Original Article

Recombinant Factor VII for the Conservative Management Trials of Intractable Postpartum Haemorrhage: Is it a Drug Effect, Operator Experience or Inherent Result of the Aetiology

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ABSTRACT

Aim: This monocentric retrospective study aimed at the evaluation of outcome of the parturients with intractable postpartum haemorrhage (P.P.H.) after the administration of recombinant activated factor VII (rFVIIa) to preserve the uterus.

Materials and Methods: this is a retrospective study conducted in a tertiary hospital . 41 patients were selected based on the inclusion criteria of both suffering from postpartum hemorrhage and received recombinant activated factor VII (rFVIIa). Patients were divided into group A who were managed by senior staff and group B who had started their management by junior staff and senior staff was called later for the case. Data was retrieved from patients' records during 2019. All patients had a preliminary evaluation and classic management measures for postpartum hemorrhage either in the emergency department or during planned cesarean section. If are still bleeding, patients were infused with rFVIIa. If the uterine bleeding didn't stop, conservative management was cancelled, and abdominal hysterectomy was done. In all cases, postpartum mortality was determined.

Results: The study included 41 parturient with P.P.H. with a mean age of 30.8±5.4 years. Eighteen patients had a cesarean section (C.S.), of whom 8 had successfully conserved the uterus, and 10 patients had a lifesaving hysterectomy using rFVIIa. On the other hand, 23 patients had been complicated with intractable postpartum haemorrhage. Twenty patients successfully had conservative management after using rFVIIa, and 3 patients had failed conservative management after using rFVIIa, and hysterectomy was lifesaving. Regarding 7-day postpartum mortality, one patient died with an intractable haemorrhage with delayed hysterectomy.

Conclusion: The operator seniority and experience is more important than the use of rFVIIa to achieve conservative management of cases suffering from or at great risk of postpartum hemorrhage and to reduce patients mortality.

Key Words: Postpartum haemorrhage, recombinant factor VIIa, rFVIIa.

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INTRODUCTION

Postpartum haemorrhage remains at the top of the causes of maternal deaths in both developed and developing countries and occurs in 1–6% of deliveries in developed countries. Primary postpartum haemorrhage is the bleeding from the genital tract equal to or exceeds 500 ml within the first 24 hours after the vaginal delivery or>1000 ml after a cesarean section. Persistent blood loss of more than 1000 ml should prompt predetermined measures to achieve resuscitation and hemostasis[1]. Major postpartum haemorrhage is a dangerous complication that accounts for the highest maternal morbidity rate. Its frequency may reach up to 6.7 per 1000 births[2].

The most common cause of postpartum haemorrhage is uterine atony[3]. Other causes include retained placental fragments, abnormal adhesion of the placenta, lower genital tract lacerations, coagulopathy, uterine inversion and uterine rupture.

Active management of postpartum haemorrhage involves controlling bleeding and restoring blood volume. Several therapies have been used to control such bleeding. Medical healings include ecbolics (oxytocin, ergot alkaloids, and prostaglandins), and surgical processes include sew and ligation of uterine and internal iliac a teries, uterine packing, and scrupulous arterial embolization[4]. Atonic postpartum hemorrahage is diagnosed afterwards excluding organs tract lacerations, uterine rupture, and retained placental tissue. In these cases, the aim of management is directed toward stimulating the uterus by bimanual compression and the use of ecbolics. If these measures fail, individual must resort to surgical maneuvers[5]. At this stage, an alternative choice is uterovaginal packing specially used to control bleeding by tamponade effect. Uterovaginal packing alone can sometimes succeed and obviates the need for surgery altogether[6]. All these methods aim at conserving the uterus to keep the fertility future of the patient. However, The obstetrician will do a

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hysterectomy in intractable bleeding that is not responsive to treatments to protect the patient's life. Hysterectomy is considered a ending measure to control the bleeding and is frequently associated with extreme morbidity[7]. The essential management of coagulopathic/diffuse postpartum bleeding is to maintain circulating volume by fluid replacement (crystalloids and colloids) and replace the blood components lost during bleeding by using blood products such as fresh frozen plasma, fresh red blood cells, cryoprecipitate or fibrinogen, and platelets. Resuscitation with large volumes of intravenous fluids, by itself, may lead to a worsening of coagulopathy and may not arrest bleeding 8. Furthermore, the overuse of blood products is associated with acute respiratory distress syndrome 23. Additionally, there is an increase in the risk of infections[8-10].

The complications of replacement therapy suggest the need for additional treatment options for severe postpartum bleeding. Hemostatic agents promise adjunctive therapy with current treatments, and there are increasing clinical trials data about it. One of these adjunctive therapies is the recombinant activated factor VII (rFVIIa, NovoSeven®; Novo Nordisk, Copenhagen, Denmark). However, the use of rFVIIa for postpartum bleeding is still off label. Its approval worldwide is only for treating bleeding in patients with haemophilia A or B with inhibitors to coagulation factors VIII or IX[11]. In Europe, rFVIIa is approved to manage factor VII deficiency and Glanzmann's thrombasthenia in patients who are refractory to platelet transfusions[12,13].

The smooth and quick administration of Recombinant FVIIa encourages its use. It is generally well tolerated. However, a primary concern of treatment with rFVIIa is the possibility of an increased incidence of thrombotic adverse events with a risk of rFVIIa-related thrombosis being 25 per 105 infusions[14].

Although the drug was initially used in patients with severe coagulopathies, recently, the spectrum of use has increased to the conditions arising from a systemic activation of the coagulation pathway. The drug is reported to be used prophylactically in surgery or patients without a coagulopathy, such as in cerebral bleeding or from tissue factor (T.F.) exposure at sites not associated with tissue injury, such as unstable coronary plaques[15,16].

PATIENTS AND METHODS

This retrospective cohort study was conducted in a tertiary hospital in Cairo, Egypt. The study was done over six month period starting from June 2019 to January 2020. There were 186 cases diagnosed as intractable postpartum haemorrhage during the period of study (based on the classic definition of bleeding that affected the patient's general condition and indicated for resuscitation). The patients included in this study are those who had marked resistant bleeding that necessitated the use of rFVIIa. Of these reported cases, only 41 patients had a massive uncontrollable postpartum haemorrhage and were not responding to the conventional management and needed the addition of rFVIIa to try to stop bleeding.

The cases are documented in the hospital administration and the Obstetrics and gynecology hospital pharmacy. This study aimed to evaluate weather the outcome of the parturients with intractable postpartum haemorrhage after the administration of recombinant activated factor VII is related to the used drug (rFVIIa) or depends on the operator experience and seniority.

Preliminary evaluation and first aid support were supplied as an initial management step, and then patients were transferred to the operating room. Patients were assessed hemodynamically, body temperature, and arterial pH were determined.

The senior staff managed the patients (lecturer, assistant professor or professor). However, some patients were managed by junior staff then the senior staff was called to complete the management (Table1).

Table 1: The frequency of cases according to the managing personnel

Managing staff personnel	Number of cases	percentage
Junior staff has started the management and called for the senior staff.	16	39
Senior staff managed the case from start	25	61
total	41	

Patients were grouped according to the management either conservative management or hysterectomy (Table 2).

Table 2: The management of intractable postpartum haemorrhage after use of rFVIIa

	Frequency	Percentage
conservative	29	70.7
hysterectomy	12	29.3
Total	41	100.0

Patients with P.P.H. Patients were given rFVIIa IV bolus in a dose of 1mg (one ampule), and the response was observed for 15-30 minutes. If the rate of blood loss was not markedly reduced, an additional dose of 1mg was infused, and in extreme cases, the third dose of 1mg was given. However, some patients received more than 3 ampules (Table3).

Table 3: Frequency of patients used rFVII ampules

rFVII ampules	Frequency of patients
1	3
2	1
3	26
4	3
5	1
6	6
7	1

STATISTICAL ANALYSIS

Statistical tests used: All data in the study is of nominal variables. The statistical tests done was the chi square test. The central tendency test used was the mode. Cross tables were used to evaluate the relation between variables and its strength. Only numerical data was the number of rFVIIa , where mean and standard deviation was used.

RESULTS

The study included 41 parturient with intractable P.P.H. The patients demographic data are presented in (Table 4).

Table 4: Demorgraphic data of the included patients in the study

No of patient (41 patients)	Outcome
Age	30.8±5.4
Gestational age	39.3±0.7

A life-saving hysterectomy was mandatory for 29% of the cases (Table 5).

Table 5: The management done for the cases studied

	Frequency	Percentage
conservative	29	70.7
hysterectomy	12	29.3
Total	41	100.0

9.8% of cases vanished due to the post partum hemorrhage inspite of management (Table 6).

Table 6: Postoperative mortality of the studied cases

	Frequency	Percent
recovered	37	90.2
mortality	4	9.8
Total	41	100.0

Cases were grouped according to the diagnosis and aetiology of bleeding (Table 7).

Table 7: diagnosis, management and operator managing the studied cases

Aetiology		operator		management	
		senior	junior	conservative	hysterectomy
aetiology	placenta accreta	3	3	5	1
	placental abruption, couvlier's uterus	1	2	0	3
	placenta previa complete centralis	7	2	4	5
	undiagnosed focal accreta	9	8	14	3
	atonic uterus	5	1	6	0
Total= 41 cases		25	16	29	12

Chi square test showed insignificant relation between the operator seniority on one side and management done weather conservative or hysterectomy, aetiology of bleeding and mortality . No significant relation was found (Table 8).

Table 8: Chi-Square Tests (Fisher's Exact Test is used as indicated statistically)

		Significance (2-sided)
aetiology* operator	Pearson Chi-Square	0.398
management* operator	Fisher's Exact Test	0.161
mortality* operator	Fisher's Exact Test	1.000

On the other hand the only significant relation was found between the type of management either conservative or hysterectomy and the aetiology of bleeding. The different managements for each diagnosis is presented in (Table 9).

Table 9: management of cases according to aetiology

	Aetiology					
	placenta accreta	placental abruption, couvlier's uterus	placenta previa complete centralis	undiagnosed focal accreta	atonic uterus	Total
conservative	5	0	4	14	6	29
hysterectomy	1	3	5	3	0	12
Total	6	3	9	17	6	41

Chi square test shows a significant relation between management and the aetiology of bleeding (P= 0.06is presented in (Table 10).

Table 10: Chi-Square Test of relation between the management done and aetiology of peripartum hemorrhage

	Value	df	Significance (2-sided)
Pearson Chi-Square	14.306	4	.006
Likelihood Ratio	15.956	4	.003
N of Valid Cases	41		

No significant relation was found between the number of rFVIIa and other parameters of the study (the operator, the aetiology, type of management or fate of the patient) (Table 11).

Table 11: Chi-Square Tests to evaluate the relation of rFVIIa to other studied parameters

	Value	df	Significance (2-sided)
Ampules used* Aetiology of bleeding	17.011[a]	24	0.848
ampules_used* operator	8.242[a]	6	0.221
ampules_used* fate	7.363[a]	6	0.289
ampules_used* management	3.409[a]	6	0.756

DISCUSSION

Postpartum hemorrhage remains a dangerous obstetrical complication, the leading cause of maternal mortality in developing countries. Rates of P.P.H. increased by 23% since 1991 till 2004, while rates of P.P.H. with hysterectomy increased by 73% [17]. Successful treatment relies on timely recognition and intervention with appropriate maneuvers when haemorrhage is severe[18]. Life-threatening P.P.H. is often due to surgical and occasionally coagulopathic bleeding. The evolution of angioembolization has assisted in successful surgical bleeding control. The coagulopathy in postpartum patients has remained problematic. The etiology is multifactorial because it involves other collateral factors like hypothermia, acidosis, consumption of clotting factors, and hemodilution. If a patient develops the lethal triad of hypothermia, acidosis, and coagulopathy, operational control is less likely to be effective alone[19]. Coagulopathy may also be due to pre-existing comorbidities requiring oral anticoagulation.

Also, Courtois *et al*.[18] found that recombinant activated factor VII is an exciting and promising hemostatic agent in managing life-threatening postpartum hemorrhage unresponsive to conventional treatment. Ahonen *et al*.,[26] tried rFVII in 23 women with P.P.H. and reported that although the response was considered useful in two-thirds of the women, several patients received rFVIIa with a poor or no response a result of atony or arterial bleeding.

The mechanism of action of aFVIIa is complex. The impact of timing on the effect of rFVIIa could be attributed to its physiological mechanism of action; rFVIIa normally circulates in minute quantities and binds to tissue factor (T.F.) expressed by the damaged vascular bed. The TF-FVIIa complex on TF-bearing cells activates factor IX. and Factor X. Factor Xa remains close to tissue factors bearing cells and activates factor V. The FXa–FVa complex on TF-bearing cells rapidly converts small amounts of prothrombin into thrombin[27]. This initial amount of thrombin activates F.XI., FVIII, F.V., and platelets. On the surface of activated platelets, FVIIIa and FIXa together activate large quantities of F.X., which finally (in conjunction with FVa) will result in the massive amount of thrombin , which enables the conversion of fibrinogen to fibrin with initial clot formation.

To avoid over transfusion of blood and blood products,the clinicians searched for alternative means of restoring homeostasis[20]. This includes expensive drugs

like rFVIIa. The results of this study shows that amount of rFVIIa has no relation to the fate of the patient or to the type of management weather conservative or hysterectomy. This is explained by the fact that the cause of bleeding in peripartum period is not related to coagulopathy. Thus adding a coagulation factor is not expected to have a significant value in management. Inspite of this, rFVIIa may still be used by the obstetrician during management of cases with intractable bleeding as a last resort that may help inspite of lacking any scientific indication.

Studying the operator effect on management results also showed an insignificant relation. This may be explained by the fact that all cases are finally managed by a senior staff even if junior staff has started the management. This is because these cases are life threatening and the most senior staff always manage the case.

The only factor that has a significant relation to management results is the aetiology of bleeding . this is because of the criticism of the cases of peripartum bleeding with more prediction of management result based on the aetiology significantly ($p< 0.01$) rather than the operator seniority or number of rFVIIa ampules used. This will save the neck of the operators from the results of the operations for post partum hemorrhage and would remove any blame for doing hysterectomy instead of conservative treatment. This is not dependent on cleverness but actually depends on the aetiology of bleeding that is critical (in this study as it necessiotated the use of expensiv rFVIIa).

These findings agreed with Bouwmeester *et al*.,[21] who reported that most of the P.P.H. have obstetrical causes, most frequently atony or laceration of the uterus.

Baudo *et al*.[22] reported that P.P.H. could occur in a series of events that lead to metabolic complications, hypoxia, disseminated intravascular coagulation, organ damage, and multiorgan failure, progressively exhaustive. Any intervention must be instituted as early as possible before permanent tissue damage occurs. This goes with the assumption that hysterectomy may be done in a suitable time to save patient's life without any relation to the cleverness of the surgeon.

In this study , after rFVIIa infusion and medical treatment of atony, bleeding failed to stop and continued in 4 patients who were exsanguinated and died.

These results agreed with previously reported literature; Holub *et al*.,[23,24] presented a case report of a 28-year old nullipara suffered from a significant P.P.H. after C.S. due to uterine atony. Conventional treatment was done , up to hysterectomy and packing of the pelvis, but failed to control diffuse pelvic and vaginal bleeding. However, rFVIIa was given as a final attempt to control the bleeding before ligation of the hypogastric artery. The response was rapid, with control of the bleeding and resolution of the coagulopathy.

Ahonen and Jokela,[1] tried rFVIIa for treatment of 12 cases of severe P.P.H.; good response to rFVIIa administration was reported in 7 women (58.3%), while in one there was no response and in four women the bleeding was significantly reduced although not completely stopped and underwent subsequent selective arterial embolization. Sobieszczyk *et al*.,[25] reported that of 25 cases of admission for hemorrhage, following administration of rFVIIa, the bleeding stopped in 18 cases (72%), decreased to different degrees in 6 (20%), and increased following rFVIIa administration in only one patient (4%). Requirements for replacement blood products and crystalloids/colloids were also significantly reduced. A full recovery was achieved by most patients (22/25, 88%) with few complications. A similar good effect on the postpartum hemorrhage control was found upon using aFVIIa but in a non randomized study by Ahonen *et al*.,[26].

The timing of the rFVIIa dosing depends on indication. An early administration (home treatment) of rFVIIa in hemophilics is successful and requires fewer doses,[27]. Friederich *et al*.,[28] gave the rFVIIa during operative procedures, just before the principal blood loss, whereas Raobaikady *et al*.,[29] and Lodge *et al*.,[30] administered rFVIIa at skin incision; given the rather short half-life of rFVIIa of approximately two hours in bleeding patients, dosing at skin incision might have been somewhat early in operations with an average duration of 3 and 4 h,[31]. In the current study, rFVIIa was infused after the occurrence of trauma and bleeding that was irresponsive to surgical hemostasis or transfusion of blood products. The timing of rFVIIa infusion was dependent on the results of pre-clinical studies.

CONCLUSION

rFVIIa infusion has a complex mechanism to generate a good coagulation process. However, its effect is isignificant on the resulting management of cases of peripartum hemorrhage. Similarly, the seniority of the operator has insigninficatn role on management results weather conservative or not. The aetiology of intractable bleeding related to placental site, attachment , and uterine atony are the most influencing factors on results of management. So these diagnoses should alarm the mind of obstetrician for instantaneous timely management independent on coagulation factors used or cleverness of the surgeon.

CONFLICT OF INTERESTS

There are no conflicts of interest.

REFERENCES

1. Franchini M. (2007) : Post-partum hemorrhage : new therapeutic options. Recenti Prog Med.; 98 (1) : 7 - 11.

2. Reynders F.C. ; Senten L. ; Tjalma W. & Jacquemyn Y. (2006): Postpartum hemorrhage: practical approach to a life-threatening complication. Oin Exp Obstet Gynecol. ; 33 (Q) : 81-4.

3. Waterstone M. ; Bewley S. & Wolfe C. (2001) : Incidence and predictors of severe obstetric morbidity : case-control study. B.M.J.; 322 : 1089- 94.

4. Salomon L.J. & Fernandez H. (2004) : Arterial embolization for postpartum hemorrhage : let's stay cautious. Hum Reprod.; 19 (2): 339 - 43.

5. Langer B.; Boudier E.; Haberstich R.; Dreyfus M ; College National des Gynecologues et Obstetricians Fran<;ais; Agence Nationale d'Accreditation et d'Evaluation en Sante (2004) : Obstetrical management in the event of persistent or worsening postpartum hemorrhage despite initial measures. J Gynecol Obstet Biol Reprod (Paris). ; 33 (8 Suppl) : 5473-5479.

6. Bagga R. ; Jain V. ; Kalra J. ; Chopra S. & Gopalan S. (2004) : Uterovaginal packing with rolled gauze in postpartum hemorrhage. Med. Gen. Med.; 6 (1): 50.

7. Landero F. & Landero A.P. (2004) : Intractable postpartum hemorrhage. Minerva Ginecol.; 56 (2): 181- 2.

8. Champion H.R.; Fingerhut A. ; Escobar M.A. & Weiskopf R.B. (2007) : The role of data and safety monitoring in acute trauma resuscitation research. J Am Coll Surg.; 204 (1): 73 - 83.

9. Oakridge J.A.; Sawyer R.G.; Schulman A.M.; McLemore E.C. & Young J.S. (2002) : Blood transfusions correlate with infections in trauma patients in a dose-dependent manner. Am Surg. ; 68 : 566 – 72

10. Moore P.A. ; Moore E.E. & Sauaia A. (1997) : Blood transfusion. An independent risk factor for post-injury multiple organ failure. Arch Surg. ; 132 : 620 - 4.

11. Malone D.L. ; Dunne J. ; Tracy J.K. ; Putnam A.T.; Scalea T.M. & Napolitano L.M. (2003) : Blood transfusion, independent of shock severity, is associated with worse outcome in trauma. J Trauma; 54 : 898 - 905.

12. Trowbridge C.C.; Stammers A.H.; Ciccarelli N. & Klayman M. (2006) : Dose titration of recombinant

13. Gunaydin B. ; Ozkose Z. & Pezek S. (2007): Recombinant activated factor VII and epsilon aminocaproic acid treatment of a patient with Glanzmann's thrombasthenia for nasal polypectomy. J Anesth.; 21 (1): 106 - 7.

14. Aledort L.M. (2004) : Comparative thrombotic event incidence after infusion of recombinant factor VIIa versus factor VIII inhibitor bypass activity. J Thromb Haemost.; 2: 1700 - 8.

15. Bosinski T.J. & El Solh A.A. (2006) : Recombinant factor VIIa, its clinical properties, and the tissue factor pathway of coagulation. Mini Rev Med Chem.; 6 (10): 1111- 7.

16. Mayo A.; Misgav M.; I<luger Y.; Greenberg R.; Pauzner D. ; Klausner J. & Ben-Tal 0. (2004) : Recombinant activated factor VII (NovoSeven™): addition to replacement therapy in acute, un<:controlled and life threatening bleeding. Vox Sanguinis; 87: 34-40.

17. Joseph K.S.; Rouleau J.; Kratrie r. M.S.; Young D.C. ; Liston R.M. ; Baskett T.F. ; Maternal Health Study Group of the Canadian Perinatal Surveillance System (2007) : Investigation of an increase in postpartum hemorrhage in Canada. BJOG.; 114 (6): 751 - 9.

18. Courtois L. ; Becher P. ; Miot S. ; Maisonnette Escot Y.; Sautiere J.L. ; Berthier F. ; Samain E. ; Maillet R. & Riethmuller D. (2007) : Life-threatening postpartum hemorrhage and recombinant.t activated factor rFVIIa NovoSeven use. J Gynecol Obstet Biol Reprod (Paris).; 36 (1): 78 - 82.

19. Chiara O. ; Cimbanassi S. ; Brioschi P.R. ; Bucci L. ; Terzi V. & Vesconi S. (2006) : Treatment of critical bleeding in trauma patients. Minerva Anestesiol.; 72 (6) : 383 - 7.

20. Mercer K.W. ; Gail Macik B. & Williams M.E. (2006) : Hematqlogic disorders in critically ill patients. Semin R·espir Crit Care Med. ; 27 (3) : 286-96.

21. Bouwmeester P.W.; Bolte A.C. & Geijn H.P. (2005) : Pharmacological and surgical therapy for primary postpartum hemorrhage. Curr Pharm Design; 11: 759 - 73.

22. Baudo F. ; Caimi T.M.; Mostarda G. ; de Cataldo F. & Morra E. (2006): Critical bleeding in pregnancy: a novel therapeutic approach to bleeding. Minerva Anestesiol.; 72 (6) : 389 - 93.

23. Holub Z.; Feyereisl J.; Kabelik L. & Rittstein T. (2005) : Successful treatment of severe post Partum bleeding after caesarean section using recombinant activated factor VII. Ceska Gynekol. ; 70 (2) : 144 - 146.

24. Ahonen J. & Jokela R. (2005) : Recombinant factor Vila for life-threatening postpartum hemorrhage. Br J Anaesth. ; 94 (5) : 592 - 5.

25. Sobieszczyk S. ; Breborowicz G.H. ; Markowitz W.; Mallinger S.; Adamski D. & Kruszynski Z. (2006) : Effect of recombinant activated factor VII (RFVIIA; NovoSeven) in a patient in hemorrhagic shock after obstetrical hysterectomy. Ginekol Pol.; 73 (3): 230 - 3.

26. Ahonen J. ; Jokela R. &: Korttila K. (2007) : An open non-randomized study o(recombinant activated factor VII in major postpartum hemorrhage. Acta Anaesthesiol Scand.

27. Santagostino E. ; Gringeri A. & Mannucci P.M. (1999) : Home treatment with recombinant activated factor VII in patients with factor VIII inhibitors: The advantages of early intervention. Br J Haematol.; 104 : 22 - 6.

28. Friederich P.W.; Henny C.P. & Messelink E.J. (2003): Effect of recombinant activated factor VII on perioperative blood loss in patients undergoing retropubic prostatectomy: a double-blind placebo:controlled randomized trial. Lancet; 361 : 201- 5.

29. Raobaikady R. ; Redman R. ; Ball J.A.S.; Maloney G. & Grounds R.M. (2005) : Use of activated recombinant coagulation factor VII in patients undergoing reconstruction surgery for traumatic fracture of pelvis and acetabulum: a double-blind, randomized, placebo-controlled trial. Br J Anaesth. ; 94 : 586 - 91.

30. Lodge J.P. ; Jonas S. ; Oussoultzoglou E. ; Malago M.; Jayr C.; Cherqui D.; Anthuber M.; Mirza D.F. ; Kuhlman L. & Bechstein W.O. (2005) : Recombinant coagulation factor VIIa in major liver resection: a randomized, placebo controlled, double-blind clinical trial. Anesthesiology ; 102 : 269 - 75.

31. Spahn D.R.; Tucci M.A. & Makris M. (2005) : Is recombinant FVIIa the magic bullet in the treatment of major bleeding. Br J Anaesth, ; 94 (5): 553 - 5.