et al. Elective administration in infants of low-dose recombinant activated factor VII (rFVIIa) in cardiopulmonary bypass surgery for congenital heart disease does not shorten time to chest closure or reduce blood loss and need for transfusions: a randomized, double-blind, parallel group, placebo-controlled study of rFVIIa and standard haemostatic replacement therapy versus standard haemostatic replacement therapy. *Blood Coagulation and Fibrinolysis*, 2006, 17:389-395.
 36. Friederich PW et al. The effect of the administration of recombinant activated factor VII (NovoSeven) on perioperative blood loss in patients undergoing transabdominal retroperitoneal prostatectomy: the PROSE study. *Blood Coagulation and Fibrinolysis*, 2000, 11(Suppl. 1):S129-S132.
 37. Lodge JP et al. Recombinant coagulation factor VIIa in major liver resection: a randomized, placebo-controlled, double-blind clinical trial. *Anesthesiology*, 2005, 102:269-275.
 38. Raobaikady R et al. Use of activated recombinant coagulation factor VII in patients undergoing reconstruction surgery for traumatic fracture of pelvis or pelvis and acetabulum: a double-blind, randomized, placebo-controlled trial. *British Journal of Anaesthesia*, 2005, 94:586-591.
 39. Diprose P et al. Activated recombinant factor VII after cardiopulmonary bypass reduces allogeneic transfusion in complex non-coronary cardiac surgery: randomized double-blind placebo-controlled pilot study. *British Journal of Anaesthesia*, 2005, 95:596-602.
 40. Key NS et al. Home treatment of mild to moderate bleeding episodes using recombinant factor VIIa (Novoseven) in haemophiliacs with inhibitors. *Thrombosis and Haemostasis*, 1998, 80:912-918.
 41. Dutton RP, Hess JR, Scalea TM. Recombinant factor VIIa for control of hemorrhage: early experience in critically ill trauma patients. *Journal of Clinical Anesthesia*, 2003, 15:184-188.