

ORIGINAL ARTICLE *Inhibitors*Consensus protocol for the use of recombinant activated factor VII [eptacog alfa (activated); NovoSeven[®]] in elective orthopaedic surgery in haemophilic patients with inhibitors

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Summary. Patients with haemophilia complicated by inhibitors have a significant burden of joint disease, which is associated with a negative impact on their quality of life. Successful elective orthopaedic surgery can result in decreased bleed frequency into a new joint, less time spent in hospital, increased mobility and improved well being. This paper describes a new protocol for use of recombinant activated factor VII (rFVIIa) in elective orthopaedic surgery, based on a review of published data as well as the personal experience of a group of expert physicians. The protocol offers guidance on the planning of the surgery and preoperative testing as well as the bolus schedule for rFVIIa and advice on the concomitant use of antifibrinolytic agents and fibrin sealants. A total of 10 operations involving 13 procedures in eight patients in five comprehensive care centres have been undertaken until now using the protocol, which

employs an initial bolus dose of rFVIIa in the range of 120–180 µg kg⁻¹ to cover surgery. The clinical experience reported here encompasses all cases of elective orthopaedic surgery using rFVIIa as initial treatment carried out in the UK and Republic of Ireland over the last 2 years. In all cases, there was good control of haemostasis during surgery and the final outcome was rated as 'excellent' or 'extremely satisfactory' by the reporting clinicians. Although the initial cost of product to cover surgery such as arthroplasty is high, it needs to be borne in mind that this may be offset in subsequent years by savings resulting from avoidance of bleeding episodes in the affected joint.

Keywords: haemophilia, inhibitors, NovoSeven[®], orthopaedic surgery, protocol, recombinant activated factor VII

1. In all cases, there was good control of haemostasis during surgery and the final outcome was rated a...
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Introduction

Advances in the treatment of haemophilia in recent decades have led to a significant increase in life expectancy, which now approaches that of the normal population in developed countries [1]. Now that the danger of infectious diseases such as human immunodeficiency virus (HIV) and hepatitis has been eliminated, the risk of development of inhibitors is now generally regarded as the most serious consequence

associated with replacement therapy. Patients with inhibitors have also benefited from improvements in treatment. In a study from the UK, the cumulative risk of inhibitor development at ages 5 and 75 were 16% and 36% respectively for patients with severe haemophilia A [2]. Inhibitor development was associated with a doubling of mortality for subjects without HIV during the period from 1977 to 1992. By contrast, the presence of an inhibitor was no longer associated with an excess of mortality during the period from 1993 to 1999. The authors of this study suggested that this reduction in mortality was likely to be the consequence of the availability of better treatment for bleeding episodes as well as immune tolerance.

Whilst patients with haemophilia, complicated by inhibitors, are now living longer, this is

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counterbalanced by a significant burden of joint disease, which is associated with a negative impact on their quality of life. A multicentre survey of 52 Italian patients with inhibitors documented problems such as synovitis, joint instability, muscle atrophy and flexion contractures in a significant proportion of patients [3]. This translated into a significant adverse impact on everyday life: 55% experienced problems with 'usual activities', 67% had problems with mobility, 75% complained of ongoing 'pain/discomfort' and 33% reported problems with 'self-care'. A clear inverse relationship between orthopaedic status and quality of life, measured using the generic EQ-5D and SF-36 questionnaires, were found [4]. An international study yielded similar results, with 9/38 (24%) males with haemophilia aged 14–35 with inhibitors reliant on a wheelchair [5].

Although many of these orthopaedic problems could potentially be corrected by surgery, this has hitherto not been entirely straightforward. Not so long ago, the opinion that 'the presence of antibodies to factor VIII or IX remains a contraindication to elective surgery' was a common view [6]. Recombinant activated factor VII (rFVIIa) was first licensed for clinical use in Europe in 1996 although its first use in elective orthopaedic surgery was published some years earlier [7]. Data from an international series of 108 cases of elective surgery performed in seven countries were published in 2004 [8]. On superficial analysis, the results were highly encouraging with results classified as 'good', 'fair' and 'poor' reported in 82, 15 and 11 patients respectively. However, 88 (81%) of these cases simply involved joint injections for radionuclide synovectomy. Just eight cases involved knee or hip arthroplasty. When taking into consideration only the 20 cases of major surgery included in the series, the outcome was described as 'good', 'fair' or 'poor' in 16, one and three cases respectively. The overall outcome was therefore significantly less than what one would have expected in uncomplicated orthopaedic patients. The initial bolus dose of rFVIIa in this series was low by modern standards, ranging from just 30 to 90 $\mu\text{g kg}^{-1}$. Initial experience with continuous infusion of rFVIIa in elective surgery was also disappointing [9]. 5/8 patients undergoing surgery experienced significant bleeding when given a continuous infusion of 16.5 $\mu\text{g kg}^{-1} \text{h}^{-1}$ which raised plasma FVII levels to 10 IU/ml. Better results were obtained in a subsequent prospective study of nine patients in which an initial bolus dose of 90 $\mu\text{g kg}^{-1}$ was followed by continuous infusion of rFVIIa at a rate of 50 $\mu\text{g kg}^{-1} \text{h}^{-1}$ [10]. Whilst the final outcome was judged to be good in all cases, six patients

experienced postoperative bleeds, which required an additional bolus dose. A recent review of published data on the use of rFVIIa in the setting of elective orthopaedic surgery noted that the optimal dose remained to be established and lamented the lack of a defined protocol [11].

Against this background, a group of physicians met in London in October 2006 to try and establish a consensus on a protocol for the use of rFVIIa to manage patients with haemophilia complicated by inhibitors undergoing elective orthopaedic surgery. The aim was to review published data, share experience and formulate a protocol with a view to ensuring a consistent approach to clinical management and optimizing outcome.

The expert group comprised six experienced haematologists and one orthopaedic surgeon from the UK, under the chairmanship of Professor Jørgen Ingerslev. A 'best practice' approach was applied to the overall management of these patients from the preoperative planning phase to hospital discharge and rehabilitation. A protocol was formulated based on published reports, including the EUREKA study (European Registry on Knee Arthroplasty performed in haemophilia patients with rFVIIa as first-line treatment) [12] as well as personal experience. The consensus protocol presented here represents the group consensus on the management of haemophilic patients with inhibitors undergoing elective orthopaedic surgery. The protocol provides guidance on the planning of the surgery and preoperative testing as well as the bolus schedule for rFVIIa and advice on the concomitant use of antifibrinolytic agents and fibrin sealant. The protocol also includes a section on troubleshooting in case of bleeding complications.

Data accumulated from the application of this dosing schedule to elective orthopaedic surgery carried out in the UK and Republic of Ireland over the last 2 years are also presented.

Protocol

Planning the operation and preoperative assessment

The following issues need to be considered:

1. Clinical experience and expertise: the challenges posed by undertaking elective orthopaedic surgery in patients with haemophilia, complicated by inhibitors, should not be underestimated. Such operations should only be undertaken in comprehensive-care centres, which have the requisite multidisciplinary experience and facilities.
2. Timing of the surgery: surgery should ideally be scheduled for the morning of a day, early in the

week. It is important that, in particular, a haematologist is readily available for the first few days after surgery to carefully monitor the patient.

3. Preoperative assessment of haemostasis:
 - a. In addition to assaying the anti factor VIII antibody titre, the platelet count and prothrombin time should be checked. Levels of other coagulation factors may be assayed if there is evidence of significant impairment of liver function.
 - b. It is imperative that the patient does not take aspirin or any other non-steroidal anti-inflammatory drugs prior to surgery. If the patient is taking such medication on a regular or irregular basis, it should be discontinued 1 week before the scheduled surgery. Aspirin should certainly not be given for postoperative thromboprophylaxis. Similarly, any drugs with an antiplatelet effect (e.g. clopidogrel) should be stopped a week before surgery. A number of herbal remedies have been suggested to impair platelet function, although data are conflicting [13–15]. In such cases, platelet function testing may be warranted if there is any doubt.
4. The previous clinical response to treatment should be carefully considered. Ideally, the patient will have a documented good response to infusions of rFVIIa for bleeding episodes. A number of groups are evaluating preoperative *ex vivo* thromboelastography and thrombin generation tests in this setting. Although there are as yet no validated guidelines or protocols for the use of these laboratory techniques, the method may provide some additional information by monitoring response to haemostatic agents such as rFVIIa or prothrombin complex concentrates [16–18]. If possible, deferring elective surgery until such time as the antibody titre is <5 BU may be considered desirable. This may facilitate rescue therapy with human factor VIII (or IX) concentrates in the event of postoperative bleeding.
5. Combined procedures may be carried out but should only be considered if the patient is willing to comply with what is likely to be a longer stay and more demanding rehabilitation programme after surgery. The haemostatic challenge will be greater with double procedures and therefore there is a rationale for administering more doses in the immediate postoperative phase.

Surgery

1. Anaesthetic: surgery should be conducted under general anaesthesia and not epidural/spinal block.

2. Use of antifibrinolytic agent: the concomitant administration of an antifibrinolytic such as tranexamic acid is recommended, unless there is a strong contraindication. There is evidence that it may enhance the effect of rFVIIa and improve haemostasis [19]. A recommended schedule is to start oral treatment with tranexamic acid the evening before surgery at a dose of 25 mg kg^{-1} every 6–8 h. The medication should be continued until discharge. The drug may be given by initial intravenous administration if preferred (although a different dose regimen will apply).
3. Dosing with rFVIIa: the consensus group recommend that bolus doses of rFVIIa should be used. As discussed above, administration by continuous infusion rFVIIa has been reported in the setting of clinical studies, but the data regarding its efficacy are variable [9,10,20–23]. It is important that the time schedule for the administration of bolus doses of rFVIIa is strictly adhered to as the omission of a dose may result in bleeding. Some brands of syringe pumps or drivers may be used to deliver bolus doses.
 - a. An initial preoperative bolus of $120\text{--}180 \text{ } \mu\text{g kg}^{-1}$ should be given at the start of surgery, just prior to the first incision.
 - b. Follow up doses of $90 \text{ } \mu\text{g kg}^{-1}$ should be given at 2-h intervals throughout surgery. A final intraoperative bolus should be given just prior to final reduction in the case of hip arthroplasty or release of the tourniquet (if used) in the case of knee arthroplasty.
4. The topical application of a fibrin sealant during the intraoperative period can help to minimize capillary oozing. The concomitant use of vasoconstrictors such as lidocaine and/or adrenaline may also be helpful in this regard.
5. Continue 2-hourly dosing for the next 48 h:
 - a. Depending on staffing levels, it may be prudent to secure the patient a bed on the Intensive Care Unit or in a High Dependency Unit, where the patient can be closely monitored and timed 2-hourly boluses can be administered without any delay.
 - b. Ensure that a bolus dose of $90 \text{ } \mu\text{g kg}^{-1}$ rFVIIa is administered 10 min prior to the removal of wound drains.
 - c. After 48 h of 2-hourly boluses, the dosing interval may be increased to 3-hourly boluses for the following 48 h if the patient has achieved good haemostasis.
 - d. At day +5 after surgery, the interval between doses may be further increased to 4-hourly boluses for the next 3 days (72 h).

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2. Dosing with rFVIIa: the consensus group recommend that bolus doses of rFVIIa should be used. As dis...

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- e. At day +8 after surgery, the interval between doses may be further lengthened to 6-hourly doses thereafter until discharge.
- f. In uncomplicated cases, discharge should be possible at around 10–12 days after surgery. A further bolus ($90 \mu\text{g kg}^{-1}$) should be given prior to removal of sutures.

Physiotherapy

The patient should be made aware during preoperative counselling of the importance of active engagement with the physiotherapy/rehabilitation programme to help to ensure a good surgical outcome. At the same time, it is important to avoid bleeding into a new joint.

1. Continuous Passive Motion (CPM): this should be gentle and conducted in the early postoperative period and timed to follow a prescribed bolus dose of rFVIIa.
2. Physiotherapy protocols should be conducted according to local protocols and on an individualized basis. Ensure that all physiotherapy sessions conducted in hospital are covered by a bolus of rFVIIa.
3. A pretraining bolus of $90 \mu\text{g kg}^{-1}$ is recommended before physiotherapy sessions after discharge.

Management of unexpected bleeding after surgery

Persistent oozing after surgery:

1. Check whether bolus doses have been administered as prescribed.
2. Stop any rehabilitation programme immediately and rest the limb.
3. Check coagulation screen, platelets and fibrinogen.
4. Bring forward the next scheduled dose of rFVIIa and consider increasing the dosage. Give further five doses of $90 \mu\text{g kg}^{-1}$ every 2 h until haemostasis is achieved. Consider increasing the dosage.
5. Consider platelet transfusion if there is evidence of thrombocytopenia (platelet count $<50,000 \times 10^9 \text{ L}^{-1}$) or abnormal platelet function.
6. Consider changing treatment to plasma-derived activated prothrombin complex concentrate (FEIBATM; Baxter) if previous measures have not been successful.

Clinical experience

We report the outcome after 10 operations in five comprehensive care centres (see acknowledgements) in which an initial bolus of $120\text{--}180 \mu\text{g kg}^{-1}$ rFVIIa was used before surgery. These data encompass all

cases of elective orthopaedic surgery using rFVIIa as initial treatment that were carried out in the UK and Republic of Ireland over the last 2 years. The operations involved 13 procedures in eight patients, including hip arthroplasty (2), knee arthroplasty (7), shoulder arthroplasty (1), ankle arthrodesis (2) and below-knee amputation of leg (1). More than one procedure was carried out in two cases (ankle fusion and knee arthroplasty in one case and leg amputation, hip and knee arthroplasty in the other case). Nine of the patients had congenital haemophilia A and one had acquired haemophilia. The age range of the patients was from 25 to 81 years and the preoperative antibody titre ranged from 0 to 80 BU. The preoperative bolus of rFVIIa was at least $120 \mu\text{g kg}^{-1}$ in all cases ($120 \mu\text{g kg}^{-1}$ in one, $150 \mu\text{g kg}^{-1}$ in one, $160 \mu\text{g kg}^{-1}$ in two and $180 \mu\text{g kg}^{-1}$ in six operations).

Intraoperative haemostasis was reported as satisfactory in all 10 operations. None of the centres reported using special assays such as factor VII levels or thromboelastography to monitor treatment. Tranexamic acid was used perioperatively in seven out of 10 operations. There were two cases of postoperative bleeding. In one case, bleeding into the knee occurred 5 days after arthroplasty. The patient had not been given tranexamic acid perioperatively and the problem resolved after increasing the dose of rFVIIa. The second instance occurred in the patient undergoing shoulder arthroplasty. This is a particularly challenging operation and the case reported in this instance is believed to be the very first case performed in a person with haemophilia and inhibitors. The patient bled 8 h after surgery: he had received tranexamic acid and in this case the clinicians switched to the use of an activated prothrombin complex concentrate (FEIBATM; Baxter). Bleeding did not stop immediately but eventually resolved some 5 days after the change in regimen. In one centre, two patients switched treatment to an activated prothrombin complex concentrate (FEIBATM; Baxter) 2 and 6 days respectively after knee arthroplasty with the perceived intention of cost saving (the supervising clinician plans to publish details of this hybrid regimen separately).

The final outcome was rated as 'excellent' or 'extremely satisfactory' in all cases by the reporting clinicians.

Discussion

Successful elective orthopaedic surgery (EOS) of an affected joint in a haemophilic patient with inhibitors

can result in a positive, life-changing experience resulting from relief of chronic pain, decreased bleed frequency into a new joint, less time spent in hospital, increased mobility and improved well-being [24]. The goal of this consensus protocol is to offer guidance to haematologists planning elective surgery for patients with haemophilia and inhibitory antibodies. A key recommendation in the protocol presented in this paper is a preoperative bolus dose of rFVIIa in the range of 120–180 $\mu\text{g kg}^{-1}$, which is somewhat higher than what has generally been used previously [11].

The clinical experience reported here encompasses all cases of elective orthopaedic surgery carried out in the United Kingdom and Republic of Ireland over the last 2 years in which rFVIIa was been used as the first line of therapy. A total of 10 operations involving 12 procedures in eight patients in five centres have now been undertaken using initial bolus doses of rFVIIa in the range of 120–180 $\mu\text{g kg}^{-1}$ to cover surgery. In all cases, there was good control of haemostasis during surgery and the final outcome was rated as 'excellent' or 'extremely satisfactory' by the reporting clinicians.

It is interesting to note that none of the haemophilia centres employed specialized laboratory assays to monitor treatment. There is no single validated laboratory test for monitoring rFVIIa therapy. The administration of rFVIIa typically shortens the prothrombin time to below-normal levels, but this shortening has no direct bearing on the clinical effect of rFVIIa in haemophilia. Equally, factor VII:C levels have not been shown to correlate directly with the haemostatic effect of rFVIIa in the patient. A shortened prothrombin time may be useful in confirming that rFVIIa has been administered and may even be useful as part of a pharmacokinetic profiling of a patient but the assay of factor VII:C levels does not enable the clinician to make therapeutic dosing decisions with regards to tailoring or adjusting rFVIIa therapy. Traditional coagulation tests such as the activated partial thromboplastin and prothrombin times are performed in platelet-poor plasma. These tests can only provide information on the initial stage of clot formation and cannot be used to evaluate continued clot development. Thromboelastography is undergoing evaluation as a possible technique for monitoring therapy as it provides objective *ex vivo* measurement of various parameters and phases of coagulation, including initiation and propagation during whole blood clot formation as well as final clot strength and fibrinolysis [17,18]. Thrombin-generation assays performed in platelet-poor plasma

are not useful for attempting to monitor the therapeutic effect of rFVIIa because platelets are an essential component for the mode of action of rFVIIa. Improved thrombin generation is only seen in test systems using platelet-poor plasma in the presence of very high levels of rFVIIa [16]. Additional work will clearly be required to determine the role of these techniques in monitoring surgery in haemophilic patients with inhibitors.

The challenges posed by undertaking elective orthopaedic surgery in patients with haemophilia, complicated by inhibitors, should not be underestimated. All the operations reported in this paper were undertaken in designated comprehensive care centres with considerable experience in dealing with such patients. Whilst the improved life-expectancy observed in patients with haemophilia and inhibitors is undoubtedly attributable largely to the development of new agents, the importance of specialist multidisciplinary care in improving outcome should not be overlooked. This was emphasized by a multicentre US study, which demonstrated that patients who were treated in the setting of specialist haemophilia centres had a better survival than others cared for in non-specialist facilities [25]. In this study of 2950 haemophilic men followed up for an average of 2.6 years during the period from 1993 to 1995, those who received care in specialist haemophilia centres were 40% less likely to die than those who did not. It is recommended that surgery in patients with inhibitors should only be undertaken in comprehensive care centres, which have the requisite multidisciplinary experience and facilities.

Activated prothrombin complex concentrates (aPCC) such as FEIBATM (Baxter) have also been used to cover surgical procedures in haemophilia patients with inhibitors [26–30]. The limited comparative data available relating to activated PCC use in this setting suggests similar efficacy to rFVIIa. Both agents are recommended in equal measure in the current UK guidelines relating to management of surgery in patients with inhibitors [31]. The members of this group wish to make it clear that they are not suggesting that activated prothrombin complex concentrates should not be used to cover surgery, but are simply recommending that if a local clinical decision is taken to use rFVIIa, then the dosing regimen described in this paper should be followed. In practice, rFVIIa is now increasingly regarded as the treatment of choice for major orthopaedic surgery in patients with congenital haemophilia complicated by inhibitors in both the UK and Republic of Ireland. This is possibly related to the fact that both countries have policies of using only recombinant factor VIII

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and IX in uncomplicated haemophilia. As a recombinant product, rFVIIa carries no risk of contamination with human pathogens. Furthermore, the use of rFVIIa does not provoke an anamnestic rise in antibody titre, which can occur in association with the administration of aPCC. Thrombotic complications have been reported with both aPCC and rFVIIa although the absolute risk seems to be very low [32, 33].

The cost of rFVIIa to cover this type of surgery is approximately UK £400,000 ($\approx$ US \$750,000; €500,000). Whilst this undoubtedly represents a significant initial financial outlay, it must be borne in mind that the costs may be recovered in due course through abolition of further bleeding episodes within the joint. An independent pharmacoeconomic study calculated that the 'break-even' time (defined as the time after surgery when cost is completely offset by savings resulting from avoided bleeding episodes) ranged from 5 to 9 years [34]. This figure was based on an assumption of an 80% reduction in bleeding frequency. This may be the case with procedures such as osteotomy and synovectomy, but complete cessation of joint bleeding is the norm after arthroplasty so costs are likely to be recovered more quickly than after other types of operation. Furthermore, this analysis only took into consideration the costs associated with bleeds in the operated joint. It is commonly observed that arthroplasty can also reduce the bleeding frequency in other joints (e.g. bleeds in the shoulder or elbow associated with dependence on crutches can be controlled by joint replacement in the lower limb). The authors of this analysis suggest that initial bleeding frequency should also be taken into consideration when deciding whether surgery is indicated. The break-even time was most sensitive to changes in the bleeding rate prior to surgery, suggesting that the pharmacoeconomic benefits of orthopaedic surgery may be particularly evident in patients with relatively frequent bleeds. Carrying out two procedures at the same time, as was done in two patients in the series presented here, will also obviously help to reduce costs even more.

In summary, we present a new protocol for the use of rFVIIa in elective orthopaedic surgery. This is based on a review of published data as well as the personal experience of a group of expert physicians. A key new recommendation is an initial bolus dose of rFVIIa in the range of 120–180 $\mu\text{g kg}^{-1}$ to cover surgery. We report a successful outcome after 10 elective orthopaedic operations involving 13 procedures in eight patients in the UK and Republic of Ireland.

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References

- 1 Darby SC, Kan SW, Spooner RJ *et al.* Mortality rates, life expectancy, and causes of death in people with

- hemophilia A or B in the United Kingdom who were not infected with HIV. *Blood* 2007; **110**: 815–25.
- 2 Darby SC, Keeling DM, Spooner RJD, Giangrande PLF, Collins PW, Hill FG. The incidence of factor VIII and factor IX inhibitors in the hemophilia population of the UK and their effect on subsequent mortality, 1977–99. *J Thromb Haemost* 2004; **2**: 1047–54.
 - 3 Gringeri A, Mantovani L, Salone L, Mannucci PM. Cost of care and quality of life in hemophilia complicated by inhibitors: the COCIS study group. *Blood* 2003; **102**: 2358–63.
 - 4 Salone L, Mantovani LG, Mannucci PM, Gringeri A, and the COCIS Study Investigators. Quality of life is associated to the orthopaedic status in haemophilic patients with inhibitors. *Haemophilia* 2006; **12**: 154–62.
 - 5 Morfini M, Haya S, Tagariello G *et al*. European study on orthopaedic status of haemophilia patients with inhibitors. *Haemophilia* 2007; **13**: 606–12.
 - 6 Duthie RB, Dodd CAF. "Reconstructive surgery and joint replacement". In: Duthie RB, Rizza CR, Giangrande PLF, Dodd CAF, eds. *The management of musculoskeletal problems in the haemophilias*. Oxford: Oxford University Press, 1994: 191.
 - 7 Hedner U, Glazer S, Pingel K *et al*. Successful use of recombinant factor VIIa in patient with severe haemophilia A during synovectomy. *Lancet* 1988; **ii**: 1193 (Letter).
 - 8 Rodriguez-Merchan EC, Wiedel JD, Wallny T *et al*. Elective orthopaedic surgery for hemophilia patients: new opportunities. *Semin Hematol* 2004; **41**(Suppl. 1): 109–16.
 - 9 Smith M, Ludlam CA, Collins PW *et al*. Elective surgery on factor VIII inhibitor patients using continuous infusion of recombinant activated factor VII. *Thromb Haemost* 2001; **86**: 949–53.
 - 10 Ludlam CA, Smith MP, Morfini M, Gringeri A, Santagostino E, Savidge GF. A prospective study of recombinant activated factor VII administered by continuous infusion to inhibitor patients undergoing elective major orthopaedic surgery: a pharmacokinetic and efficacy evaluation. *Br J Haematol* 2003; **120**: 808–13.
 - 11 Obergfell A, Auvinen M-K, Mathew P. Recombinant activated factor VII for haemophilia patients with inhibitors undergoing orthopaedic surgery: a review of the literature. *Haemophilia* 2008; **14**: 233–41.
 - 12 Bossard D, Carrillon Y, Stieltjes N *et al*. Management of haemophilic arthropathy. *Haemophilia* 2008; **14**(Suppl. 4): 11–9.
 - 13 Ang-Lee MK, Moss J, Yuan C-S. Herbal medicines and perioperative care. *JAMA* 2001; **286**: 208–16.
 - 14 Abebe W. Herbal medication: potential for adverse interactions with analgesic drugs. *J Clin Pharm Ther* 2002; **27**: 391–401.
 - 15 Beckert BW, Concannon MJ, Henry SL, Smith DS, Puckett CL. The effect of herbal medicines on platelet function: an in vivo experiment and review of the literature. *Plast Reconstr Surg* 2007; **120**: 2044–50.
 - 16 Sørensen B, Johansen P, Christiansen K, Woelke M, Ingerslev J. Whole blood coagulation thromboelastographic profiles employing minimal tissue factor activation. *J Thromb Haemost* 2003; **1**: 551–8.
 - 17 Sørensen B, Ingerslev J. Tailoring haemostatic treatment to patient requirements – an update on monitoring haemostatic response using thromboelastography. *Haemophilia* 2005; **11**(Suppl.1): 1–6.
 - 18 Pivalizza EG, Escobar MA. Thromboelastography-guided factor VIIa therapy in a surgical patient with severe hemophilia and factor VIII inhibitor. *Anesth Analg* 2008; **107**: 398–401.
 - 19 Schulman S, d'Oiron R, Martinowitz U *et al*. Experiences with continuous infusion of recombinant activated factor VII. *Blood Coagul Fibrinolysis* 1998; **9**(Suppl. 1): 97–101.
 - 20 Tagariello G, Bisson R, Radossi P *et al*. Concurrent total hip and knee replacements in a patient with haemophilia with inhibitors using rFVIIa by continuous infusion. *Haemophilia* 2003; **9**: 738–40.
 - 21 Mauser-Bunschoten EP, de Goede-Bolder A, Wielenga JJ, Levi M, Peerlinck K. Continuous infusion of recombinant factor VIIa in patients with haemophilia and inhibitors: experience in the Netherlands and Belgium. *Neth J Med* 1998; **53**: 249–55.
 - 22 Santagostino E, Morfini M, Rocino A, Baudo F, Scaraggi FA, Gringeri A. Relationship between factor VII activity and clinical efficacy of recombinant factor VIIa given by continuous infusion to patients with factor VIII inhibitors. *Thromb Haemost* 2001; **86**: 954–8.
 - 23 Pruthi RK, Mathew P, Valentino LA *et al*. Haemostatic effect and safety of bolus and continuous infusion of recombinant factor VIIa are comparable in haemophilia patients with inhibitors undergoing major surgery. Results from an open-label, randomized, multicenter trial. *Thromb Haemost* 2007; **98**: 710–2.
 - 24 Peacock K. Quality of life before and after surgery: mobility issues, the fear of surgery, impatient recovery and outpatient rehabilitation. *Haemophilia* 2005; **11**(Suppl. 1): 30–1.
 - 25 Soucie JM, Nuss R, Evatt B *et al*. Mortality among males with hemophilia: relations with source of care. *Blood* 2000; **96**: 437–42.
 - 26 Negrier C, Goudemand J, Sultan Y *et al*. Multicenter retrospective study on the utilization of FEIBA in France in patients with factor VIII and factor IX inhibitors. *Thromb Haemost* 1997; **77**: 1113–9.
 - 27 Hvid I, Rodriguez-Merchan EC. Orthopaedic surgery in haemophilic patients with inhibitors: an overview. *Haemophilia* 2002; **8**: 288–91.
 - 28 Goudemand J, Tagariello G, Lopaciuk F. Cases of surgery in high responder haemophilia patients. *Haemophilia* 2002; **10**(Suppl. 2): 46–9.
 - 29 Tjønnfjord GE. Activated prothrombin complex concentrate (FEIBA) treatment during surgery in patients with inhibitors to FVIII/IX: the updated Norwegian experience. *Haemophilia* 2004; **10**: 41–5.

- 30 DiMichele D, Negrier C. A retrospective postlicensure survey of FEIBA efficacy and safety. *Haemophilia* 2006; **12**: 352–62.
- 31 Hay CRM, Brown S, Collins PW, Keeling DM, Liesner R. The diagnosis and management of factor VIII and IX inhibitors: a guideline from the United Kingdom Haemophilia Centre Doctors Organisation. *Br J Haematol* 2006; **133**: 591–605.
- 32 Aledort LM. Comparative thrombotic event incidence after infusion of recombinant factor VIIa versus factor VIII inhibitor bypass activity. *J Thromb Haemost* 2004; **2**: 1700–8.
- 33 Hay CRM. Thrombosis and recombinant factor VIIa [commentary]. *J Thromb Haemost* 2004; **2**: 1698–9.
- 34 Lyseng-Williamson KA, Plosker GL. Recombinant factor VIIa (eptacog alfa): A pharmacoeconomic review of its use in haemophilia in patients with inhibitors to clotting factors VIII or IX. *Pharmacoeconomics* 2007; **25**: 1007–29.