Control of bleeding in patients with haemophilia A with inhibitors: a systematic review

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CRD summary
This review evaluated the effectiveness of treatments for acute bleeding in patients with haemophilia A with inhibitors. The authors concluded that bleeding control varied from 60 to 100%. The authors undertook a systematic search but the lack of detail on review methodology and the poor quality of many included studies make the reliability of the conclusions uncertain.

Authors' objectives
To evaluate the effectiveness of treatments for acute bleeding in patients with haemophilia A with inhibitors.

Searching
BIOSIS Previews (1985 to 2001), EMBASE (1980 to 2001), MEDLINE (1966 to 2001), the Cochrane Database of Systematic Reviews (2001, Issue 2), the Cochrane CENTRAL Register (2001, Issue 2), DARE, HTA, NHS EED, the National Research Register (2001, Issue 4) and ISI Web of Science (1981 to 2001) were searched without any language restrictions; the search strategy was reported. The reference lists of included studies and review articles were checked, and conference abstracts and the Internet were also searched. Novo Nordisk was contacted for further studies. Numerous additional sources were consulted; these were listed in full.

Study selection

Case studies of one or two bleeding episodes were excluded.

Specific interventions included in the review
Studies of any treatment for a bleeding episode, with any comparator, were eligible for inclusion. The interventions evaluated in the included studies were: high-dose human factor VIII (hFVIII) concentrate; highly purified porcine factor VIII (pFVIII); bypassing products such as prothrombin complex concentrates (PCCs), activated PCCs and activated recombinant factor VIIa (rFVIIa); high-dose FVIII with or without plasmapheresis, cimetidine or immunosuppression; and hFVIII with or without immunosuppression.

Participants included in the review
Studies of patients with haemophilia A with inhibitors were eligible for inclusion. Studies of patients with haemophilia B or acquired inhibitors were also included. When the results for patients with haemophilia A were reported separately, only these were extracted. Where the results for patients with haemophilia A were not reported separately, the results for the whole population were utilised and the number of patients with other conditions recorded. The included studies were conducted in patients with bleeding episodes and patients undergoing surgery (including dental surgery).

Outcomes assessed in the review
Studies that reported any outcomes were eligible for inclusion. The primary outcome discussed was control of bleeding. The secondary outcomes were the number of bleeding episodes, tolerance to treatment and adverse events. The outcomes were discussed separately for surgical and nonsurgical patients.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The quality of the randomised controlled trials (RCTs) was assessed using the Jadad scale. The authors did not state how the quality of the papers was assessed, or how many reviewers performed the quality assessment.
Data extraction
One reviewer extracted the data into a prepared extraction form.

Methods of synthesis
How were the studies combined?
The studies were grouped by intervention and by type of bleeding (nonsurgical or surgical) and discussed in a narrative synthesis.

How were differences between studies investigated?
Study details and results were tabulated. Differences in study quality were considered in the narrative.

Results of the review
Fifty-two studies were included in the review (n at least 1,333; some studies reported the number of bleeding episodes but not the number of patients). This included 8 RCTs (3 of crossover design), 27 uncontrolled prospective studies, 10 case series, 2 retrospective studies, 1 study described as a prospective comparative study, 1 comparative study, 1 uncontrolled study, 1 prospective pilot and 1 report of pooled data. The number of participants in the included studies, where reported, ranged from 2 to 253.

High-dose hFVIII (4 studies).
Acute bleeding episodes: evidence from 2 RCTs and one small case series was of poor quality. The RCT reported no statistically significant difference in the control of acute bleeding between patients receiving hFVIII and PCCs.

Surgical procedures: one case series reported that treatment additional to high-dose FVIII was not required in surgical patients. Success of hFVIII was reported in 67 and 100% of patients when used in conjunction with plasmapheresis, 80% in conjunction with extracorporeal protein A adsorption, and 100% in conjunction with cimetidine. Two studies did not report on bleeding control and were not discussed.

Highly purified pFVIII (5 studies).
Acute bleeding episodes: the highest quality evidence came from 2 uncontrolled prospective studies, one of which reported an excellent response in the 5 patients studied, and the other that bleeding was stopped in all 11 patients. A third study reported an excellent response in 48% of participants, a good response in 28%, and a fair to no response in 7%, with 17% unable to be evaluated. A case series reported that 2 patients achieved tolerance to pFVIII while a third was intolerant.

Surgical procedures: the highest quality evidence came from one multicentre retrospective survey and one uncontrolled prospective study. The retrospective study reported a success rate of 93% in surgical patients, while the uncontrolled prospective study reported good or excellent results in 57% of surgical cases. An uncontrolled prospective study reported successfully controlled bleeding in 3 patients undergoing dental extraction.

Bypassing products.

PCCs (6 studies).
Acute bleeding episodes: 3 RCTs reported PCCs to be effective in 48 to 64% of cases. One RCT reported no statistically significant difference between PCC and controls. Two further studies reported either 63% or 42% of episodes were resolved after one PCC infusion, 22% or 13% after two infusions, and 17% or 26% required further infusions or other treatments.

Surgical procedures: only one case series of 2 patients undergoing dental surgery was identified. There was no good evidence for the use of PCCs in surgery.
aPCCs (7 studies).

Acute bleeding episodes: one RCT reported 52% effectiveness of aPCCS, and another that FEIBA and prothromblex were 64% or 52% effective/partially effective, respectively. One uncontrolled prospective trial reported an excellent response in 56% of minor bleeding episodes or 75% of major bleeding episodes, and a good response in 32% and 25%, respectively. Another reported an excellent or good outcome in 87% of episodes overall, 92% of open bleeding episodes and 84% of closed bleeding episodes. Two uncontrolled prospective trials reported episodes controlled within 72 hours in 91% of episodes, or within 36 hours in 78% of episodes.

Surgical procedures: the highest quality evidence for surgery was from an uncontrolled prospective trial that reported that 72% of bleeding episodes during surgery were controlled within 12 hours. A retrospective study reported that surgery was performed without bleeding complications in 93% of cases, with one excessive bleed controlled using FEIBA alone. The highest quality evidence for dental surgery was from one retrospective study (number of dental cases not reported) and one case series (4 patients). The studies found that FEIBA controlled all episodes of bleeding.

aPCC versus PCC (2 RCTs).

Acute bleeding episodes: one crossover RCT (26 patients) found no significant difference between single doses of the treatments in control of bleeding; the other RCT (15 patients) found aPCC increased control of bleeding in comparison with PCC (64% versus 52%).

rFVIIa (15 studies).

Acute bleeding episodes: the studies were of a poor quality. rFVIIa was reported as being effective in: 71 to 93% of patients with joint, muscle or mucocutaneous bleeding (4 uncontrolled prospective trials); 62 to 100% of patients with severe bleeding (6 uncontrolled prospective trials, 1 study of pooled data and 1 case series); 78 to 88% of patients with central nervous system bleeding (3 uncontrolled prospective trials); and in 75 and 100% of patients during immune tolerance induction (1 uncontrolled prospective trial and 1 case series).

Surgery: rFVIIa was reported as being effective in 60 to 100% of patients with bleeding events during surgery (1 RCT, 3 uncontrolled prospective trials and 3 case series). The highest quality evidence for surgery was from one small RCT, which reported treatment success as being 67% with low-dose rFVIIa and 93% with high-dose rFVIIa.

Adverse events.

Several studies reported adverse events, including mild pyrogenic reactions/fevers, rashes/hives/urticaria, chills/shivering, dizziness, nausea, headache, lumbar pain, anaphylactic reactions, thrombocytopaenia, anamnesis, abdominal pain and a transient drop in blood-pressure. These were discussed in more detail in the review.

Authors' conclusions

There was no evidence to support the use of high-dose FVIII in bleeding episodes, although it was found to be successful for low-titre, low-responding inhibitors in surgery. pFVIII was effective in controlling severe bleeding with high-titre or high responding inhibitors, and in 60 to 90% of surgical procedures. aPCCs appeared more effective than PCCs in the control of mild to severe bleeding, rFVIIa controlled 70 to 100% of mild to severe bleeding episodes with high-responding inhibitors, and achieved better results when used early. There was no evidence for the use of PCCs in surgery. However, aPCCs controlled 90% of surgical episodes while rFVIIa controlled 60 to 100%.

CRD commentary

The authors searched extensively for both published and unpublished data, with no language or date restrictions, thus reducing the risk of language and publication bias. The inclusion criteria were broad. The authors did not state how the studies were selected, and a single reviewer extracted data from the included studies without it being checked by a second reviewer; there was therefore the potential for error and bias to be introduced into the review. The decision to combine the studies in a narrative synthesis was appropriate. The search was systematic but the lack of details on the methods used during the review process, and the poor quality of many of the included studies, should be kept in mind.
when considering the conclusions of the review and implications for practice.

**Implications of the review for practice and research**

**Practice:** The authors made several recommendations. In particular, the daily dose of FEIBA should not exceed 200 U/kg, owing to the risk of thrombosis; PCCs and aPCCs are not recommended as first-line treatment in life-threatening haemorrhages unless the patient's inhibitor titre is too high to permit successful treatment with high-dose FVII; PCCs and aPCCs can be used when the bleeding is not life-threatening; rFVIIa appears preferable as the first line of treatment in patients with high-responding inhibitors; plasmapheresis, with or without immunoadsorption, followed by high-dose FVIII can be used as a last resort in patients with high-titre inhibitors in whom other approaches have failed; and aPCCs and antifibrinolytic agents should be used consecutively rather than simultaneously during dental surgery.

**Research:** The authors suggested that further research to evaluate the use of rFVIIa would be useful.

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