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REVIEW

Recombinant Activated Factor VII: A Solution to Refractory Haemorrhage in Vascular Surgery?

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Objectives. *Post-operative haemorrhage is a recognised complication and independent predictor of outcome in complex vascular surgery. The off-license administration of activated Recombinant Factor VII (rFVIIa) to treat haemorrhage in other surgical settings has been investigated, but concerns over potential adverse events have limited its use in vascular surgery. This article reports rFVIIa's method of action and systematically reviews rFVIIa's role in complex vascular surgery.*
Methods. *A systematic literature search identified articles reporting on rFVIIa administration within vascular surgery patients. Patient-specific data regarding transfusion requirements was extracted and pooled statistical analysis performed.*
Results. *15 articles reporting 43 patients were identified. RFVIIa has been administered in open and endovascular procedures and in both elective and emergency settings. Major aortic surgery accounted for 75% of cases. The range of rFVIIa administered as a cumulative dose was large, as was the variation in initial dose. Transfusion data from 9 patients was pooled and analysed. Significant differences were found between pre- and post- rFVIIa for packed red cell transfusions (mean 29.2 vs. 8.2,* $p = 0.015$*). Intra-arterial thrombosis was reported in 3 cases.*
Conclusions. *RFVIIa may reduce haemorrhage in selected vascular surgical patients. Randomized controlled trials are justified to definitively investigate its role within this setting.*

Keywords: Haemorrhage; Recombinant FVIIa; Vascular Diseases; Surgery; Aneurysm.

Introduction

Complex vascular surgery, with or without extracorporeal circulatory support, is associated with altered haemostasis and increased post-operative bleeding, even in patients with normal preoperative coagulation parameters.[1,2] Excessive blood loss, and blood product transfusion requirements, are two key independent predictors of outcome in major vascular surgery patients.[3,4] Research into haemorrhage reduction in this setting includes the use of antifibrinolytics (e.g. aprotinin) and intra-operative autologous transfusion devices.[5–7] However these have met with limited results. The need for novel haemostatic solutions to refractory haemorrhage in vascular surgical patients therefore persists.

Recombinant factor VIIa (rFVIIa) (NovoSeven; NovoNordisk®, Bagsvaerd, Denmark) was first licensed for the treatment of haemorrhage in patients with hemophilia A or B with neutralizing auto-antibodies (coagulation inhibitors) to factor VIII or IX.[8,9] In 2005 the United States Food and Drug Administration increased rFVIIa's license to include surgical procedures in the same patient group, and patients with congenital factor VII (FVII) deficiency.[10] The surgical literature increasingly reports the off-license administration of rFVIIa to arrest haemorrhage refractory to other interventions.[11–13]

Whilst off-label use of rFVIIa within vascular surgical practice has been reported, this has been predominantly within case reports or series [14–18] or as part of larger cohort studies of mixed patient groups,[19–21]

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and thus the role of rFVIIa in vascular surgery is currently unclear. In this paper we describe the mechanism of action of rFVIIa, systematically review the available evidence on the efficacy, dosage, safety and cost implications of rFVIIa use in vascular surgery, and formulate proposals for future research.

Mechanism of Action of rFVIIa

The molecular mechanisms by which rFVIIa induces the formation of a stable haemostatic plug remain unclear. Whilst it is generally agreed that rFVIIa enhances thrombin generation at sites of tissue injury, controversy exists regarding the mechanisms by which this comes about, particularly the source and role of the protein, Tissue Factor (TF).

In physiological conditions, TF is absent from vascular cells that come into contact with flowing blood and is present as an inactive pool on sub-endothelial cells. Vessel injury exposes this TF to the blood, where it binds and activates FVII. The resulting TF-FVIIa complex catalyzes the conversion of factor X into its active form (Xa), induces thrombin generation, and leads to fibrin formation and platelet activation.

The situation differs in pathological conditions. Within atherosclerotic plaques, vascular smooth muscles cells, monocytes and endothelial cells have all been reported to aberrantly express and expose TF to the circulation.[22] Not only has this been shown to be a critical event in atherothrombosis, but this expression and exposition has been shown to occur at higher levels in patients with symptomatic coronary and carotid disease, suggesting a role for TF in plaque instability.[23,24] Elsewhere, pro-inflammatory cytokines released during the acute phase response, have been shown to induce the production and expression of TF on circulating neutrophils and monocytes.[25,26] Recently, controversy has arisen over the presence, concentration and function of 'micro-particles' of TF within circulating blood[27]; some authors have reported the presence of physiologically active blood-borne TF[28–30] whilst others have refuted it's existence.[31,32]

Regardless of location, the exact role that TF plays in Recombinant FVIIa's mechanism of action requires further clarification. Knowledge of the normal haemostatic process, plus the fact that rFVIIa appears to induce thrombosis at sites of tissue injury, led to the hypothesis that rFVIIa acts via a TF-dependent mechanism.[33–35] Whilst supported by various studies using different models,[36] the high plasma concentrations of rFVIIa required to induce haemostasis suggest that TF-dependent activation cannot be the sole mechanism. RFVIIa has been shown to directly activate Factor X on phospholipid vesicles, activated platelets or monocytes independently of TF,[37–39] although this process is much less efficient and has not been replicated by all groups.[40]

It is likely that rFVIIA probably functions via a combination of TF-dependent and TF-independent pathways. The level and location of TF expression in patients undergoing vascular surgery are likely to be significantly higher and more widespread than in normal subjects, due to their pre-existing atherosclerotic disease as well as the acute physiological disruption caused by major vessel surgery. Therefore the appropriateness of administering rFVIIa to these patients requires careful review.

Methods

Literature search

A Medline, Google Scholar, Embase, Ovid and Cochrane database search was performed to identify all studies concerned with the use of rFVIIa in vascular surgery. The following MeSH headings were used: ''recombinant FVIIa'', and ''vascular diseases'', ''aorta'', ''haemorrhage'', ''aneurysm'' and ''surgery''. The ''related articles'' function was utilised to broaden the search, and all abstracts, studies, and citations scanned and reviewed. Based on the title and abstract of the publication, we retrieved articles containing clinical data on the use of rFVIIa. References of the articles acquired were also searched manually. No language restrictions were made. Laboratory and animal studies were excluded. The latest date for this search was 1st May 2007.

Inclusion and exclusion criteria

We included any article that reported on the administration of rFVIIa to stop haemorrhage in patients who had undergone vascular surgery. For the purpose of this review, we defined 'vascular surgery' to include intervention upon the descending thoracic aorta (distal to the left subclavian artery), the remainder of the aorta distally and peripheral arteries. Aortic arch, valvular or coronary artery surgery was deemed to be the domain of the cardiothoracic surgeon. This area has been recently reviewed [11] and thus these patients or studies were excluded. In one instance, peripheral vascular intervention was required as a complication of cardiothoracic surgery and this patient was included as haemorrhage pertained to this portion of the procedure. Articles that studied the effect of

rFVIIa on a mixed cohort of patients, e.g. those in Intensive Care Units, were studied and data for vascular patients involved in those studies was extracted as far as possible. Publications or patients were excluded if they involved complex multiple trauma or the prophylactic impact of rFVIIa. Articles were classified as case reports or series, retrospective database (or chart) reviews, and clinical studies.

Data extraction and validation of studies

Three reviewers (EA, IVH, and DL) independently extracted the following data from each study: first author, year of publication, study population characteristics, study type, number of subjects, pathology and procedure type. Data was retrieved on the following outcomes of interest: Dosage (initial and cumulative), pre- and post-intervention transfusion requirements, adverse events (stroke, myocardial infarction and other thromboembolic effects) and mortality.

Data analysis

Outcome data was heterogeneous, and in some cases unavailable, and this prevented a formal meta-analysis being performed. However, where articles reported individual patient-specific data regarding blood product requirements prior to and after RFVIIa infusion this was extracted and a pooled analysis performed. Data are expressed either as raw count and percentages or as mean value plus or minus standard deviation. Kolmogorov-Smirnov test was performed to test normality of distributions and revealed the data to be normally distributed. Thus Paired Samples T-Test was performed. All statistical analysis was performed using SPSS 14.0 (SPSS Inc., Chicago, IL).

Results

Study identification

Fig. 1 outlines the systematic search strategy and results. 377 publications were identified of which 357 were excluded following title and abstract review. 21 publications were investigated in full. Of these, 6 further articles failed to meet our inclusion criteria and 1 study was excluded due to duplication in a report published by the same group one year earlier.[41] 1 further study was identified from a detailed reference check. 15 articles were therefore included in our study, 5 purely on vascular patients [14–18] and the remaining 10 regarding mixed populations containing some vascular patients.[19–21,42–48] Of the 15 articles, 5 were case reports or series,[15–18,42] and 10 were retrospective database or chart reviews.[14,19–21,43–48]

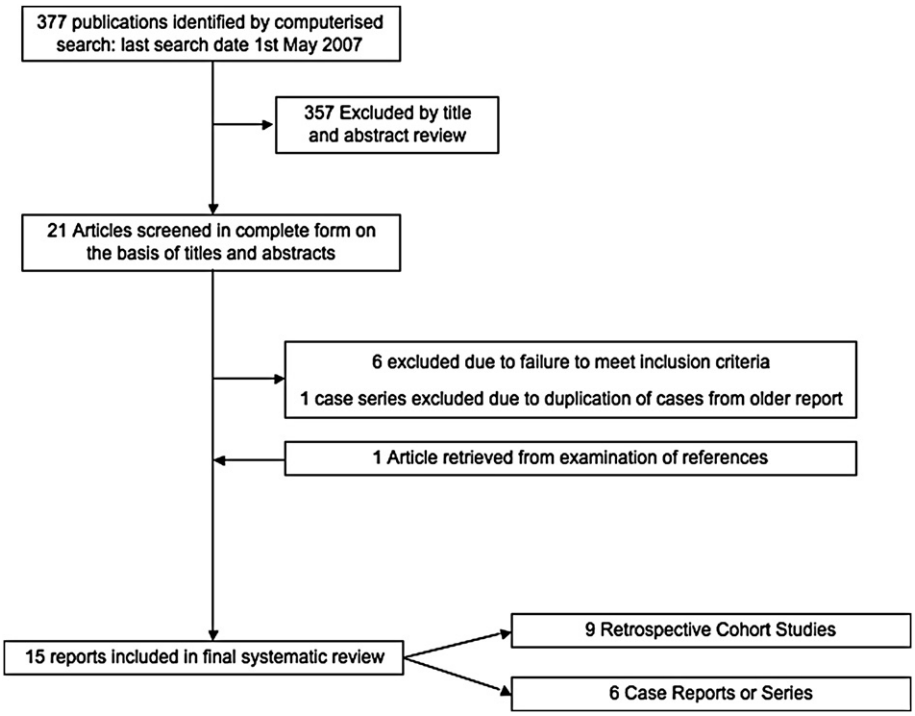

Fig. 1. 'Systematic Search Strategy'.

Case mix and patient demographics

The 15 articles reported on the administration of rFVIIa to a total of 273 patients, of whom 43 had undergone vascular surgery as previously defined. The patients ranged from 39 to 83 years of age, 51% were male, 26% female and in 23% the gender of the patient was not declared.

The variety of procedures performed upon rFVIIa-treated patients is outlined in Table 1. One patient received rFVIIa after two different operations separated by a 34 day period on the Intensive Care Unit,[16] and thus 44 procedural episodes are described in 43 patients. Unsurprisingly major thoracoabdominal or abdominal aortic (both supra- and infrarenal) surgery accounts for the vast majority of cases (75%). RFVIIa has been administered in both elective[18,48] and emergency[43] settings, to assist in the management of perioperative complications, such as evacuation of post-operative haematoma[14] and repair of leak,[42] and in both open and endovascular procedures. One major venous injury has been treated with rFVIIa,[19] and one patient had rFVIIa administered via a standard catheter directly into a false aneurysm of the descending thoracic aorta which had developed following thoracoabdominal aortic replacement.[17]

It was not possible to ascertain any accurate data on the proportion of patients who had a declared degree of pre-operative coagulopathy e.g. secondary to hepatic disease, or anticoagulant or antiplatelet therapy, predominantly because this was not stated in the paper. However, three patients who received major thoracic surgery underwent intra-operative cardiopulmonary bypass, a recognised contributor to peri-operative coagulopathy.[49]

Studies were searched to find any potential conflicts of interest. None of the authors of the fifteen articles had a financial arrangement with NovoNordisk.®

Table 1. Case Mix

Procedure	Number (%)
Thoracoabdominal Aortic Surgery	**7 (15.9)**
Descending thoracic reconstruction	*4*
Descending thoracic, aorto-femoral and aorto-iliac reconstruction	*1*
Thoracoabdominal aneurysm repair	*1*
Allograft replacement of infected descending thoracic prosthesis	*1*
Abdominal Aortic Surgery	**26 (59.1)**
Suprarenal aneurysm repair	*9*
Open infrarenal aneurysm repair	
Post-operative leak	*2*
Ruptured	*2*
Elective	*2*
Unspecified	*6*
Endovascular infrarenal aneurysm repair	*2*
Re-do Aorto-bifemoral bypass grafting	*2*
Aorto-iliac pseudoaneurysm ligation & axillo-femoral bypass grafting	*1*
Non-Aortic or Non-specified Vascular Surgery	**11 (25)**
'Major vascular procedure'	*4*
Evacuation of post-operative haematoma and repair of leak	*3*
Femoro-femoral crossover graft (following type a aortic dissection)	*1*
'Perioperative haemorrhage'	*1*
Inferior vena caval thrombus removal and repair	*1*
Local infusion into false aneurysm	*1*
Total	**44 (100)**

Dosage and frequency of administration

To allow data synthesis, we arbitrarily chose three dosing levels of rFVIIa (see Table 2). The frequency of rFVIIa administration was variable. Whilst some groups prescribed only a single bolus [17–19] others administered further doses if bleeding failed to stop.[42,48] Therefore if patients received multiple doses, their cumulative dose per kilogram body weight was recorded. The range of rFVIIa administered as a cumulative dose was large (24 μg/kg − 360 μg/kg, mean = 87.6 μg/kg) as was the variation in initial dose (24 μg/kg − 120 μg/kg), and the total number of doses (1 - 4). 59.1% of the patients within the series had documented cumulative doses $\leq$ 90 μg/kg. The mode dose was 90 μg/kg, the recommended dose in haemophiliacs. The timing of administration, and the criteria upon which the decision to do so was made are frequently unclear. Some groups rely on surgeon and haemaologist 'discretion',[14,21] whilst others specify the receipt of specific quantities of blood products by the patient.[19] RFVIIa is manufactured in vials of 1.2, 2.4 and 4.8 mg and is expensive (approaching US$1/μg),[50] and this appears to have led some centres to utilise a 'best-fit' dosing regimen to avoid opening more vials than necessary.[44,48]

Table 2. Variations in Dosing

Dosing ($n = 44$)	Frequency (%)
Low Dose (< 60 μg/kg)	15 (34.1)
Mid−Dose (60−90 μg/kg)	11 (25)
High Dose (> 90 μg/kg)	6 (13.6)
Undisclosed	12 (27.2)
Total	44 (100)

Effect on haemorrhage

Whilst the majority of articles reported some reduction in blood loss, either as witnessed by the clinician [18,47] or a reduction in the need for further blood products,[46] this was not a uniform finding.[48] Furthermore, this was frequently a subjective assessment. 5 articles presented patient-specific transfusion data, both pre- and post-rFVIIa administration, on 9 different patients.[15,16,42,43,48] This data, along with mean and standard deviation is presented in Table 3. A statistically and clinically significant reduction in packed red cell transfusions following rFVIIa administration was demonstrated ($p = 0.015$), as was a reduction of borderline statistical significance in platelet transfusions ($p = 0.057$). No significant effect on fresh frozen plasma or cryoprecipitate administration was found. To ensure the findings were not related to the papers studied, regression analysis was performed, taking into account the article from which the data was extracted. A group effect (using rFVIIa = yes as an independent group variable and blood product loss as dependent variable) was detected.

Adverse events and mortality

Patient specific thromboembolic adverse event data was not available for 62% of the cohort, and thus calculation of an estimated adverse event rate would be inappropriate. Intra-arterial thrombosis was reported in 3 patients, the risk of which may be increased in vascular patients due to rFVIIa's proposed mechanism of action. It is worth noting however that these cases were all reported by the same group, who administered rFVIIa alongside human factor VIII-von Willebrand factor concentrate and/or human fibrinogen, both of which increase the risk of coagulation and make it unclear as to how much these events are attributable to rFVIIa.[45] 16.3% of patients in the cohort were reported to have died as a result of refractory haemorrhage, due predominantly to two studies, one of which reported a 22% mortality rate [14] and the other 100%.[48]

Discussion

We have synthesised all of the available data within the surgical literature on the administration of rFVIIa to vascular patients suffering from haemorrhage refractory to other conditions. By combining data originally reported in case reports or series, we have demonstrated a clinically significant reduction in blood and platelet transfusion requirements following the administration of rFVIIa, a finding supported by work in other surgical settings.[12,13] Whilst our findings must be interpreted cautiously, as these cases are highly heterogeneous and there is an inherent publication bias in non-comparative reports, we feel they justify more research being performed in this setting. This may help to eradicate the significant variation in practice we have demonstrated.

Ever since Kenet *et al*. reported the successful use of rFVIIa in military trauma in 1999,[51] research has been undertaken in most surgical specialities to identify any potential role for rFVIIa. Vascular surgery lagged behind the other surgical specialities in this regard. One reason for this may be theoretical concern regarding the exacerbation of conditions mediated by TF exposure to the circulation. Atherosclerotic plaques

Table 3. Blood Product Requirements Pre- and Post-RFVIIa administration

Patients	Pre-rFVIIa PRC	Post-rFVIIa PRC	Pre-rFVIIa Plts	Post-rFVIIa Plts	Pre-rFVIIa FFP	Post-rFVIIa FFP	Pre-rFVIIa Cryo	Post-rFVIIa Cryo
1. Pugh et al.[42]	29	40	2	4	18	22	10	40
2. Pugh et al.[42]	14	4	2	3	5	8	0	10
3. Cheng et al.[15]	17	0	32	0	19	0	0	0
4. Clark et al.[48]	27	6	1	1	8	4	10	0
5. Clark et al.[48]	28	14	2	2	8	7	10	10
6. Clark et al.[48]	25	6	1	1	4	4	10	10
7. Raux et al.[16]	66	2	51	0	64	0	0	0
8. Raux et al.[16]	18	0	20	0	9	0	0	0
9. Aggarwal et al.[43]	39	2	37	6	32	4	50	0
Mean Units (± S.D)	29.2 ± 15.7	8.2 ± 12.6	16.4 ± 19.3	1.9 ± 2.1	18.6 ± 19.2	5.4 ± 6.9	10 ± 15.8	7.8 ± 13

PRC = Packed Red Cells, Plts = Platelets, FFP = Fresh Frozen Plasma, Cryo = Cryoprecipate, S.D = Standard Deviation.

express TF, and both surgical injury and extracorporeal circulation up-regulate systemic TF expression. Thus patients undergoing major vascular surgery who receive rFVIIa may be at increased risk of unwanted systemic thrombosis. These concerns are not unwarranted; A recent review of thromboembolic complications in patients treated with rFVIIa reported to the FDA database from 1999 to end 2004 suggested an increased rate in those treated for unlabelled conditions,[10] an alarming result considering the morbidity and mortality from events such as stroke and myocardial infarction is so high. Furthermore, whilst an estimated adverse event rate for the cohort was not possible in our review due to absence of data, three patients were identified who suffered intra-arterial thrombosis following rFVIIa administration. However, similar theoretical concerns also apply to cardiac surgical patients. This group was recently reviewed by Warren *et al*., who aggregated the available data within cardiac surgical patients treated with rFVIIa for refractory haemorrhage and found a thromboembolic adverse event rate of 5.3% for adult patients.[11] This figure tallied with that of Levy *et al*. who reviewed 13 NovoNordisk®-sponsored clinical trials of rFVIIa in patients with coagulopathy secondary to anti-coagulation, cirrhosis or severe traumatic injury and found an adverse thromboembolic event rate of 6% with no significant difference between treated patients and placebo ($p = 0.57$).[52] Similarly a recent randomized controlled trial of rFVIIa in trauma patients did not find an increased risk of thromboembolic events in the treatment group.[53]

Recommendations for the administration of rFVIIa in major vascular surgery have been made previously by Shander *et al*. [54] Based on an expert panel's experience and a literature review they deemed the use of rFVIIa as a rescue therapy to be 'appropriate' in thoracic aortic surgery if significant clotting factor replacement had been attempted, but suggested that the evidence for its use in abdominal aortic surgery was less certain. They suggested a dose of 41 to 90 μg/kg but we have demonstrated a significant range of dosage currently in reported practice. Similar recommendations were made by Goodnough and colleagues, who advised caution in those with a history of vascular disease.[55] Whilst it is difficult for us to make clear evidence-based recommendations regarding the appropriate indications for rFVIIa in vascular surgery patient, there seems little evidence to suggest a dose of greater than 90 μg/kg is any more efficacious than that recommended by these groups. Furthermore, in all cases where rFVIIa has been reported to be effective adequate clotting replacement therapy has been undertaken prior to administration, a practice supported by physiological knowledge of it's mechanism of action.

The key for vascular surgeons when considering the risk-benefits of rFVIIa administration likely lies in the clinical situation; we would argue that on occasion some vascular patients have life threatening bleeding so severe as to warrant the consideration of any therapy that may potentially prevent mortality. This viewpoint is supported by Roberts who advocated rFVIIa for life-threatening refractory haemorrhage in most scenarios, despite sometimes the absence of controlled clinical trials.[56]

Limitations and recommendations for further research

The major limitation of this systematic review and pooled data analysis is the paucity of current evidence; the number of patients within the literature is small and they are derived from 15 different papers, all of which are retrospective and non-comparative. Therefore we are unable to perform meta-analysis. However, the primary value of our systematic review and critique of the available literature is to make the vascular surgical community aware of rFVIIa's proposed method of action, highlights it's potential role in haemorrhage refractory to all other interventions and outline the deficiencies within the literature, thus guiding future research. To this end we have formulated recommendations using the 'EPICOT' guidelines.[57] Firstly, having reviewed all the data, we believe that well-designed, randomized controlled trials are required to definitively answer questions on the cost effectiveness, appropriate dosing regime, and safety profile of rFVIIa. With the justifiable concerns regarding inappropriate intra-arterial thrombosis, trials must initially focus on patients *in extremis*, in whom all other efforts to staunch haemorrhage have been exhausted. This will allow rFVIIa to be, at least initially, compared to placebo, and avoid the confusion in results interpretation that may arise if rFVIIa is given in combination with other pro-coagulants, such as Factor VIII.[45] Outcomes must include subsequent requirement for transfusion, with strict protocols for triggering blood product administration in place prospectively, thromboembolic adverse event rates and 30-day mortality. Any study should also include a cost-effectiveness analysis.

Conclusion

Recombinant factor VIIa is a potent pro-haemostatic agent, which vascular surgeons should consider as a potential therapeutic agent in patients with severe haemorrhage refractory to conventional treatments.

However, administration of rFVIIa is not without risk, and should only occur in line with current literature guidelines. Well-designed randomized controlled trials are required to fully elucidate the cost effectiveness, appropriate dosing regime, and safety profile of rFVIIa within vascular surgery patients.

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Authors' contributions

OW, NC, AC and TA were responsible for the study conception, design, data interpretation, manuscript drafting and for important intellectual content. EA, IVH, and DL were responsible for the collection, extraction and synthesis of data. TA and OW were responsible for statistical analysis. AD, OW and TA were responsible for providing important intellectual content throughout the manuscript's production and for approval of the final version. NC is the guarantor. His involvement was critical to every phase of this work and he had access to the data and controlled the decision to publish. All authors read and approved the final manuscript.

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