British Journal of Medicine & Medical Research
11(6): 1-14, 2016, Article no.BJMMR.20737
ISSN: 2231-0614, NLM ID: 101570965

SCIENCEDOMAIN *international*
www.sciencedomain.org

Use of Recombinant Factor VIIa in Obstetrics

Neena Chuni[1*] and Sachchithanantham Kanagasabai[1]

[1]Department of Obstetrics and Gynaecology, Melaka Manipal Medical College, Malaysia.

Authors' contributions

This work was carried out in collaboration between both authors. Author NC planned the study, managed literature search and wrote the manuscript. Both authors NC and SK read, edited and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2016/20737
Editor(s):
(1) Yoshihiro Nishida , Department of Obstetrics and Gynecology, Faculty of Medicine, Oita University, Yuhu-City, Japan.
Reviewers:
(1) Magdy Abdelrahman Mohamed, Sohag University, Egypt.
(2) D. S. Sheriff, Benghazi University, Benghazi, Libya.
Complete Peer review History: http://sciencedomain.org/review-history/11632

Review Article

Received 6th August 2015
Accepted 14th September 2015
Published 29th September 2015

ABSTRACT

The objective of this review article was to evaluate the current literature on the increasing off-label use of rFVIIa in the management of critical obstetric haemorrhage. Given the lack of high-level evidence, there is a need to review the clinical indications, observed response and adverse events. This review is designed to aid practitioners in deciding when and how to administer rFVIIa; since the current evidence from observational studies shows that benefits outweigh risks in its use as an adjunct to conventional treatment in massive haemorrhage. However, pregnancy is a potentially thrombogenic state, hence a cautious approach is required in patients with risk factors for thromboembolic complications.

Keywords: rFVII; obstetric haemorrhage; postpartum acquired haemophilia; Jehovah's witnesses.

1. INTRODUCTION

Recombinant Factor VIIa (rFVIIa) was first introduced in 1998 for patients deficient in factor VIII and factor IX, who did not respond to replacement therapy due to presence of inhibitory antibodies [1]. It is currently licensed for the treatment of bleeding episodes in patients with congenital haemophilia A or B and who have developed inhibitors to factors VIII and IX, and in patients with factor VII deficiency or Glanzmann's thrombasthenia who are refractory to treatment [2]. In 2001 successful off-label use was reported during caesarean delivery and

**Corresponding author: e-mail: nchuni@gmail.com;*

several other case reports and small series have been published in 2003-2004 [3]. When medical agents and conservative surgical procedures fail, hysterectomy is usually needed as a final measure to control the bleeding. However, peripartum hysterectomy is a radical procedure causing loss of fertility and physical and psychological trauma and carries a significant morbidity even when performed by experienced surgeons [4]. Depressive disorders are known to impair the QOL of women who have to undergo peripartum hysterectomy [5]. rFVIIa has shown promise in averting a life saving hysterectomy.

No study has so far specifically addressed the question whether fertility can be preserved by the use of rFVIIa through avoided postpartum hysterectomy; most studies have included patients who were treated with rFVIIa only at the time or soon after postpartum hysterectomy had been performed [6].

Major obstetric haemorrhage still contributes to maternal mortality and morbidity worldwide, with an incidence ranging from 1% of deliveries in developed countries to 10% in developing countries [7,8,9,10]. The incidence of PPH not responding to classic obstetric manouvres and uterotonic drugs is reported to be 1.0-1.8 in 1000 deliveries [11].

One woman in every 4300 giving birth in the UK is managed with rFVIIa, surgical or radiological therapies for postpartum haemorrhage (PPH). Recombinant FVIIa was used as an initial second line therapy in 6% of the women and was successful in 31%. Majority of the women required additional management, suggesting that it may be used as part of a combination approach to treating PPH [12].

We performed a literature (MEDLINE) search to review the relevant articles in English literature on the use of rFVIIa. Randomised studies usually the best way to compare different second line therapies are not available and it is unlikely they will ever be performed in patients with life-threatening haemorrhage. The results of the two registries (North European [13] and Australia and New Zealand [6]) have included larger series, however, these are collected data from many centres with different inclusion criteria and different management strategies for PPH. Comparison between different second line therapies is difficult, as usage depends on the clinical situation and available resources and each treatment has its own indications.

2. MECHANISM OF ACTION

Recombinant FVIIa works locally where tissue factor is exposed at sites of injury and activated platelets are found. The role of FVIIa in the induction of haemostasis includes direct activation of factor IX to factor IXa and factor X to factor Xa following the binding of FVIIa to exposed tissue factor. Binding of factor VIIa or rFVIIa to tissue factor initiates the coagulation cascade. At pharmacological doses, rFVIIa directly activates factor X on the surface of activated platelets at the site of injury independently of tissue factor, and factors VIII and IX. The mechanism of action involves activation of platelets via a tissue factor dependent and a tissue factor independent pathway which leads to a thrombin burst and formation of a stable clot at pharmacological doses [14]. In addition, rFVIIa also inhibits fibrinolysis by activating thrombin-activable fibrinolysis inhibitor (TAFI) [15]. The effect is theoretically localized only at the site of vessel injury without systemic activation of the coagulation cascade [16]. Since its action is reported to be direct and localized at damaged sites, therefore interest in potential uses of rFVIIa in cases of haemostatic failure has become widespread as an off-label indication [17].

3. EVIDENCE FROM PUBLISHED LITERATURE

3.1 Use in Obstetric Haemorrhage

A survey from UK suggested that life threatening haemorrhage might occur in 6.7 per 1000 deliveries [18] due to uterine atony, placenta praevia or accreta, uterine rupture, birth canal injuries or amniotic fluid embolism. Management involves the newer, less radical measures that may preserve reproductive function, such as angiographic embolization, uterine compression sutures and methods involving uterine tamponade and if all else fail, long established surgical measures such as internal iliac artery ligation and subtotal or total hysterectomy. Embolization of both uterine arteries is an option to treat severe PPH, however 24 hour availability of emergency interventional radiology service is necessary. Administration of rFVIIa has been reported to be life saving in many institutions [19], but the practice of using rFVIIa in PPH is not uniform [20], although some preliminary guidelines have been published [21,22].

In obstetrics, the experience with the use of rFVIIa to control haemorrhage has been limited to case reports and retrospective studies. To our knowledge, there has not been any randomized trial. The main indications for its use include diffuse bleeding as a sign of coagulopathy, or deranged haematological values particularly where there is evidence of coagulation defect that is most likely manifested as prolonged INR, as a life saving alternative to extreme surgical procedures such as hysterectomy. It would be of no value in the event of arterial bleeding, when surgical intervention or embolization is required. In a series of 12 cases of major obstetric haemorrhage, rFVIIa was used with a dose range of 42-120 µg/kg with good or partial response in 11 cases with a dramatic reduction in transfusion requirements [2]. In another report, rFVIIa was effective in three cases of obstetric haemorrhage [23]. In two out of these three cases, bleeding continued inspite of hysterectomy and internal iliac artery ligation. It has also been used in two cases of uncontrolled haemorrhage secondary to extensive vaginal lacerations and amniotic fluid embolism where a favourable outcome was observed [24].

As a prophylactic treatment, intravenous rFVIIa was used at a dose ranging between 35-50 µg/kg in a primigravida who was diagnosed at 20 weeks with factor VII deficiency, which is a rare autosomal recessive hereditary condition. She had a normal labour and uncomplicated postpartum period [25]. Glanzmann's thrombus-thenia is another rare hereditary autosomal recessive platelet function disorder, which can cause major haemorrhage at delivery. Prophylactic use of rFVIIa together with platelet transfusion could effectively prevent PPH in these patients [26].

Although questions relating to the role of rFVIIa in fertility or reducing maternal morbidity or mortality can only be answered by a randomized controlled trial, analysis of registry data may provide information relating to the current clinical use of rFVIIa and identify major trends in outcome or adverse events and provide hypothesis for future studies. There have been large studies of registry data: The North European FVIIa in Obstetric Hemorrhage Registry (NEFOH) and a registry from Australia and New Zealand.

The Australian and New Zealand Haemostasis Registry, one of the largest reported case series of rFVIIa use in PPH was developed to analyse safety and efficacy data on the increasing off-label use of rFVIIa, including use in obstetric haemorrhage. The Australian study considered 694 cases from 37 hospitals who reported to the Hemostasis registry which collects retrospective and contemporaneous data on all use of rFVIIa at participating institutions for non haemophiliac patients with critical bleeding [27]. Obstetric bleeding totalled 4% (n=27) of these cases; 68% of the obstetric patients were deemed to have shown a decrease or cessation in bleeding and 85% of patients survived upto 28 days. Overall, forty-four adverse events (6% of patients) were considered to be possibly linked to the administration of rFVIIa and two adverse events were thought to be directly related to the administration of rFVIIa (clots in drains with tamponade and right atrial thrombus formation). The events considered possibly related to rFVIIa include three pulmonary emboli and eight cerebrovascular accidents. No adverse events associated with rFVIIa were identified in the obstetric group. The clinically determined positive response rate with severe PPH was 76% with 64% (forty-three patients) responding after a single dose and a reduction in blood product use after administration; despite institutional variability and the absence of standardized protocol guiding timing of rFVIIa administration. 41% had a hysterectomy before administration of the drug. Only 13 (21%) required hysterectomy following administration of rFVIIa. Two women developed VTE after receiving the drug. Although the lack of a control group and variations in the clinical situations limits the conclusion that can be drawn from this large series, the strength of this dataset is an obligation of participating hospitals to provide complete patient capture, thus avoiding bias from selective case reporting. It should be noted however, that this outcome measure is a subjective judgment made by the treating clinician and is one of the limitations of this study.

NEFOH collected data from 9 European countries between 2000 and 2004 [13]. In all, 65 out of 531 hospitals known to use rFVIIa reported its use in primary PPH in a total of 128 patients, 113 forms were returned (88%), with 97 (86%) classified as treatment (where other interventions had failed) and 16 (14%) as secondary prophylaxis (usage to support other successful interventions): Five cases were excluded due to secondary haemorrhage (Four) and DIC (one). Improvement (defined as reduced bleeding) was found in 80% of treatment patients and in 75% of the secondary prophylaxis group. Failure to

respond (defined as bleeding unchanged or worse) was seen in 15 cases.

The most recent review on the use of rFVIIa in life threatening PPH was carried out by Franchini et al. [28]. Efficacy in stopping or reducing the bleeding was reported in 88% cases, but the authors advised caution in interpreting these results. They suggested a bolus dose of rFVIIa of 60-90 μg/kg should be given before considering hysterectomy, but they also pointed out that rFVIIa should not be considered as a substitute, nor should it delay the performance of an invasive procedure such as embolization or conservative surgery. An earlier review article published by Franchini in 2007 [29] presented data on 65 patients who received rFVIIa for obstetric PPH, although 7 of these had a congenital disorder of coagulation. The efficacy of the drug was defined as reduction or cessation of haemorrhage but, when used as secondary prophylaxis in patients with congenital coagulation disorders, the desired endpoint was prevention of further bleeding. The efficacy was deemed to be 95% in PPH. There were no adverse events reported in any of the cases reviewed, but the authors were unable to determine whether the use of factor VIIa reduced the rate of hysterectomy, as in many cases this had been performed before administration of the product.

The largest case series is that reported by Ahonen and Jokela [2] who presented 12 cases of severe PPH treated with rFVIIa in addition to standard surgical and medical interventions; a good response was obtained in 11 of these cases. In 5 of these 12 cases, hysterectomy was performed before the administration of rFVIIa. They reported a 50% incidence of partial failure and 5% complete failure rate. All patients required radiological embolization. However, as rFVIIa was effective in avoiding hysterectomy in most of the remaining women, the authors concluded that in cases of intractable PPH with no other obvious indications for hysterectomy, administration of rFVIIa should be considered before surgery, however the indications for rFVIIa administration rather than selective arterial embolization remain to be determined.

Ahonen et al. [21] retrospectively compared 26 parturients who had received rFVIIa with 22 parturients also treated for PPH but without rFVIIa during the same period. Haemorrhage was more severe in the group receiving rFVIIa (more blood loss, coagulopathy and need for transfusion). Nevertheless, the response was considered good in 66% of these women and no additional interventions were required except suturing vaginal lacerations. In those showing poor or no response, the ongoing bleeding was arterial. One patient treated with rFVIIa suffered a pulmonary embolism and was subsequently found to have antithrombin deficiency. The study concluded that there was no evidence to extend the use of rFVIIa into less severe cases of PPH as this policy would result in a profound increase in the overall costs of the treatment. The value of these two studies is limited by their retrospective nature and small patient numbers.

A further study retrospectively identified 34 patients with PPH of greater than 1500 ml over a 19-month period, 18 of whom had received rFVIIa [19]. Patient treatment and data collection were performed at a single centre in Pakistan, and statistical analysis undertaken in Yale university, USA. The subjects who had been given rFVIIa had lower maternal mortality [28% vs 50%; OR 0.04] and received a lower number of packed red-cell transfusion, (p=0.007) than the comparison group, despite lower hemoglobin levels (p=0.02) and more severe coagulopathies determined by PT and APTT (p=0.03 and p=0.05). There was no difference in the rate of hysterectomy between the two groups, drug was administered as a last resort when all other treatment options (including hysterectomy) failed to control bleeding. Their experience suggests that earlier drug administration may improve fertility outcomes and also avoid dilutional coagulopathy.

Another large review of published case reports performed by Scarpelini et al. [30] in 2007, examined 24 publications describing the use of rFVIIa in 56 patients. In 50 cases (89%) the drug was used in patients without pre-existing disorders of coagulation, with the most common pathology being PPH; bleeding related to gynaecological oncology surgery (for pelvic sarcoma, vaginal sarcoma and endometrial cancer) and congenital haematological disease. The majority of patients received 90-120 μg/kg of rFVIIA repeated shortly afterwards if necessary. The efficacy of the drug, defined as cessation or significant decrease in bleeding, was 98% and no adverse events were reported.

Eight cases receiving recombinant activated factor VII in postpartum haemorrhage refractory to the conventional therapy in a Taiwanese hospital were analyzed retrospectively [31]. A good response, defined as bleeding control in 15 minutes was achieved in 6 patients (75%) with a

single dose ranging from 55 to 105 µg /kg. The 2 patients with poor response had unsolved birth canal injuries. The authors recommend that any surgical bleeding should first be controlled, as well as the correction of metabolic and hematological abnormalities, however, in intractable PPH, rFVIIa offers a salvage therapy and should be considered early, even before hysterectomy.

3.2 Use of rFVIIa in Postpartum Acquired Haemophilia A

Postpartum acquired haemophilia A, characterized by postpartum development of an inhibitor against FVIII, constitutes 7-21% of acquired haemophilia A cases and is a rare but serious complication of pregnancy associated with PPH [32,33]. Pregnancy associated FVIII inhibitors must be recognized early to decrease maternal morbidity and mortality, since these women do not usually have a personal or family history of bleeding episodes; the presence of unexplained excessive and /or prolonged vaginal bleeding or large soft-tissue haematomas from multiple sites during the postpartum period may lead the obstetrician to suspect a coagulation inhibitor [34]. The diagnosis of an inhibitor is confirmed by specific assays of the factor and the inhibitor using Bethesda assay. Vaginal bleeding is the predominant symptom if the inhibitor develops within few days after delivery, while ecchymoses and soft-tissue bleeding are more frequent if the postpartum FVIII inhibitor appears later. The therapeutic options used to control bleeding include agents which can increase plasma FVIII levels (i.e. desmopressin and FVIII concentrates) in clinically mild cases with low inhibitor titres; and by-passing agents (activated prothrombin complex concentrates and rFVIIA) in patients with high titre FVIII antibodies and severe bleeding [35,36].

Mazzucconi et al. described four postpartum inhibitor cases treated with high dose immune-globulin and dexamethasone; in two women, symptoms were stopped by the concomitant use of rFVIIa at a dose of 90 µgm/kg every 12 hours for 12 days. rFVIIa has been successfully used for the home treatment of women with postpartum FVIII inhibitors [37].

3.3 Management of Uterine Atony

The most common indication for obstetric hysterectomy is atonic PPH. Successful use of rFVIIa has been reported along with infusion of sulprostone (a metabolism resistant PGE_2 analogue) where uterotonics had failed [2]. In patients where hysterectomy is not desired for preservation of fertility, continued haemorrhage would lead to tissue hypoxia and exacerbate the atony. In such situations the role of rFVIIa in controlling bleeding would be uterus and fertility preserving.

3.4 Temporary Haemostasis While Awaiting Vascular Embolization

The use of recombinant activated factor VIIa to stabilize haemodynamics has been reported as a temporary measure while awaiting vascular embolization which finally stopped the bleeding [38]. Bleeding in traumatic PPH is sometimes difficult to control. In such cases, the most effective approach is vessel ligation. However, it might be difficult to stop the bleeding surgically in case of arterial bleeding caused by a deep vaginal laceration. Radiological arterial embolization takes a long time to perform, and this is not indicated when haemodynamics are not stable [39]. When surgical haemostasis is deemed to be prohibitive, treatment similar to blunt trauma (e.g. compression) should be performed to stabilize haemodynamics, and low dose rFVIIa to temporarily stop the bleeding should be considered for the purpose of transitioning to interventional radiology [39].

3.5 Fertility Preservation-preventing Hysterectomy in PPH

There is a potential role of rFVIIa in the modification of surgical management of major PPH. Angiographic embolization and hysterectomy are both accepted therapies in major PPH refractory to conservative treatment [40]. Where fertility is desired embolization maybe the treatment of choice; the major limitation is access to interventional radiology on site. Choosing between options maybe difficult in clinical situations as clear evidence based indications are yet undefined. Recombinant FVIIa would be more appropriate in diffuse bleeding but bleeding which is localized and not amenable to surgical measures, such as bleeding from the lower uterine segment, where hysterectomy is traditionally done [41], embolization would be an option for fertility preservation [40]. Administering rFVIIA may allow time to transfer the patient to facilities where interventional radiology is available [40]. In a series of cases of use of rFVIIa in obstetric haemorrhage, five out of 12 patients underwent embolization after rFVIIa use:

Four patients responded to rFVIIa even though bleeding did not completely stop [2]. Earlier case series have reported on patients who underwent hysterectomy before rFVIIa was administered [2,19,20,30]. Some recent case reports confirm that use of rFVIIa may prevent hysterectomy [24]. Therefore a fertility saving role for rFVIIa exists, due to its quick onset of action, by observing patients for some time after administering the drug, before a decision is taken to proceed with hysterectomy [40,42].

3.6 Use After Surgery

Patients often need management in intensive care or high dependency units after surgery for massive haemorrhage, especially in cases where exploratory laparotomy has not revealed a traumatic cause such as uterine rupture or bleeding vessels. Cases have been reported where rFVIIa led to quick postoperative recovery in terms of drain outputs, use of blood components and need for return to operation theatres for additional procedures [43,44].

3.7 Use in Jehovah's Witnesses

Transfusion of blood and blood products is regarded as unacceptable, while rFVIIa a synthetic agent, remains an acceptable treatment to many Jehovah's witnesses. A case report on successful treatment of postpartum haemorrhage in a Jehovah's witness patient, controlled with Tissel, tranexemic acid and recombinant factor VIIa has been described [45]. Hysterectomy is reserved for intractable haemorrhage in the unstable patient – Internal iliac artery ligation maybe riskier in a patient who cannot be resuscitated with blood products, because there is always a risk of inadvertent vascular injury occurring during the procedure. The optimal dose for the arrest of PPH has not been described, but standard dose is 40 µg/kg to 65 µgm/kg with repeated administration if no clinical improvement is seen after 15 to 30 minutes. The management of these patients experiencing massive haemorrhage is a clinical challenge that requires a multidisciplinary approach, as well as a combination of traditional and novel therapies, to optimize the outcome [46].

4. ADMINISTRATION OF rFVIIa

There is paucity of data on the dosage and frequency and timing of administration of rFVIIa in non obstetric haemorrhage. The evidence presented below is based on experience of its use in obstetric, trauma, cardiac surgery and orthopaedic haemorrhage.

4.1 Guidelines on the Use of rFVIIa

Alec Welsh, Claire McLintock et al. have described guidelines for the use of rFVIIa [22]. Since its use in post-partum haemorrhage is off-label, the decision to use rFVIIa rests with the treating clinician. Patients at high risk of postpartum haemorrhage should be identified early; anaemia should be corrected in the antenatal period and ideally all patients should have active management of third stage of labour [22]. Interventions to control critical bleeding should be carried out before initiating administration of rFVIIa. Local transfusion experts should be informed early for a possible need for activating massive blood transfusion protocols and if bleeding is persistent and unresponsive to medical therapy, transfusion of blood and blood components should be considered as necessary. Appropriate surgical or radiological intervention should be carried out based on local practice and resources. Once all surgical and non-surgical definitive haemostasis procedures have been attempted, and bleeding continues with between 8 and 12 units of packed red blood cells transfused, rFVIIa could be considered prior to hysterectomy. If bleeding persists after two doses of rFVIIa, hysterectomy should be considered [22]. The authors advise that rFVIIa should be used where the clinician is of the opinion that benefits outweigh the risks of critical bleeding. Following administration of rFVIIa women have to be monitored for signs of improvement and adverse events [22]. Where there is increased thrombogenic risk, physical methods should be adopted immediately, and pharmacological measures (prophylactic dose of unfractionated or Low molecular weight heparin) should be considered within 24 hours of cessation of haemorrhage [22].

Wolfgang Henrich et al. [47] have outlined certain indications about off-label use of rFVIIa in obstetrics.

1. Serious obstetric bleeding refractory to adequate pharmacotherapy, surgery and blood component therapy.
2. rFVIIa does not replace adequate surgical, embolizing and conventional hemostatic measures; however rFVIIa may possibly avoid postpartum hysterectomy.
3. The decision to administer rFVIIa is jointly made by obstetricians, intensive care

specialists and, if possible, haemostasio-logists.
4. The effect of rFVIIa depends on several concomitant factors. Therefore, the maintenance of the parameters such as fibrinogen levels>100 mg/dl, Platelets >50,000 µL, Hb.8.0 gm/L and pH≥7.2 is paramount.
5. Informed consent of patient/relatives if possible.

Recombinant factor VIIa is expensive and should not be used to compensate for inadequate transfusion therapy; and is ineffective if there is shortage of the basic components of the coagulation cascade such as fibrinogen [48]. Furthermore, in case of no response to the first dose of rFVIIa, every effort should be made to treat localised bleeding by surgical intervention or selective arterial embolization [20]. There are some important factors which could reduce the efficacy of rFVIIa in treatment of coagulopathy, such as acidosis, hypoxia, hypothermia and a platelet count of less than $50x10^9$/L. A drop in pH from 7.4 to 7.0 could reduce rFVIIa activity by more than 90% [49]. Another study has recommended the following measures before considering administration of rFVIIa [50]:

1. Transfuse Red blood cells to aim for a haemoglobin level of 90-100 gm/L
2. Transfuse platelets to aim for a platelet count of more than $70x10^9$/L
3. Transfuse FFP/fibrinogen/cryoprecipitate to aim for a fibrinogen level of more than 2 gm/L.
4. Transfuse FFP to aim for prothrombin time and APTT less than 1.5 x the normal range
5. Try to avoid/ correct acidosis and hypothermia
6. Correct low ionized calcium
7. Rule out arterial bleeding (surgical interventions/arterial embolization)

It is of paramount importance to apply the rules of ITU care, in order to optimize the body homeostasis and to maximize the benefit of rFVIIa.

The only exception, for use of rFVIIa without blood product transfusion, is for the treatment of an unstable patient in an environment in which blood products are not immediately available or there is shortage of blood products. rFVIIa may be used as a temporary measure to reduce bleeding where the patient is transferred to a centre where more surgical expertise and selective arterial embolization are available [2].

4.2 Dosage and Frequency of Administration

The Australia and New Zealand guidelines suggest a dosing at 90 µgm/kg [6]. Most of the women (81%) were given a single dose of rFVIIa. Overall clinical response was 86% and 80% responded after a single dose [51]. It is recommended that all conventional procedures to control active bleeding should be attempted first, including transfusion of 8-12 units of packed red blood cells. Prior to making a decision to perform hysterectomy, 90 µgm/kg of rFVIIa can be injected as a bolus over 3-5 minutes; and repeated after 20 minutes if there is no response, provided that biochemical derangements (such as pH, calcium, platelets- target count >50,000/ µl and fibrinogen levels >100 gm/l) have been identified and corrected.

The dose used in several reports where bleeding was successfully controlled with a dramatic reduction in transfusion requirements when other conventional treatments had failed varied from 20 to 120 µgm/kg and there is no clear evidence of a dose-response relationship [2,3,52,53,54]. There have been no studies on the optimum dose of rFVIIa in obstetric haemorrhage. According to the consensus recommendations for the off-label use of rFVIIa therapy a mean dosage of 71 µgm/kg was capable to arrest bleeding with the lowest dosage of 36 µgm/kg body weight [55]. In most case series women received a single 90 µgm/kg dose, which is the recommended dose for patients with haemophilia [6,21,23]. The time elapsed until bleeding stopped ranged between 15 and 40 minutes.

In refractory PPH, it maybe recommended to start using the 90 µgm/kg dose and repeat if necessary. Because of off-label use the appropriate frequency of dosage in critical acute bleeding is not known. Typically a single dose is administered, but doses can be repeated every 2 hours with the number of doses varying from one to eighteen [40,50].

The short half life of rFVIIa has to be kept in mind but new long acting substitutes are being developed. Measuring the plasma level of rFVIIa may prove to be a helpful guide in determining the dose. Recent case reports suggest that rFVIIa at a dose of 90-100 µgm/kg maybe beneficial as a haemostatic agent in obstetric haemorrhage even in the presence of disseminated intravascular coagulation [23, 24,40,53].

In a large series of European patients , the most common recorded dose was ≤7.2 mg, which worked out to be a dose of ≤90 µgm/kg, for women weighing upto 80 kg. In 80% cases, an improvement was noticed after that single dose [13]. Ahonen and Jokela suggested that a lower dose (42-44 µgm/kg) was one of the reasons for a partial response compared with doses of 74-120 µgm/kg[2]. Sixty to 120 µg/kg body weight rFVIIa are commonly administered as a bolus. If severe bleeding persists, a second bolus of 60-120 µgm/kg body weight rFVIIa maybe administered following a period of 15 minutes to a maximum time of 60 minutes.

Pharmacokinetic studies have demonstrated that rFVIIa plasma clearance appears to be higher in patients with a high level of active bleeding, and this may have implications in adapting the dose regimen [54]. Since there is no biochemical test to monitor the clinical efficacy of rFVIIa, all studies have used a subjective assessment by the clinician. A reduction in the need for transfusing blood components, visual impression of decreasing blood loss and improvement in vital signs appear to be the best indicators of response to rFVIIa [56].

4.3 Timing of Use

Audits from trauma and cardiac surgery point towards increasing early use of rFVIIa as experience in its use increases [57]. A learning curve for anesthetists' and surgeons has been suggested [40]. Although evidence for timing of use in obstetrics is scant, audit from a recent case series has reported that use of blood products decreased from an average of 67.6 units to 37.2 units before administering rFVIIa, indicating a trend towards earlier use [57]. Choosing the optimal timing for its administration requires detailed assessment of the condition of the patient. The criteria should include haemoglobin, platelet count and most importantly the prothrombin time.

In most relevant reports, rFVIIa was applied in life threatening PPH as a desperate adjuvant after standard treatments failed. Nevertheless, Ahonen and Jokela recommended that rFVIIa should be considered before hysterectomy, especially in patients without requisite indications such as placenta accrete [2]. In their experience of 12 case series, rFVIIa was given early in seven cases, none of whom then required a hysterectomy. This is particularly meaningful for women who are concerned about their fertility or body image, however, applying such an expensive and unlicensed therapy still produces some hesitation. In addition, the risk benefit ratio may change with only mild-moderate PPH, although the current data regarding rFVIIa related adverse reactions appears reassuring.

Early use of rFVIIa following uterotonic agents and blood components and also shown to be effective in combination with surgical procedures for uterine atony, other than hysterectomy, such as square and B-lynch sutures. It was also used as a salvage treatment when hysterectomy failed to control bleeding. If rFVIIa is administered early, not only a hysterectomy but also the surgery related complications may be prevented [31].

In situations of intractable PPH, where a hysterectomy is otherwise not indicated, administration of rFVIIa can be considered as soon as possible in a few special situations: When blood is not available, in patients with acquired haemophilia, before packing the uterus or pelvis, and before resorting to laparotomy and peripartum hysterectomy. With a badly lacerated and edematous vagina after vaginal or instrumental delivery especially in cases of prolonged labour where traumatic PPH and atony maybe both contributing to haemorrhage rFVIIa should be considered early before haemodynamic instability sets in [58].

Before administering rFVIIa, haemoglobin levels should be preferably above 7 gm /dl, INR <1.5, and platelet levels above 50,000/µl. Fibrinogen levels of a minimum of 100mg/dl, preferably more than 150 mg/dl must be ensured. In case these parameters are deranged, they must be corrected by using appropriate therapy before rFVIIa administration. Also correction of the pH to ≥7.2 is recommended before rFVIIa administration because efficacy of rFVIIa decreases at a pH of ≤7.1. If required, bicarbonate maybe used to elevate the serum pH. Furthermore, body temperature should be restored to physiological values if possible, although rFVIIa is active in the presence of hypothermia. Therefore, it is recommended that decision to use rFVIIa should be taken early before metabolic derangements and features of disseminated coagulopathy set in [58].

The timing of use of rFVIIa in relation to a peripartum hysterectomy has been the subject of debate [57]. Whether rFVIIa should be given first in an attempt to avoid a hysterectomy should depend on the underlying cause of haemorrhage.

Clearly, an early hysterectomy would be needed for severe bleeding as a result of placenta accreta or uterine rupture. In women with uterine atony who have ongoing bleeding inspite of correction of coagulopathy, hypothermia, acidosis and hypocalcaemia, it may be reasonable to consider a trial of rFVIIa before a hysterectomy. When effective, an improvement in bleeding is seen within 10-15 minutes after the dose of rFVIIa, a short enough time to wait except in women with a very rapid ongoing blood loss. If ineffective, a second dose maybe tried, but further doses are not recommended [21].

There is controversy about the timing of use of rFVIIa with respect to peripartum hysterectomy [59]. The decision is to be based on the underlying cause of haemorrhage. An early hysterectomy would be appropriate for severe bleeding as in cases of placenta accreta or uterine rupture as the definitive management in these cases would be surgical whereas in women with atonic uterus it would be appropriate to consider pharmacological agents [60]. An improvement in bleeding is seen within 10-15 minutes after one dose of rFVIIa, a second dose maybe tried in the absence of severe ongoing haemorrhage but further doses are not recommended [22].

Franchini in 2007 [29] presented data on 65 patients. The efficacy was deemed to be 95% in PPH with a median dose (in those without congenital factor VII deficiency) of 73 ugm/kg. More than one dose of RFVIIa was administered in 27% cases. There were no adverse events reported in any of the cases reviewed, but the authors were unable to determine whether the use of factor VIIa reduced the rate of hysterectomy, as in many cases this had been performed before administration of the product.

According to the consensus recommendations for the off-label use of rFVIIa therapy [53] rFVIIa was given as the last resort before proceeding with hysterectomy as has been also proposed by a recently published Australian clinical guideline [22]. The treatment success of 91% to avoid hysterectomy is therefore evident even in the absence of an appropriately randomized control group. Thus the optimal timing of its usage should be prior to hysterectomy. Though protocols for optimal timing and use exist in other surgical specialities, there are no protocols developed for use in obstetrics, but it has been proposed that blood loss exceeding 1.5 maternal blood volumes should be an appropriate indicator to administer rFVIIa [57].

4.4 Safety, Adverse Events and Treatment Costs

Safety analysis data demonstrate very few non serious adverse events (13%) and less than 1% serious adverse events [61]. The non serious adverse events reported are vomiting, fever, pain at the local infusion area, headache, alterations in blood pressure and cutaneous hypersensitivity reactions.

Serious adverse events include arterial thrombotic events such as MI or ischemia, cerebrovascular disorders and bowel infarction, and thrombosis (25 per 100,1000 infusions) [62] and thrombotic events such as pulmonary embolism and thrombophlebitis [63]. It is recommended that rFVIIa is used with caution in the presence of sepsis, disseminated malignancy or following the use of other coagulation bypassing agents.

Recombinant FVIIa is a recombinant product and is not subject to paucity of blood, has no human protein and carries no risk of viral transmission. It causes a very low risk of anaphylaxis, has no anamnestic response and is an effective drug during and after surgery. However, it has a very short half-life and may require frequent, repetitive dosing, Inspite of which response is not always guaranteed and failure to respond may delay surgery and worsen the patients haemodynamic status. Cost and availability are also limitations to its use.

It has no measurable laboratory parameter for efficacy, which is judged only subjectively. It requires a venous access. It's high cost is one of the major drawbacks in its more liberal and frequent dosage. However it is pertinent to point out that rFVIIa may reduce costs of therapy and use of blood components in massive PPH. Ahonen and Jokella reported from Finland that a single dose of rFVIIa maybe equivalent to transfusing 50 units of red blood cells, treatment in ICU for 2 days or undergoing an embolization procedure [21].

Safety record of rFVIIa in its licensed indications is good to excellent with very few complications reported. However is it really so safe in off-license indications, especially in patients with risk factors for thrombotic complications? Pregnant patients are hypercoagulable. When rFVIIa is given early during life-threatening bleeding before severe coagulation abnormalities are present, thrombosis may occur. In fact, in the

excellent review by Haynes et al. [20] of all reported cases in which rFVIIa was used, thrombosis of the brachial artery occurred in one patient. One woman in registry data from Australia and New Zealand sustained an MI, although she had suffered a cardiac arrest before the administration of rFVIIa. Five of the treated women died and four women developed VTE after receiving FVIIa, one of these was felt to be unrelated to rFVIIA [13]. No thromboembolic complications due to rFVIIa were described in 140 patients treated with rFVIIA for PPH [21,64]. Thromboembolic events seem to occur at a low rate following rFVIIA use in obstetric haemorrhage: No cases were reported in the review by Franchini et al. [28] and only a few in the two registries, which could fall in the range of the incidence expected after severe PPH requiring surgery [6,13]. In other studies published to date no significant increase of thromboembolic events were found in the randomized and placebo-controlled studies on rFVIIa. In previously healthy patients with serious bleeding, the risk seems to be low even in patients with DIC [65].

The randomized evidence available for its off-license use is at best contradictory and inconclusive. Caution is required with input from haematology experts, prior to its use. Recent, European guidelines have pointed out that rFVIIa maybe considered as treatment for life threatening post-partum haemorrhage, but should not be considered as a substitute for, nor should it delay, the performance of a life saving procedure such as embolization or surgery, nor the transfer to a referring centre [66].

Despite having a very short half-life (2-6 hours), concerns about thromboembolism as a complication are real. A recent systematic review of the literature showed higher risk of arterial thrombosis (not venous) among patients who received rFVIIa as an adjuvant therapy for life–threatening bleeding [32]. Recombinant factor VIIa is not a substitute for surgical measures or transfusion of appropriate blood products. Fulfilling the pre-conditions will facilitate adequate functioning of the coagulation cascade [13]. Irrespective of whether a patient receives rFVIIa, massive PPH is by itself a risk factor for thrombosis and thromboprophylaxis should be given once the patient is stable [13,51]. Following administration of rFVIIA for PPH, it is recommended to monitor the patient for thromboembolic events [65].

5. CONCLUSION

The obstetric literature has numerous case reports and case series and registries involving the use of rFVIIa and response rates have varied from 75% to 88%, with one study reporting a 98% benefit. Overall, it appears that rFVIIa is effective in limiting the amount of blood products transfused, but data on survival benefit are lacking. Seventeen randomised controlled trials involving the use of rFVIIa have been published. Inspite of four studies reporting reduced blood loss and lesser need for transfusion of blood products, none of the studies have reported a survival benefit [67].

Publication bias is a major concern, as case reports and case series often focus on publishing successful cases and there is a lack of published randomized trials involving rFVIIa in obstetric practice. rFVIIa might prevent hysterectomy and appears to reduce bleeding. Ideally, a randomized controlled trial is needed to clarify whether rFVIIa is really this effective, although the difficulties of randomization in this setting are recognized. Multiple interventions have occurred in the studies quoted above and attribution of benefit to any of them is difficult.

The optimal dose is still unknown. Many reports in obstetric haemorrhage have used a dose of 90 µg/kg. If used in obstetric cases, deep vein thrombosis prophylaxis is recommended once the bleeding risk is considered low [68]. The drug maybe useful in obstetric cases with life threatening haemorrhage in the presence of coagulopathy. It may help in halting the coagulopathy process and lead to prompt control of bleeding. However it is necessary to simultaneously correct substrates deficiency, namely fibrinogen and platelets, for it to fulfill its role.

Injection of rFVIIa should also be considered for fertility preservation before hysterectomy in a young parturient with severe bleeding. It maybe difficult to set up an RCT to assess rFVIIa role in major obstetric haemorrhage, as the obstacles will include an insufficient number of cases to produce statistically significant results as well as the ethical issues related to withholding treatment in critically ill patients. Cohort studies may provide an alternative.

Major limitations to its use include information about safety when used in obstetric patients, cost and non-response in minority of patients.

An important clinical decision is to determine the optimal time to administer rFVIIa during the treatment pathway for PPH. This decision may vary depending on available resources, cost of blood products, depletion of blood bank stores and possible adverse effects related to massive transfusion per-se such as increased risk of thromboembolism.

In patients who do not accept blood or component transfusions (e.g. Jehovah's witnesses) rFVIIa is among one of the options which maybe life-saving and fertility preserving.

Close monitoring, and adherence to currently practiced dosage and timing schedules, is recommended until further results are available from randomized controlled trials or cohort studies.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Hedner U, Erhardsten E. Potential role of rFVIIa in transfusion medicine. Transfusion. 2002;42:114-24.
2. Ahonen J, Jokela R. Recombinant factor VIIa for life threatening postpartum haemorrhage. Br J Anaesth. 2005;94(5): 592-595.
3. Mercier FJ, Van de Velde M. Major obstetric haemorrhage. Anesthesiol Clin. 2008;26:53-66.
4. Knight M. UKOSS. Peripartum hysterectomy in the UK. Management and outcomes of the associated haemorrhage. BJOG. 2007;114(11):1380-7. Epub 2007 Sep 17. PMID: 17877772.
5. Lalinec-Michaud M, Engelsman F. Anxiety, fears and depression related to hysterectomy. Can J Psychiatry. 1985;30: 44-7.
6. Phillips LE, McLintock C, Pollock W, Gatt S, Popham P, Jankelowitz G, Ogle R, Cameron PA. australian and new zealand haemostasis registry. Recombinant activated factor VII in obstetric hemorrhage: Experiences from the Australian and New Zealand Haemostasis Registry. Anesth Analg. 2009;109(6):1908-15.

   DOI: 10.1213/ANE.0b013e3181c039e6.
7. Wissa I, Ebeid E, El-Shawarby S, Chandakas S, Kamal T, Hill N. Role of recombinant activated FVII in major obstetric haemorrhage: The farnborough experience. J Obstet Gynaecol. 2009; 29(1):21-4.

   DOI: 10.1080/01443610802628692.
8. Brice A, Hibert U, Roger-Christoph S, Fernandez H, Dumenil AS, Descorps-Declere A, et al. Recombinanat activated factor VII as a lifesaving therapy for severe postpartum haemorrhage unresponsive to conservative traditional management. Annales Francaisis Dánesthesie et de Reanimation. 2004;23:1084-1088.
9. Mousa HA, Walkinshaw S. Major postpartum haemorrhage. Curr Opin Obstet Gynaecol. 2001;13(6):595-603.
10. Sobieszczyk S, Breborowicz GH, Markwitz W, Mallinger S, Adamski D, Kruszynski Z. Effect of recombinant activated factor VII (RFVIIa) in a patient in haemorrhagic shock after obstetrical hysterectomy. Ginekol Pol. 2002;73(3):230-3. PMID: 12092258.
11. Bouma LS, Bolte AC, Van Geijn HP. Use of recombinant activated factor VII in massive PPH. Eur J Obstet Gynecol Reprod Biol. 2008;137:172-7.
12. Kayem G, Kurinczuk JJ, Afirevic Z, P Spark P, Brocklehurst P, Knight M. Specific second-line therapies for postpartum haemorrhage: A national cohort study. BJOG. 2011;118(7):856-64. DOI: 10.1111/j.1471-0528.2011.02921.x. Epub: 2011 Mar 10.
13. Alfirevic Z, Elbourne D, Pavord S, Bolte A, Van Geijn H, Mercier F, Ahonen J, Bremme K, Bødker B, Magnúsdóttir EM, Salvesen K, Prendiville W, Truesdale A, Clemens F, Piercy D, Gyte G. Use of recombinant activated factor VII in primary postpartum haemorrhage: The Northern European registry. 2000-2004. Obstet Gynecol. 2007;110(6):1270-8.
14. Franchini M. The use of recombinant activated factor VII in platelet disorders: A

critical review of the literature. Blood Transfuse. 2009;7(1):24-8.
DOI: 10.2450/2008.0015-08.

15. Hardy JF, Belisle S, Van der Linden P. Efficacy and safety of recombinant activated factor VII to control bleeding in nonhemophiliac patients: A review of 17 randomized controlled trials. Ann Thorac Surg. 2008;86(3):1038-48.
DOI: 10.1016/j.athoracsur.2008.05.013.
16. Hsia CC, Chin-Yee IH, Mc Alister VC. Use of recombinant activated factor VII in patients without hemophilia: A meta-analysis of randomized control trials. Ann Surg. 2008;248(1):61-8.
DOI: 10.1097/SLA.0b013e318176c4ec.
17. Mittal S, Watson HG. A critical appraisal of the use of recombinant factor VIIa in acquired bleeding conditions. Br J Haematol. 2006;133(4):355-63.
18. Waterstone M, Bewley S, Wolfe C. Incidence and predictors of severe obstetric morbidity: Case control study. British Medical Journal. 2001;322:1089-1094.
19. Hossain N, Shansi T, Haider S, Soomro N, Khan NH, Memon GU, Farzana T, Ansari S, Triche EW, Kuczynski E, Lockwood CJ, Paidas MJ, et al. Use of recombinant activated factor VII for massive postpartum haemorrhage. Acta Obstet Gynecol Scand. 2007;86(10):1200-6.
20. Haynes J, Laffan M, Plaat F. Use of recombinant activated factor VII in massive obstetric haemorrhage. Int J Obstet Anesth. 2007;16(1):40-49.
21. Ahonen J, Jokela R, Korttila K. An open non-randomized study of recombinant activated factor VII in major postpartum haemorrhage. Acta Anaesthesiol Scand. 2007;51(7):929-36. Epub 2007 May 4.
22. Welsh A, Mclintock C, Gatt S, Somerset D, Popham P, Ogle R. Guidelines for the use of recombinant activated factor VII in massive obstetric haemorrhage. Aust N Z J Obstet Gynaecol. 2008;48(1):12-6.
DOI: 10.1111/j.1479-828X.2007.00823.x.
23. Segal S, Shemesh IY, Blumenthal R, Yoffe B, Laufer N, Ezra Y, Levy I, Mazor M, Martinowitz U. Treatment of obstetric haemorrhage with recombinant activated factor VII (rFVIIa). Arch Gynecol Obstet. 2003;268(4):266-7. Epub 2002 Nov 7.
24. Boumeester FW, Jonkhoff AR, Verheijen RH, Van Geijn HP. Successful treatment of life-threatening postpartum haemorrhage with recombinant activated factor VII. Obstet and Gynecol. 2003;101(6):1174-6.
25. Eskandari N, Feldman N, Greenspoon JS. Factor VII deficiency in pregnancy treated with recombinant factor VIIa. Obstet Gynecol. 2002;99(5 part2):935-7.
26. Kale A, Bayhan G, Yalinkaya A, Yayla M. The use of recombinant factor VIIa in a primigravida with Glanzmann's thrombus-thenia during delivery. J Perinat Medicine. 2004;32(5):456-8.
27. Isbister J, Phillips L, Dunkley S, Jankelowitz G, McNeil J, Cameron P. Recombinant activated factor VII in critical bleeding; experience from the Australian and New Zealand Haemostasis Register. Intern Med J. 2008;38(3):156-65. Epub 2007 Oct 3.
28. Franchini M, Franchi M, Bergamini V, Salvagno GL, Montagnana M, Lippi G. A critical review on the use of recombinant factor VIIa in life-threatening obstetric postpartum haemorrhage. Semin Thromb Hemost. 2008;34(1):104-12.
DOI: 10.1055/s-2008-1066022.
29. Franchini M, Lippi G, Franchi M. The use of recombinant activated factor VII in obstetric and gynaecological haemorrhage. BJOG. 2007;114(1): 8-15.
30. Scarpelini S, Nascimento B, Tien H, Netto FACS, Tremblay L, Rizoli S, et al. Overview on the use of recombinant factor VIIa in obstetrics and gynaecology. Expert Rev Obstet Gynecol. 2007;2(2):217-26.
31. Jing-Yi Jan, Shin-Yu Lin, Chia-Hui Lin, Chien-Nan Lee, Shou-Zen Fan, Yin-Yi Han. Recombinant activated factor VII as a promising adjuvant therapy for postpartum haemorrhage in the practice of obstetric anesthesia: Experience from a university hospital in Taiwan. J Obstet. Gynaecol. Res. 2011;37(7):901-7. Epub 2011 Mar 9.
32. Franchini M, Gandini G, Di Paolantonio T, Mariani G. Acquired hemo-philia A: Concise review. Am J Hematol. 2005; 80(1):55-63.
33. Franchini M. Postpartum acquired factor VIII inhibitors. Am J Haematol. 2000; 81(10):768-73.
34. Hay CR. Acquired haemophilia. Baillieres Clin Haematol. 1998;11(2):287-303.
35. Shobeiri SA, West EC, Kahn MJ, Nolan TE. Postpartum acquired hemophilia (factor VIII inhibitors): A case report and review of the literature. Obstet Gynaecol Surv. 2000;55(12):729-37.

36. Mazzucconi MG, Bizzoni L, Giorgi A, Morano SG, Peraino M, Russo M, Alimena G. Postpartum inhibitor to factor VIII: Treatment with high-dose immunoglobulin and dexamethasone. Haemophilia. 2001; 7(4):422-7.
37. Santagostino E, Gringeri A, Mannucci PM. Home treatment with recombinant activated factor VII in patients with factor VIII inhibitors: The advantages of early intervention. Br J Haematol. 1999;104(1): 22-6.
38. Ogawa M, Akahira Y, Takahashi S, Shimoda Y, Sato M, Sato A, Terada Y. Low-dose recombinant activated factor VII temporally stopped bleeding from small artery in severe postpartum haemorrhage: A case report. Blood Coagul Fibrinolysis. 2013;24(3):344-6.
39. Dupont C, Touzet S, Colin C, Deneux-Tharaux C, Rabilloud M, Clement HJ, Lansac J, Colle MH, Rudigoz RC; Groupe PITHAGORE 6. Incidence and management of postpartum haemorrhage following the dissemination of guidelines in a network of 16 maternity units in France. Int J Obstet Anesth. 2009;18(4):320-7.
40. Karalapillai D, Popham P. Recombinant factor VIIa in massive postpartum haemorrhage. Int J Obstet Anesth. 2007; 16(1):29-34.
41. Mitty HA, Sterling KM, Alvarez M, Gendler R. The surgical management of postpartum haemorrhage; Prophylactic and emergency arterial catheterization and embolotherapy. Radiology. 1993;188(1): 183-7.
42. Spahn DR, Tucci MA, Makris M. Is recombinant FVIIa the magic bullet in the treatment of major bleeding? Br J Anaesth. 2005;94:553-5.
43. Price G, Kaplan J, Skowronski G. Use of recombinant factor VIIa to treat life-threatening non-surgical bleeding in a post-partum patient. Br J Anaesth. 2004; 93(2):298-300.
44. Zupancic Salek S, Sokolic V, Viskovic T, Sanjung J, Simic M, Kastelan M. Successful use of recombinant factor VIIa for massive bleeding after caesarean section due to HELLP syndrome. Acta Haematol. 2002;108(3):162-3.
45. Tarek SA, Ahmad BA, Ken M. J Obstet Gynaecol Can. 2010;32(10):984-87.
46. Milligan L, Bellamy M. Anaesthesia and critical care of Jehovah's witnesses. Br J Anaesth (CEACCP). 2004;4:33-5.
47. Henrich W, Surbek D, Kainer F, Grottke O, Hopp H, Kiesewetter H, Koscielny J, Maul H, Schlembach D, von Tempelhoff GF, Rath W. Expert panel recommendation: Diagnosis and treatment of peripartum bleeding. J Perinat Med. 2008;36(6):467-78.
48. Lewis LR, Brunken P, Lemire SJ, Lemire SJ, Kaufman RM. Failure of recombinant factor VII a to correct the coagulopathy in a case of severe postpartum hemorrhage. Transfusion. 2009;49(4):689-95.
49. Meng ZH, Wolberg AS, Monroe DM III, Hoffman M. 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(5): 886-91.
50. Ahonen J. The role of recombinant activated factor VII in obstetric haemorrhage. Curr Opin Anesthesiol. 2012;25(3):309-14.
51. James AH, McLintock C, Lockhart E. Postpartum haemorrhage: When uterotonics and sutures fail. Am J Hemat. 2012;87(1):S16-22.
52. Tanchev S, Platikanov V, Karadimov D. Administration of recombinant factor VIIa for the management of massive bleeding due to uterine atonia in the post-placental period. Acta Obstet Gynecol Scand. 2005; 84(4):402-3.
53. Boehlen F, Morales MA, Fontana P, Ricou B, Irion O, Moerloose P. Prolonged treatment of massive postpartum haemorrhage with recombinant factor VIIa: Case report and review of the literature. Br J Obstet Gynaecol. 2004;4:284-7.
54. Huber AW, Raio L, Alberio L, Ghezzi F, Surbek DV. Recombinant human factor VIIa prevents hysterectomy in severe postpartum hemorrhage: Single center study. J. Perinat Med. 2012;40(1):43-9.
55. Shander A, Goodnough LT, Ratko T, Matuszewsi KA, Cohn S, Dhringer M, et al. Consensus recommendations for the off-label use of recombinant human factor VIIa (Novoseven) therapy. P&T. 2005;30:644-56.
56. Martinowitz U, Michaelson M. Guidelines for the use of recombinant activated factor VII (rFVIIa) in uncontrolled bleeding: A report by the Israeli Multidisciplinary rFVIIa task force. J Thromb Hemost. 2005;3(4):640-8.

57. Mc Call P, Story D, Karalapillai D. Audit of factor VIIa for bleeding resistant to conventional therapy following complex cardiac surgery. Can J Anaesth. 2006;53: 926-33.
58. Magon N, Babu KM, Kapur K, Chopra S, Joneja GS. Recombinant activated factor VII in postpartum haemorrhage. Niger Med J. 2013;54(5):289-294.
59. Nicklin J, Perrin L, Crandin A, Land R, Nascimento M, Obermair A. Re: Guidelines for the use of recombinant activated factor VII in massive obstetric haemorrhage. Aust N Z J Obstet Gynaecol. 2008;48(4):447.
60. McLintock C, James AH. Obstetric hemorrhage. J Thromb and Haemost. 2011;9:1441-51.
61. Roberts HR, Monroe DM, Hoffman M. Safety profile of recombinant factor VIIa. Semin Hematol. 2004;41(1 Suppl 1):101-8.
62. Aledort LM. Comparative thrombotic event incidences after infusion of recombinant factor VIIA versus factor VIII inhibitor bypass activity. J Thromb Haemost. 2004;2(10):1700-8.
63. Vincent JL, Rossaint R, Riou B, Ozier Y, Zideman D, Spahn DR. Recommendations on the use of recombinant activated factor VII as an adjunctive treatment for massive bleeding-A European perspective, Crit Care. 2006;10(4):R120.
64. Moscardo F, Perez F, de la Rubia J, Balerdi B, Lorenzo JI, Senent ML, et al. Successful treatment of severe intra-abdominal bleeding associated with disseminated intravascular coagulation using recombinant activated factor VII. Br J Haematol. 2001;113:174-6.
65. Levi M, Levy JH, Anderson HF, Truloff D. Safety of recombinant activated factor VII in randomised clinical trials. N Engl J Med. 2010;363(19):1791-800.
66. Surbek D, Huber A, Alberio L, Meyer-Wittkopf M, Raio L. The role of recombinant factor VIIa in the treatment of severe postpartum haemorrhage: Can fertility be preserved? Am J Obstet Gynecol. 2006;195(Suppl 1):S92.
67. Johansson PI, Ostrowski SR, Secher NH. Management of major blood loss: An update. Acta Anaesthesiol Scand. 2010;54(9):1039-49.
68. Pacheco LD, Saade GR, Gei AF, Hankins GD. Cutting-edge advances in the medical management of obstetrical haemorrhage. 2011;205(6):526-32.

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/11632