

REVIEW ARTICLE

Managing acute bleeds in the patient with haemophilia and inhibitors: options, efficacy and safety

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Summary. The options available for treating the patient with haemophilia and inhibitors undergoing surgery or with other acute bleeds include high-dose factor VIII (FVIII) (human or porcine), prothrombin complex concentrates (PCCs), activated PCCs (aPCCs), recombinant activated factor VII (rFVIIa), and factor replacement combined with immunoadsorption or immunosuppression. Human FVIII is effective in patients with low-titre inhibitors. Porcine FVIII is currently not available, and PCCs and aPCCs, although effective, have been associated

with a high incidence of adverse events. Immunoadsorption and immunosuppression offer excellent long-term solutions, but the duration of these techniques makes them less attractive for use in acute settings. Recombinant FVIIa has demonstrated excellent efficacy and safety, even in patients refractory to other therapies.

Keywords: coagulation factor, factor replacement, haemophilia, immunoadsorption, immunosuppression, inhibitors

Introduction

In patients with haemophilia, antibodies directed against factor replacement products are common. The presence of these inhibitors can complicate prophylaxis and replacement therapy and may neutralize factor replacement, rendering the therapy ineffective.

There are several available techniques for the management of the haemophilia patient with inhibitors. In the long term, immune tolerance may be induced, desensitizing the immune system and eradicating the inhibitor by the infusion of frequent large doses of factor replacement. Short-term solutions may also be required, particularly during the management of acute bleeding episodes. This article will focus on the safety and efficacy of these short-term solutions in patients with inhibitors undergoing surgery.

The strategies available for the management of acute bleeds in patients with haemophilia and inhibitors include:

1 Replacement therapy

- i. High-dose human factor VIII (FVIII) concentrate,
- ii. Highly purified porcine FVIII concentrate.

2 Inhibitor bypassing products

- i. Prothrombin complex concentrates (PCCs),
- ii. Activated PCCs (aPCCs),
- iii. Recombinant activated factor VII (rFVIIa, NovoSeven[®], Novo Nordisk, Bagsvaerd, Denmark).

3 Inhibitor removal strategies

- i. Combination of FVIII and immunoadsorption (using protein A or anti-human immunoglobulin columns),
- ii. Combination of FVIII plus immunosuppression,
- iii. New approaches such as rituximab.

The indications for use, safety and efficacy of each will be reviewed below.

Replacement therapy

Human FVIII

Replacement with high-dose human FVIII is the generally preferred treatment option, especially for patients with low-responding inhibitors (≤ 5 BU). Patients with low-responding inhibitors often respond favourably to high-dose human FVIII, producing measurable increases in FVIII concentration and activity, and achieving haemostasis. In patients

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with high-responding inhibitors (>5 BU), infusion of human FVIII results in a large and counterproductive increase in inhibitor titre and a failure to achieve haemostasis; any response usually declines after 4–5 days, although it may be prolonged with the use of concurrent immunosuppression.

The different responses of these two patient groups are evident in a small retrospective study [1]. In five patients with low-responding inhibitors (mean peak 1.8 BU, range 1.2–2) undergoing various surgical procedures, a mean total dose of 50 000 units (range 6000–91 960) of FVIII was 100% successful in achieving haemostasis [1]. These patients suffered no bleeds and required no other haemostatic cover during the peri- and postoperative period. In nine patients with high-responding inhibitors (mean peak 305 BU, range 9–1500), undergoing various surgical procedures (multiple dental extractions), a mean total dose of 67 732 units (range 8000–174 750) of FVIII was only 78% successful [1], with two of nine patients requiring additional aPCC treatment for bleeds (wound haematoma).

The presence of any inhibitor (high- and low-responding) modifies the pharmacokinetics of the infused FVIII. This is a patient-specific effect requiring that the dose be tailored according to the half-life and recovery characteristics of FVIII for each individual patient with inhibitors. Furthermore, the inhibitor characteristics of each patient may change over time, with around 75% of low-responding inhibitor types converting into high-responders [2], often due to repeated doses of FVIII [3]. The dose of human FVIII suitable to saturate a low-titre inhibitor can be calculated as follows [4]:

$$2 \times \text{BW} \left[\frac{80(100 - \text{Hct})}{100} \right] \text{IB},$$

where BW is body weight in kg, Hct is haematocrit and IB is inhibitor titre in BU.

Porcine FVIII

The use of porcine-derived FVIII has largely been replaced by human products. Porcine-specific inhibitors may develop and, in addition, some human-specific inhibitors may cross-react with porcine FVIII products.

Adverse events pose a serious problem with these products and include allergy and anamnestic responses [5]. Allergic transfusion and pyrogenic reactions occur in around 40% of cases, resulting in fever, rash, hives, chills, flushing, shivering, thrombocytopenia and lumbar pain. Anamnestic responses against both human and porcine FVIII also occur.

Approximately 50% of all adverse events following porcine FVIII infusion are severe, requiring treatment. In addition, availability of porcine FVIII is currently limited by viral contamination; to date, there has been no viral inactivation step during production, and sourcing parvovirus B19-negative donor pigs may be necessary before the product is returned to the market.

Acceptable efficacy of porcine FVIII has been demonstrated in patients with inhibitor titres <20 BU [6], although this must be weighed against the adverse effects. Two small studies demonstrate this trade-off [5, 7]. In an uncontrolled prospective study of seven patients (mean pre-treatment inhibitor 180 BU, range 10–1050) undergoing various surgical procedures, the authors reported an excellent overall response in 29%, with other patients achieving a 'good' response (29%), and 'fair/no' response (29%); the remaining patients were not evaluated [5]. Adverse events included allergic responses, thrombocytopenia and anamnestic responses.

In a retrospective multicentre survey of 57 surgical episodes, including 22 elective and 35 emergency procedures, there was an overall success rate of 93% [7]. However, four patients with high-titre, cross-reacting inhibitors suffered excessive bleeding. Adverse events included allergic responses, thrombocytopenia and anamnestic responses.

Inhibitor bypassing products

Prothrombin complex concentrates

Prothrombin complex concentrates contain factor II (FII), FVII, factor IX (FIX), factor X (FX) and trace amounts of FVIII, activated FVII and activated FIX. The presence of activated components is minimized in current preparations, although the presence of any FVIII can result in anamnestic responses. PCCs are effective in bypassing inhibitors, although the exact mechanism of action is unknown and there is no reliable laboratory monitoring assay. Hence, although PCCs have been used since the 1970s to treat patients with inhibitors, and continue to be used in countries with no access to other therapies, this practice has been discontinued in recent years in the UK as well as in other European countries.

A randomized, controlled, crossover study of single-dose PCC vs. placebo in 51 surgical patients with haemophilia and FVIII inhibitors demonstrated a significant benefit for PCC [8]. During 157 acute bleeding episodes (haemarthrosis of elbow, knee and ankle) in the 51 patients (aged 4–54 years), a preoperative dose of PCC providing 75 U FIX per kg BW

resulted in efficacy of 48% and 53% (for Konyne® and Proplex™, respectively) vs. 29% for placebo.

The postoperative use of PCC (75 U FIX per kg BW, 12-hourly doses) was also reported in three dental extractions undertaken in two patients (aged 24 and 26 years) with inhibitor titres of 0–320 BU. However, the findings are confounded by concurrent epsilon-aminocaproic acid/aPCC administration during two of the procedures [9].

Activated PCCs

Activated PCCs contain FII, FVII, FIX, FX and trace amounts of FVIII. Some activation of factors occurs during production.

A prospective study of seven surgical procedures in seven patients with inhibitors (preoperative titre ≥ 4 BU) utilized up to three doses of 75 U aPCC per kg BW administered at 12-h intervals [10, 11]. Although the type of surgical procedure was not documented, the efficacy of aPCC was good. Bleeding in most procedures was controlled within 12 h (single dose); bleeding in one procedure was controlled within 36 h (multiple doses).

A retrospective, multicentre study of 15 surgical procedures (12 minor, three major) used doses of 78–210 U aPCC per kg BW for minor procedures and 210 U aPCC per kg BW for major surgery [12]. Fourteen procedures were completed without complications, although anamnestic responses occurred in up to 35% of cases. Adverse events were mostly minor, including chills, fever, nausea, dizziness, flushing or rash in 4%, and chest pain, drowsiness or breathing discomfort in 2%. Major adverse events (myocardial infarction and disseminated intravascular coagulation) were rare (<1%).

Adverse events are of concern with aPCCs, although if mild, the patient may benefit from continued aPCC administration. Most clinicians advise avoiding the concurrent use of antifibrinolytics, especially in cases where high doses of aPCC are used for prolonged periods.

Recombinant activated FVII

Recombinant FVIIa is effective in achieving haemostasis in patients with haemophilia and in normal individuals with acquired inhibitors to FVIII or FIX. Its precise mechanism of action is still under investigation although it appears that rFVIIa activity is localized on activated platelets; this restricts its procoagulant activity to the site of injury and accounts for the product's safety and efficacy [13].

A prospective, double-blind, randomized, multicentre study of rFVIIa use in haemophilia patients with inhibitors (FVIII, $n = 26$; FIX, $n = 3$) undergoing elective surgery (minor or major) compared two doses (35 or 90 $\mu\text{g kg}^{-1}$) administered for up to 5 days [14]. Recombinant FVIIa was administered during surgery and as boluses in the postoperative period. Haemostasis was achieved in 28 of 29 patients during the surgical procedures, and in all high-dose patients and 12 of 15 low-dose patients over the subsequent 48 h. Both dose regimens performed similarly, regardless of surgical procedure (minor vs. major) for the first 48 h. From day 3, the higher dose (90 $\mu\text{g kg}^{-1}$) performed significantly better. This suggests that elective surgery for patients with bleeding disorders can be safely undertaken when rFVIIa is used as a haemostatic agent, although the optimal dose is yet to be established.

A compassionate use clinical programme was developed in 1988 to allow access to rFVIIa as salvage therapy, prior to the product's licensure, in patients who had failed to respond to conventional therapies and interventions [15]. Patients included individuals with haemophilia A or B and inhibitors ($n = 211$), acquired haemophilia ($n = 53$) and FVII deficiency ($n = 27$). The recommended dosage was 90 $\mu\text{g kg}^{-1}$ every 2 h in patients with inhibitors, and 25–30 $\mu\text{g kg}^{-1}$ in patients with FVII deficiency. A composite 93.9% control rate of bleeding episodes was achieved; 96% of muscle/joint bleeds, 91% of surgery/wound bleeds, and 88% of central nervous system or life/limb-threatening bleeds were controlled. These patients were not entered into the programme in a uniform, controlled, clinical condition, and they had failed prior interventions. Furthermore, a 2003 review of the use of rFVIIa revealed that, since its introduction, the drug had controlled >1000 life-threatening bleeds in patients resistant to other therapies, with an efficacy of >90% [12].

In a prospective, uncontrolled study of rFVIIa use in 103 surgical procedures (patient number was not reported), efficacy was rated as 'excellent' or 'effective' in 81% of major (17/21), 86% of minor (49/57) and 92% of dental (23/25) procedures [16].

The safety profile of rFVIIa when used in inhibitor patients is good. Minor adverse reactions may include hypertension, skin reactions, fever, headache and epistaxis. Major events, including early recurrence of bleeding, thrombosis, thrombophlebitis and disseminated intravascular coagulation, have been reported in 116 of 140 000 administrations [12].

There has been some discussion about the appropriate dose of rFVIIa, with UK guidelines recom-

mending a bolus of 70–90 $\mu\text{g kg}^{-1}$ [17], and others maintaining it should be higher (150–200 $\mu\text{g kg}^{-1}$) [18] for elective surgery. However, guidelines are currently under review.

Inhibitor removal strategies

FVIII combined with immunoadsorption

Immunoadsorption can be used to remove inhibitors, and is particularly useful in patients with very high inhibitor titres. The technique was invented by Inga Marie Nilsson who used immunoadsorption to decrease inhibitor titres to <10 BU [19]. Nowadays, the process is continued until inhibitors are undetectable (0 BU). The process involves passing the patient's entire plasma pool through columns, which remove the inhibitor. The columns contain protein A or sheep anti-human immunoglobulin, which binds and traps the inhibitor as the plasma passes through, before the plasma is returned to the patient's body (Fig. 1). Concurrent treatment with prednisolone (1 mg kg^{-1} BW, oral) is usually prescribed. This process has a high success rate.

When immunoadsorption is combined with FVIII replacement, almost all hospitals report a dramatic improvement in bleeding tendency, although this may take 24-h preparation and 24–48 h to achieve, and so is not always practical for the management of severe acute bleeds. The technique is particularly useful for patients undergoing elective surgery or prophylaxis. In high-responder inhibitor patients,

immunoadsorption can reduce the inhibitor titre to <5 BU, a level that is sufficient to allow high-dose FVIII replacement and improve clinical bleeding tendency. Immunoadsorption can completely eliminate inhibitors, thereby removing the risk of future anamnestic responses, and can be used in conjunction with immune tolerance induction protocols.

In a study of 14 patients, 5.4 ± 4.9 immunoadsorption protocols per patient were required to increase FVIII recovery to 30%, whilst after 13.6 ± 11 protocols, complete remission was achieved in 13 of 14, with partial remission in the remaining patient [20]. This remission was long-term (mean follow-up 29.5 ± 16.3 months).

The safety of immunoadsorption is generally considered to be good. Sometimes short-term changes in electrolytes, creatinine, haemoglobin, liver function tests or fibrinogen levels are encountered. Immune system components may also be transiently affected, with increased leucocyte concentrations, and activation of the complement system (decreased C3 and C4; increased C3a; unchanged C5a). No column-related side effects are observed, although there may be a few moderate and transient side effects related to the associated extracorporeal circulation and anticoagulation.

FVIII combined with immunosuppression

Immunosuppression of inhibitor-producing B lymphocytes is a strategy that has been used successfully in patients with acquired haemophilia inhibitors, as

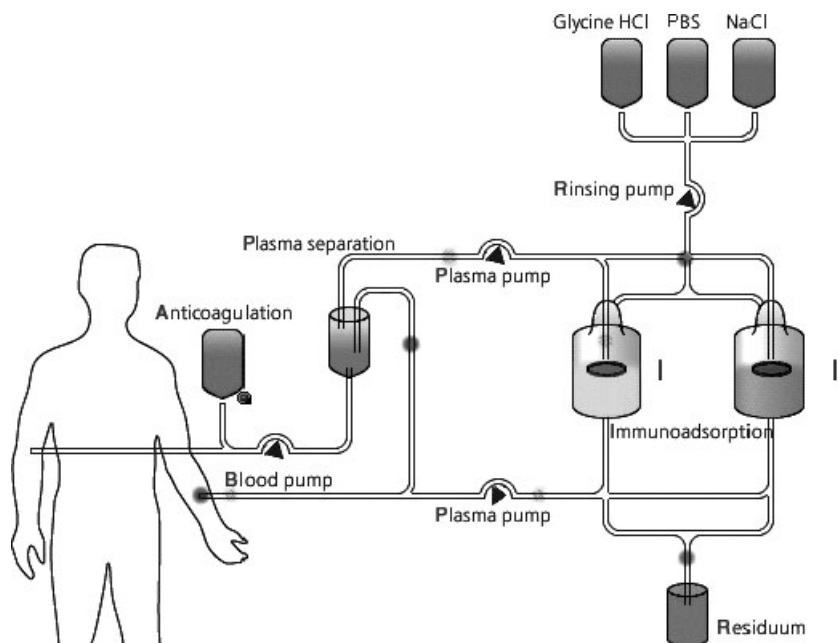


Fig. 1. The process of immunoadsorption. The patient's plasma is passed through columns containing protein A or sheep anti-human immunoglobulin, which binds and traps the inhibitor; reproduced with permission from von Depka and Huth-Kuehne 2002 [20].

well as in a range of autoimmune diseases, including idiopathic and autoimmune thrombocytopenia purpura, autoimmune haemolytic anaemia, essential cryoglobulinaemia, systemic lupus erythematosus and rheumatoid arthritis. Selective depletion of B lymphocytes can be achieved with the use of rituximab, an anti-CD20 monoclonal antibody (a chimera of mouse anti-human CD20 Fab combined with human IgG1 Fc).

This strategy was first used in 2002, when rituximab was administered to one patient with mild congenital haemophilia and three patients with acquired haemophilia [21]. Inhibitor titres ranged from 5 to 60 BU. A weekly rituximab dose of 375 mg m⁻² was used for 1–4 weeks, in combination with immunosuppressive drugs (e.g. prednisolone) in three of four patients. All four patients responded favourably, with a rapid improvement for the patient with congenital haemophilia during the first few days of therapy. The reduction of inhibitor titres and improved FVIII activity persisted for >7 months, and in some cases >12 months.

These findings are supported by the results of an uncontrolled cohort study of 10 patients with acquired haemophilia and low-titre inhibitors [22]. Rituximab (375 mg m⁻²) was administered once weekly for 4 consecutive weeks. Complete remission was achieved in eight of 10 patients (initial inhibitor titres 4–96 BU mL⁻¹), with return to normal FVIII activity and undetectable FVIII inhibitor titres. Partial and transient responses were obtained in two of 10 patients with higher inhibitor titres (>100 BU), but following rituximab plus pulse intravenous cyclophosphamide, a complete response was achieved in these patients too. Infusion-related side effects were observed in three patients but were of mild intensity and did not require discontinuation of treatment. With a median follow-up of 28.5 months, long-term complete remission was achieved in five of 10 patients, with three of 10 relapsing although responsive to repeat therapy, and two of 10 were refractory.

Considering the half-life of inhibitors, the response to rituximab is very rapid, and this speed of response is not fully understood. The response is also dose-dependent, so it is possible that the drug will be of particular benefit in patients with a low inhibitor titre.

Conclusions

The options available for treating the patient with haemophilia and inhibitors, undergoing surgery or with other acute bleeds, include high-dose FVIII

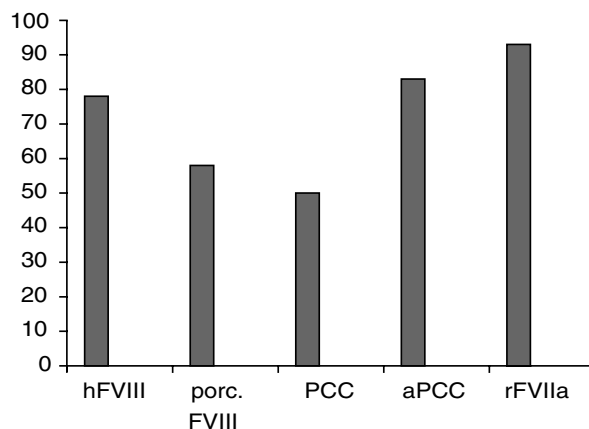


Fig. 2. A comparison of inhibitor bypass strategies in patients with inhibitor responses >5 BU. [1, 5, 8, 10, 15]

(human or porcine), PCC, aPCC, rFVIIa and FVIII combined with immunoabsorption or immunosuppression. It is difficult to compare the efficacy of these techniques due to the variability in patient characteristics and changes in the formulation of some drugs (especially PCC) over time. Few randomized controlled trials have been conducted to date, and those that have been completed have tended to compare like with like: FVIII with PCC [23,24], PCC with PCC [8], aPCC with aPCC [25–27] and low-dose with high-dose rFVIIa [14]. However, a composite comparison of efficacy rates from several representative studies using different coagulation factor concentrates demonstrates a benefit for rFVIIa (Fig. 2).

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