A Systematic Review of the Efficacy of Recombinant Activated Factor VII and Activated Prothrombin Complex Concentrate in the On-Demand Treatment of Minor to Moderate Bleeding Episodes for Haemophilia Patients With Inhibitors

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Introduction

The management of minor to moderate bleeding episodes for patients with haemophilia A or B with inhibitors to factor VIII primarily is undertaken by the administration of either recombinant activated factor VII (rFVIIa) (NovoSeven®; Novo Nordisk, Bagsvaerd, Denmark) or a plasma-derived activated prothrombin complex concentrate (aPCC) (FEIBA®; Baxter, Vienna, Austria). The administration of both rFVIIa and aPCC has been shown to be safe. Furthermore, the effectiveness of these agents in resolving a minor to moderate bleeding episode has been reported in numerous individual studies, although the quality of the available studies has not been evaluated. The level of effectiveness of these treatments is important both from the patient perspective and from the health care payer perspective.

Objective

The aim of the study was to establish robust estimates of the efficacy, speed of bleed resolution, and adverse event profile of both rFVIIa and aPCC in the treatment of minor to moderate bleeding episodes for patients with haemophilia A or B with inhibitors to factor VIII.

Methods

A systematic review was undertaken using MEDLINE, EMBASE (for articles published from 1990 to April 2008), and the Cochrane Library (Issue 1, 2008), including the Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. In addition, both general and targeted internet searches were carried out. Two reviewers independently selected the relevant clinical studies by screening first the study titles and then the study abstracts based on the inclusion criteria (Table 1).

Results

The systematic search identified 910 references. After screening, a total of 18 studies were included in the review. Of these, 6 were randomized, controlled trials; 11 were prospective or retrospective cohort studies; and 1 was a meta-analysis (Figure 1).

Efficacy Assessment

The primary goals of haemostatic agents are to stop the current bleeding episode and to alleviate pain (Hay et al., 2006). Although the definition of efficacy varied among the studies identified, efficacy was usually defined as a combination of definite relief of pain, reduction in the size of the haemorrhage, and cessation of bleeding. Overall, the studies do report higher efficacy and bleeding cessation rates for rFVIIa than for aPCC. Some studies also reported the rate of stopped or controlled bleeding as a secondary outcome. Figure 2 shows the rates of controlled or stopped bleeding for the eight studies identified as reporting this outcome. The FEIBA NovoSeven Comparative (FENOC) study (Astermark et al., 2007) reported that 76.1% of bleeding episodes treated with aPCC and 65.2% of bleeding episodes treated with rFVIIa were controlled or stopped within 6 hours after treatment initiation. The other four studies examining rates of controlled or stopped bleeding with rFVIIa reported rates of 85% and above (Kavakli et al., 2006; Young et al., 2007; Key et al., 1998; Parameswaran et al., 2005). Three of the other five studies examining bleed controlled/stopped rates with aPCC reported rates in excess of 88%. However, DiMichelle & Negrier (2006) and Young et al. (2007) reported bleed controlled/stopped rates with aPCC of 65% and 63.6%, respectively.

Time to Cessation of Bleeding

The time taken to stop a bleeding episode is very important to the patient because it reduces the time a patient is in pain, the amount of haemostatic agent required, the potential long-term damage to the joint, and the subsequent cost of undergoing a joint arthroplasty. With the exception of the Astermark et al. (2007) trial data, the rFVIIa and aPCC data suggest that bleeds would be more quickly resolved if treated with rFVIIa rather than with aPCC. Young et al. (2007), Key et al. (1998), Hilgartner et al. (1983), and Hilgartner et al. (1990) suggest that bleeding episodes would be more quickly resolved if treated with rFVIIa rather than with aPCC; at 9 hours, more than 90% of bleeding episodes were resolved with rFVIIa, and at 12 hours, between 36% and 52% of episodes were resolved with aPCC.

Dosage Administered

The amount of rFVIIa and aPCC administered may affect efficacy rates. Most of the clinical trials of rFVIIa reported dosing regimens in line with treatment guidelines. Although the optimal dosing schedule remains to be determined, the product label suggests that the dosing schedule for rFVIIa should be three doses of 90 µg/kg every 2 hours, a maximum of 270 µg/kg. For aPCC, treatment guidelines recommend 50 to 100 IU/kg every 6 to 12 hours.

Adverse Events

The only significant adverse event reported was anamnestic response (AR), which was identified in aPCC studies (Hilgartner et al., 1983; Negrier et al., 1997). This adverse event was expected; patients with factor VIII inhibitors who are exposed to a product containing a small amount of factor VIII can experience an AR (specifically, an increase in the inhibitor level); for example, Negrier et al. 1997 reported a risk of AR of 32% defined as an increase in the inhibitor level by > 50%. An AR could have a significant impact on patients undergoing immune tolerance induction (ITI) to eradicate the inhibitors, as titer level is related to an increase in the duration of ITI and to a decrease in the probability of success for ITI therapy (Mauser-Bunschoten et al., 1995; Brackmann et al., 2000).

Reliability/Accuracy of Response

The Astermark et al. (2007) and the Young et al. (2007) studies are currently the only direct comparison of rFVIIa and aPCC in haemophilia patients with inhibitors. The Astermark study was designed to demonstrate equivalence between one dose of aPCC (85 IU/kg) with a rFVIIa regimen of 2 × 90 µg/kg. The criteria for equivalence, defined as ≤ 15% difference in the confidence intervals of the proportion of patients who reported that bleeding was treated effectively or partially effectively within 6 hours of treatment initiation, was not met.

Additionally, with only 48 patients and 96 bleeding episodes, this trial may have been underpowered to show equivalence. The distribution of the study joints between the treatments was not equal: in the rFVIIa treatment group, 58.4% of bleeding episodes occurred in the knee, and in the aPCC group, only 31.3% of episodes occurred in the knee. The bleeding-cessation rate reported in the Astermark trial for aPCC (53.2% at 2 hours and 78% at 12 hours for 1 infusion) is higher than that reported by any other aPCC trial or cohort study for one infusion in these time periods. Since the Astermark study was designed to test equivalence of the products, and the criteria was not met at any time point, any statement regarding differences favouring one product over the other is inappropriate.

The primary outcome in the Young et al. (2007) study was the percentage of patients who required additional haemostatic medication 9 hours after initiation of treatment. A significantly lower percentage of patients in the 270 µg/kg rFVIIa and 3 × 90 µg/kg treatment groups required rescue medication compared with the aPCC treatment group. The limitations of the study relate to the small sample size. Overall, the Young et al. (2007) study is well designed and compares appropriate regimens of rFVIIa and aPCC treatment. The authors' conclusions suggest that the efficacy of the two rFVIIa regimens are equivalent and that rFVIIa treatment is potentially more effective than 75 IU/kg of aPCC.

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Table 1. Inclusion/Exclusion Criteria

Criteria	Included	Excluded
Study type	Clinical trials (randomized and nonrandomized) Observational studies Retrospective or prospective cohort analyses Database/registry analyses Surveys	Editorials Commentaries Case studies Economic evaluations Discussion papers Letters
Patient population/type of bleed	Patients of all ages with haemophilia A or B and inhibitors with acute bleeding	Patients with acquired haemophilia Patients with other congenital bleeding disorders Patients undergoing surgery or other related procedures Serious bleeds

Figure 1. Inclusion/Exclusion Flow Diagram

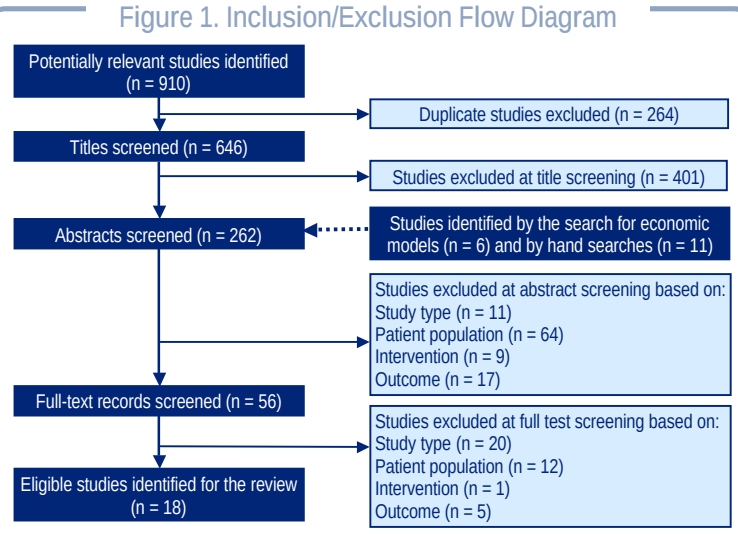
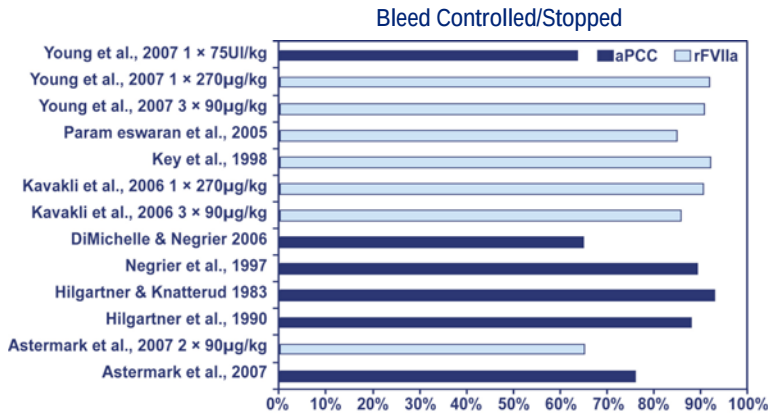


Figure 2. Comparison of the Bleed Controlled Rates



Conclusions

- Although randomized trials examining the efficacy of rFVIIa and/or aPCC exist, there is a paucity of comparative studies, with currently only two direct head-to-head trials.
- Overall, the studies do report higher efficacy and bleeding cessation rates for rFVIIa than for aPCC; however, the measurement of effectiveness of the agents is open to interpretation due to a wide variety of methods being used to evaluate effectiveness.
- Conclusions from the meta-analysis undertaken by Treur et al. (2007) suggest that treatment with rFVIIa may be associated with a faster time to joint bleeding resolution than aPCC due to higher efficacy levels at 12-, 24-, and 36- hour time points. The results from the Young et al. (2007) comparative trial support the improved efficacy rates associated with rFVIIa compared with aPCC.
- There is an apparent need for the employment of a standardized, validated efficacy assessment tool in all future studies to facilitate a comparison of results from different studies. In conclusion, further head-to-head, randomized, controlled trials should incorporate a validated standard method of efficacy assessment.

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