REVIEW ARTICLE

Comprehensive care of the patient with haemophilia and inhibitors undergoing surgery: practical aspects

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Summary. Congenital haemophilia is a rare and complex condition for which dedicated specialized care has produced measurable improvements in clinical outcomes and advances in patient management. Among these advances is the ability to safely perform surgery in patients with inhibitor antibodies to factors VIII and IX, in whom all but the most necessary of surgeries were once avoided due to the risk for uncontrollable bleeding due to ineffectiveness of replacement therapy. Nevertheless, surgery continues to pose a major challenge in this relatively rare group of patients because of significantly higher costs than in patients without inhibitors, as well as a high risk for bleeding and other complications. Because of the concentration of expertise and experience, it is recommended that any surgery in patients with haemophilia and inhibitors be planned in conjunction with a haemophilia treatment centre (HTC) and performed in a hospital that incorporates a HTC. Coordinated, standard pre-, intra- and postoperative assessments and planning are intended to optimize surgical outcome and utilization of resources, including costly factor concentrates and other haemostatic agents, while minimizing the risk for bleeding and other adverse consequences both during and after surgery. This article will review the special considerations for patients with inhibitors as they prepare for and move through surgery and recovery, with an emphasis on the roles and responsibilities of individual members of the multidisciplinary team in facilitating this process.

Keywords: activated prothrombin complex concentrate, comprehensive health care, haemophilia, inhibitors, recombinant activated FVII, surgery

Introduction

Congenital haemophilia, a rare and complex condition, requires a lifetime of specialized care. A network of haemophilia treatment centres (HTCs) has been established in many developed countries to provide dedicated comprehensive, multidisciplinary care in a single setting [1]. In the United States, the provision of haemophilia care by these centres has led to an array of documented improved outcomes, including substantial reductions in hospital visits, health care costs, work and school absenteeism and even mortality [2,3]. Even in developing countries with limited haemostatic treatment options, the establishment of local expertise via such initiatives as ‘twinning’ programmes has resulted in improvements in patient care [1].

Approximately 20–30% and 1–6% of patients with severe haemophilia A and B, respectively [4], develop inhibitory antibodies that render replacement therapy ineffective, potentially leading to life-threatening bleeding events. Inhibitors are the most serious and costly complication of haemophilia, and they particularly pose a challenge when surgical intervention is necessary. In patients with low-titre inhibitors (<5 Bethesda units [BU]), haemostasis is achievable with higher-than-normal doses of factor that overwhelm the inhibitor. However, for those with high-titre inhibitors (≥5 BU), bypassing agents that circumvent the need for factor VIII (FVIII) or FIX concentrates are used to achieve haemostasis. Until recently, perioperative prophylaxis with bypassing agents was not considered in congenital haemophilia with inhibitors (CHwl) [5], and elective (especially major) surgery was rarely performed [6]. Consequently, potentially beneficial surgeries and invasive screening procedures may have been deferred.
in this population, to the detriment of affected patients [7,8]. Given the availability of effective bypassing agents, coupled with the increasing experience of HTCs in managing the surgical needs of patients with CHwI, even complex surgery is now feasible in this population [6,9–12]. However, the risk for uncontrollable bleeding remains a serious threat. Because of the specialized expertise required to ensure proper perioperative haemostasis, monitoring, and care of patients with inhibitors undergoing surgery, these procedures should ideally be performed in hospitals affiliated with HTCs, where there is a concentration of expert multidisciplinary resources [13].

The objective of this article is to summarize key practical aspects of the comprehensive care approach to surgery in CHwI, including important considerations before, during and after surgery.

Methods

A search of the PubMed database-indexed literature was undertaken, using a combination of the keywords ‘hemophilia,’ ‘inhibitor’ and ‘surgery,’ to identify English-language articles describing general considerations for and anecdotal experience with surgery in patients with inhibitors published between January 1990 and July 2012. Original articles, review articles and case reports and series were consulted for general principles and recommendations for perioperative assessment and management of patients with inhibitors. Predominately larger case series consisting of more than 10 cases and consensus protocols were referenced for perioperative haemostatic strategies; care was made to avoid inclusion of case series with potentially overlapping data. Smaller case series and case reports were primarily reviewed to identify any considerations for specific surgery types or novel approaches to surgery in CHwI overall. Supplemental literature searches were conducted around specific aspects of surgery (e.g. anaesthetic management, physiotherapy) as needed. Information from the literature was complemented by the author’s clinical experience in this area.

Practical aspects of the surgical comprehensive care approach

The comprehensive care approach ideally incorporates a number of specific pre-, intra-, and postoperative objectives for all patients with CHwI undergoing surgery, regardless of the procedure to be performed (Table 1). There may also be specific perioperative considerations for individual surgical procedures (Table 2). The primary goal of this coordinated, multidisciplinary approach is to optimize operative results and recovery, while limiting adverse outcomes. The most common types of surgeries that have been performed in patients with CHwI include central venous access device (CVAD) placement/removal and orthopaedic and dental procedures, although many other procedures have also been reported in this patient population [5,11].

General preoperative assessments and considerations

Approximately 2–3 weeks prior to elective surgery, a member (or members) of the standard multidisciplinary core HTC team – consisting of a haematologist, nurse coordinator, social worker and physical therapist – will typically conduct an evaluation of whether or not the patient is an appropriate surgical candidate, based on a thorough familiarity with the nature and progression of the condition for which surgery is advocated, and will prepare the patient for surgery, including any necessary preoperative assessments and referrals. Specifically, the haematologist provides a written detailed treatment plan including duration and dosage of haemostatic therapies, the HTC nurse communicates with the operating room and hospital nurses to ensure that the plan is carried out appropriately, and the physical therapist estimates when to initiate and how long to continue physical therapy in cases of orthopaedic surgery. Prior to surgery, several aspects of surgical readiness should be explored, including the patient’s history of adherence to prior treatment recommendations, patient expectations regarding surgical outcome and recovery and certain psychosocial elements, including current patient support systems. In cases in which they have not been previously assessed, these factors may be addressed during a formal preoperative visit, ideally several weeks before the scheduled surgery [14]. The preoperative visit also provides an opportunity to educate the patient and family about the surgical procedure itself and the expected course of recovery.

In addition to a general health appraisal, the preoperative medical assessment should include a history, including history of prior surgery as well as response to bypassing agents, and an evaluation for comorbid conditions, such as hepatitis C or HIV infection or cardiopulmonary, renal, or liver disease, for the purposes of appropriate anaesthetic management and medication dosing. A comprehensive laboratory evaluation, including complete blood count; tests for liver and renal function; blood type; and haemostatic workup, including prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, inhibitor assay, and for patients who have a low-titre inhibitor or who are undergoing immune tolerance therapy (ITT), a review of their pharmacokinetics study, which may be used to guide the dosing frequency of factor concentrates. A thrombophilia workup (factor V Leiden, prothrombin mutation, proteins C and S, and antithrombin levels), although not
Table 1. Perioperative checklist for the patient with haemophilia and inhibitors undergoing surgery.

<table>
<thead>
<tr>
<th>Preoperative</th>
<th>Intraoperative</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Identify patient as a suitable surgical candidate</strong></td>
<td><strong>Administer preplanned haemostatic regimen and monitor response</strong></td>
<td><strong>Analgesic regimen taking prior analgesic use into account</strong></td>
</tr>
<tr>
<td>with regard to:</td>
<td><strong>Apply surgical and anaesthetic practices and techniques that minimize the risk for bleeding both during and after surgery [including long term (e.g. avoid need for prolonged antithrombotic therapy)]</strong></td>
<td><strong>Use mechanical techniques for thromboprophylaxis; consider pharmacological prophylaxis in patients with underlying thrombophilia only</strong></td>
</tr>
<tr>
<td><strong>Readiness for anticipated recovery programme</strong></td>
<td><strong>Tests of hepatic and renal function, if indicated</strong></td>
<td><strong>Observe patient for infection and maintain strict aseptic care</strong></td>
</tr>
<tr>
<td><strong>Perform relevant laboratory testing, including:</strong></td>
<td><strong>Evaluate current and prior analgesic usage and any illicit drug use</strong></td>
<td><strong>Monitor wound healing; continue haemostatic therapy through beginning of healing</strong></td>
</tr>
<tr>
<td>Haemostatic workup (PT, aPTT, fibrinogen, inhibitor titre, CBC, thrombophilic markers, if indicated)</td>
<td><strong>Refer to physical therapist to devise a plan for ‘prehabilitation’ and assess postsurgical rehabilitative needs</strong></td>
<td><strong>Avoid premature mobilization and physical therapy; pretreat with bypassing agent prior to therapy sessions, once initiated</strong></td>
</tr>
<tr>
<td><strong>Refer patient for nutritional assessment</strong></td>
<td><strong>Plan perioperative i.v. access</strong></td>
<td><strong>Notify blood bank to hold potentially needed blood products; devise a plan for intra- and postoperative haemostasis</strong></td>
</tr>
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<td><strong>Identify patient as a suitable surgical candidate</strong></td>
<td><strong>Refer patient for nutritional assessment</strong></td>
<td></td>
</tr>
<tr>
<td>with regard to:</td>
<td><strong>Plan perioperative i.v. access</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Expectations for surgical outcome</strong></td>
<td><strong>Notify blood bank to hold potentially needed blood products; devise a plan for intra- and postoperative haemostasis</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Readiness for anticipated recovery programme</strong></td>
<td><strong>Refer to physical therapist to devise a plan for ‘prehabilitation’ and assess postsurgical rehabilitative needs</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>Evaluate current and prior analgesic usage and any illicit drug use</strong></td>
<td><strong>Refer to physical therapist to devise a plan for ‘prehabilitation’ and assess postsurgical rehabilitative needs</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Request a dental evaluation (and treatment, if necessary)</strong></td>
<td><strong>Plan perioperative i.v. access</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Refer to physical therapist to devise a plan for ‘prehabilitation’ and assess postsurgical rehabilitative needs</strong></td>
<td><strong>Notify blood bank to hold potentially needed blood products; devise a plan for intra- and postoperative haemostasis</strong></td>
<td></td>
</tr>
</tbody>
</table>

§ Cases in patients with inhibitors are limited and describe primarily patients with low-titre inhibitors. In all cases, high-dose factor replacement was used minimizing bleeding risk in any patient or in patients with an increased risk for bleeding. Recommendations or considerations that apply specifically to patients without inhibitors (but may be extrapolated to patients with inhibitors) are denoted.

‡ Applies primarily to patients with inhibitors receiving factor replacement for haemostatic coverage.

Table 2. Specific considerations for individual surgical procedures in patients with haemophilia and inhibitors.*

**Cardiac valve replacement**

- Bioprosthetic valve recommended in lieu of mechanical valve, which requires long-term anticoagulation [55]
- LMWH recommended for immediate postoperative thromboprophylaxis in patients with haemophilia, in conjunction with CFC [55]†

**Cardiac surgery requiring ECCS**

- Consider FFP vs. saline prime of bypass circuit to avoid dilution of coagulation factors [12]†
- Standard heparinization generally employed after CFC in patients with haemophilia without inhibitors [56]§
- To maintain factor levels after surgery, consider reinfusing entire pump volume instead of just the RBC fraction (may require additional protamine to reverse heparin in perfusate) [12]

**Hepatic procedures and surgeries**

- Maintenance of a low CVP may be considered to minimize hepatic venous bleeding [57]
- Transjugular biopsy has been described in a patient with haemophilia A and high-titre inhibitor; may reduce the risk for bleeding compared with percutaneous biopsy [58]
- In addition to haemostatic treatments targeting the inhibitor, FFP may be necessary in patients with pre-existing hepatic dysfunction to replace other deficient coagulation factors (FII, FVII, or FX) [59]

**Synovectomy**

- Radiosynovectomy is first-line treatment, particularly in patients with inhibitors [60]
- Should proceed to arthroscopic synovectomy if radiosynovectomy is unsuccessful after three consecutive attempts [60]
- Osteotomy
  - Internal fixation is preferred for stabilization of osteotomy site because external fixators may be associated with soft tissue bleeding and infection along the pin tracks [8]
- Bony pseudotumour excision
  - Surgical excision is treatment of choice for proximal pseudotumors, but may be associated with profuse bleeding and infection [60]
- Consider embolization or radiotherapy in lieu of surgical removal in patients with inhibitors [60]

*CFC, clotting factor correction; CVP, central venous pressure; ECCS, extracorporeal circulatory support; FFP, fresh frozen plasma; FII, factor II; FVII, factor VII; FX, factor X; LMWH, low-molecular weight heparin; RBC, red blood cell.

*In most cases, in the absence of evidence specifically in patients with CHW1, individual considerations are based on theoretical principles aimed at minimizing bleeding risk in any patient or in patients with an increased risk for bleeding. Recommendations or considerations that apply specifically to patients without inhibitors (but may be extrapolated to patients with inhibitors) are denoted.

*Recommendations are specifically for patients with haemophilia without inhibitors; no corresponding recommendations exist for patients with inhibitors at present.

*Cases in patients with inhibitors are limited and describe primarily patients with low-titre inhibitors. In all cases, high-dose factor replacement was used intraoperatively; heparinization protocols were not described.

routinely performed, can be undertaken in those with a prior history or family history of thrombosis. In conjunction with the pain management team, a preoperative assessment of pain and current and prior use of prescribed opioids, illicit drugs or recreational substances should be performed. Dental evaluation and treatment may be warranted, particularly if implantation of a prosthetic device or CVAD is expected. A physical therapy evaluation may also be warranted for patients undergoing elective orthopaedic surgery (EOS). During the initial preoperative visit, the therapist will typically evaluate the patient’s baseline musculoskeletal and functional status and bleeding patterns in preparation for planning a post-
operative rehabilitative regimen and initiate a plan for preoperative therapy, or ‘prehabilitation,’ as needed [8]. In addition, the therapist can determine the necessity for mobility aids or adaptations to the home environment that may facilitate mobility and prevent injury after discharge.

Additional preoperative considerations may include devising a plan for perioperative intravenous access. For long-term postoperative access, placement of a CVAD or a peripherally inserted central catheter (PICC) may be considered in lieu of peripheral access [14]. However, given that the presence of inhibitors is an independent risk factor for infection after total knee replacement (TKR) [15], the potential benefits of CVAD placement must be weighed against the risk for infection in patients with inhibitors. Patients should be advised to discontinue any non-steroidal anti-inflammatory drugs or antiplatelet agents a week prior to surgery [13]. Referral should be made to a dietician to evaluate nutritional status, since obesity or malnourishment as determined by body mass index is an important predictor of postoperative complications [16,17]. Finally, as part of the holistic approach to preparing a patient with inhibitors for surgery, the HTC social worker should conduct a full psychosocial assessment, including identification of potential barriers to and requirements for optimal recovery.

The consulting surgeon should have experience operating on patients with CHwI in addition to performing the specific indicated surgery. Solimeno et al. [15] reported that the experience and expertise of the operating surgeon was an independent predictor of infection risk following TKR in patients with haemophilia, with and without inhibitors. The preoperative surgical evaluation provides the surgeon with an opportunity to examine the patient and review or obtain relevant studies, and discuss the surgical procedure and expected outcome and recovery with the patient as part of the informed consent process. The surgeon should be made aware of the patient’s HIV and hepatitis C status, as affected patients are more susceptible to postoperative infections. In addition, to reduce the risk for transmission of these blood-borne pathogens to the surgical team, personal protective equipment and appropriate disposal of contaminated materials is warranted [8]. If use of ethanol lock to prevent CVAD infections [18] is intended, the surgeon, in consultation with the HTC staff, should determine catheter compatibility with ethanol [19].

To ensure access to relevant laboratory studies and specialists, elective procedures should be scheduled for early in the week and as early in the day as possible [13,20]. For maximal effectiveness, the time between administration of haemostatic treatments and surgery should be minimized. This is possible if the haematology team is informed of the precise time (within 1–2 h) at which surgery will occur [20]. A haematologist should also be readily available for consultation during at least the first few days after surgery [13]. Often, in cases of orthopaedic procedures, the surgeon may consider performing multiple surgeries during a single operative session; patients with CHwI frequently require multiple such surgeries [8,14]. However, patients must be informed in advance of the compounded duration and rigour of recovery following multiple procedures under a single anaesthetic administration [13].

The coordination of urgent or emergent procedures in patients with CHwI poses a particular challenge, given the need for rapid mobilization of resources and multidisciplinary collaboration in such cases. Sufficient supplies of haemostatic agents must be readily accessible, along with laboratory, blood bank and pharmacy support. When possible (e.g. for pending organ transplantation), advance planning should be undertaken to ensure prompt availability of these resources at the time of surgery [12].

For elective procedures, the initial plan for perioperative haemostasis is devised by the haematologist before surgery, based on such factors as the patient’s inhibitor titre and prior responses to specific haemostatic agents, as well as the expected magnitude and risk for bleeding based on whether the surgery is major or minor [10]. Preoperative planning should incorporate a determination of the specific haemostatic therapies to be used during and after surgery, including dosing regimens and whether continuous or bolus treatment will be used. It is often helpful for a member of the HTC team to be present in the operating room (OR) to assist in communication between the OR staff and the patient/family and to provide on-site guidance regarding haemostatic management, if needed.

The use of high-dose FVIII or FIX concentrates to overcome inhibitors in CHwI undergoing surgery, although ideal and measurable [8,21], is often restricted to those with low-titre or low-responding inhibitors or those who have successfully achieved tolerance. Both bolus and continuous administration of replacement factor have been effectively used in this setting, although in patients with haemophilia B and inhibitors, the use of high doses of FIX may increase the risk for anaphylaxis [10]. In patients with haemophilia A receiving FVIII replacement for surgery, an anamnestic increase in inhibitor titre may occur, necessitating a switch to bypassing therapy [22]. Although preoperative attempts to reduce the inhibitor titre using rituximab [9] and ITT [6] have been described, these treatments have limitations, most notably the time required for such regimens to take effect and, with immunosuppressive eliminative agents, the potential for susceptibility to infections.

Bypassing agents are the haemostatic products of choice for patients with high-titre or high-responding inhibitors or those with haemophilia B and inhibitors. Each of the commercially available bypassing agents –
recombinant activated FVII (rFVIIa; NovoSeven® RT; Novo Nordisk A/S, Bagsvaerd, Denmark) and activated prothrombin complex concentrate (aPCC; FEIBA®, Factor Eight Inhibitor Bypassing Agent); Baxter Healthcare Corporation (Westlake Village, CA, USA) – have been successfully used for haemostatic coverage for surgery in both children and adults with CHwI, with comparable efficacy and safety. However, there are no evidence-based guidelines for the use of either agent in this setting. Recombinant FVIIa has a relatively short half-life of 2.7 h in adults and 1.3 h in children [23]. Optimal dosing remains uncertain.

The choice of product for those with high-titre inhibitors is dependent on the age of the patient, prior exposure to plasma products, type of bleeding episode, volume-of-reconstitution cost, efficacy and safety. At most institutions, for patients who are plasma-naïve or for those with haemophilia B and inhibitors, rFVIIa is used to achieve rapid haemostasis (recombinant porcine FVIII may likewise be used for the same purpose in patients with haemophilia A and inhibitors who are plasma-naïve, when it becomes available). However, for patients with haemophilia A who have been previously exposed to plasma products, either aPCC or rFVIIa may be used [24]. The accompanying algorithm provides some guidance regarding haemostatic therapy (Fig. 1), although therapy is often highly individualized. In particular, the limited availability of bypassing agents or even factor concentrates in certain parts of the world may necessitate an individualized approach to management and adaptations in haemostatic regimens, such as the intra- and postoperative use of low-dose aPCC, cryoprecipitate, or adjunctive therapies like antifibrinolytics and fibrin glue [25,26].

The use of rFVIIa for haemostatic coverage in major and minor emergency and (mostly) elective surgeries in paediatric and adult patients with CHwI has been described in several retrospective series [6,27–31], a recent literature review [32], and a more recent analysis by Valentino et al. of data from two prospective studies, the Hemophilia and Thrombosis Research Society registry and the literature [5]. Dosing varied substantially across these sources. In most cases, initial rFVIIa doses of 90–120 µg kg⁻¹ were used, with a tendency towards higher initial doses for major surgeries [27–29]. Subsequent intra- and postoperative rFVIIa dosing varied and incorporated both bolus and continuous administration of rFVIIa. In some of the centres represented in retrospective case series, standardized regimens were described [6,27]. Overall, rFVIIa was reported as effective in the vast majority of cases encompassed by the aforementioned sources. In the analysis by Valentino et al. [5], which incorporated a small number of medical procedures (n = 45) in addition to surgical and dental procedures, rFVIIa was deemed effective in 333 (84%) of the 395 cases represented. Thromboembolic complications attributable to rFVIIa were reported in 0.025% of procedures included in that analysis.

Consensus recommendations for rFVIIa dosing for minor and intermediate or major surgical procedures in both adult and paediatric patients with CHwI have been published (Table 3) [33]. Subsequently, a consensus protocol [13] for rFVIIa dosing was devised specifically for EOS based on published data and expert opinion, incorporating recommendations for concomitant tranexamic acid dosing (Table 4), provided there are no contraindications. Satisfactory intraoperative haemostasis was achieved utilizing the higher initial rFVIIa dosing endorsed by this protocol in 13 procedures performed in five comprehensive haemophilia care centres in the United Kingdom and Ireland [13]. More recently, Caviglia et al. [34] recommended the following for optimal perioperative dosing of rFVIIa and aPCC: for rFVIIa, 120–180 µg kg⁻¹ preoperatively followed by 90 µg kg⁻¹ every 2 h postoperatively, and for aPCC, 100 U kg⁻¹ preoperatively followed by 75–100 U kg⁻¹ postoperatively, to a maximum of 200 U kg⁻¹.

First-line use of aPCC for major and minor emergency and (again mostly) elective surgeries in paediatric and adult patients with CHwI has been described in several retrospective series comprising 11 or more surgeries [6,22,27,35–39]. In general, initial doses of 50–100 U kg⁻¹ were given prior to surgery, either as a single dose or as multiple doses in the days or hours preceding surgery. Subsequent aPCC doses totalling up to 200 U kg⁻¹ day⁻¹ were administered beginning 6–8 h after surgery at 6- to 12-h intervals for variable durations of time. Consensus recommendations for aPCC dosing for both major and minor surgeries have been developed (Table 3) [33]. Criteria for satisfactory haemostasis were met in 80% or more of cases in each of the aforementioned series. There was a single thromboembolic event reported across more than 170 surgeries in the combined series.

The sequential or combined use of rFVIIa and aPCC for haemostatic coverage during surgery and the early postoperative period has also been described in patients with CHwI [35,40]; in some cases, this strategy was adopted due to prior clinical response to one or both bypassing agents or bleeding complications relative to the current surgery [35,40], while in others, patients were switched to aPCC after initial coverage with rFVIIa because of cost [35]. With combined therapies, one should be cautious about the occurrence of thromboembolic events [40], although none have been reported in patients with CHwI undergoing surgery.

Although not available at all institutions, preoperative evaluation of haemostatic response to bypassing agents using thrombin generation testing (TGT) or thromboelastography (TEG) has been proposed as a means to optimize the haemostatic management of individual patients with inhibitors for surgery [13,41].

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Intraoperative 90 µg generation correlated with clinical haemostasis in this study, and preoperative TGT results were generally predictive of perioperative haemostatic response. Thromboelastography was similarly used to guide rFVIIa therapy in a patient with CHwI undergoing urgent evacuation of a spinal cord haematoma [42]. Although these preliminary findings suggest the potential utility of these techniques for optimizing haemostatic therapy in individual patients with CHwI.

In a small prospective study of 10 surgeries in patients with inhibitors, *in vitro* and *ex vivo* TGT were used to assess the dose-dependent haemostatic response to each bypassing agent preoperatively; TGT was then used intra- and postoperatively to monitor the response to haemostatic therapy, which was selected based on the preoperative TGT results [41]. Thrombin generation correlated with clinical haemostasis in this study.

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**Table 3.** Consensus recommendations for rFVIIa and aPCC dosing for surgery in patients with haemophilia and inhibitors [33].

<table>
<thead>
<tr>
<th>Dosing Type</th>
<th>Preoperative Dosing</th>
<th>Days 1–5</th>
<th>Days 6–14</th>
</tr>
</thead>
<tbody>
<tr>
<td>rFVIIa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor surgery</td>
<td>90–120 µg kg⁻¹ q2 h max.</td>
<td>90–120 µg kg⁻¹ q2 h up to four times then q3–6 h for 24 h</td>
<td></td>
</tr>
<tr>
<td>Intermediate/major surgery</td>
<td>120 µg kg⁻¹ q2 h</td>
<td>90–120 µg kg⁻¹ q2 h Day 1, then q3 h Day 2, then q4 h Days 3–5</td>
<td>90–120 µg kg⁻¹ q6 h</td>
</tr>
<tr>
<td>Continuous infusion</td>
<td>15–50 µg kg⁻¹ h⁻¹</td>
<td>15–50 µg kg⁻¹ h⁻¹</td>
<td>15–50 µg kg⁻¹ h⁻¹</td>
</tr>
<tr>
<td>aPCC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor surgery</td>
<td>50–75 U kg⁻¹</td>
<td>50–75 U kg⁻¹ q12–24 h one to two times</td>
<td></td>
</tr>
<tr>
<td>Intermediate/major surgery</td>
<td>75–100 U kg⁻¹</td>
<td>75–100 U kg⁻¹ q8–12 h</td>
<td>75–100 U kg⁻¹ q12 h</td>
</tr>
</tbody>
</table>

aPCC, activated prothrombin complex concentrate; rFVIIa, recombinant-activated factor VII.

*Recommended initial preoperative paediatric dose is 120–150 µg kg⁻¹ q2 h.

**Table 4.** Consensus protocol for rFVIIa dosing in EOS patients with haemophilia and inhibitors [13].

<table>
<thead>
<tr>
<th>Dosing Type</th>
<th>Preoperative Dosing</th>
<th>Intraoperative Dosing</th>
<th>Postoperative* Dosing *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>90 µg kg⁻¹ q2 h; final intraoperative bolus before final reduction in hip arthroplasty and before release of tourniquet (if used) in knee arthroplasty</td>
<td>90 µg kg⁻¹ q2 h for first 48 h, then q3 h × 48 h, then q4 h × 72 h, then q6 h through discharge*</td>
</tr>
</tbody>
</table>

EOS, elective orthopaedic surgery; PO, per os (by mouth); rFVIIa, recombinant activated factor VII; TXA, tranexamic acid.

*Discharge should occur in ~ 10–12 days after surgery in uncomplicated cases.
undergoing surgery, further study and validation are needed before they can be more widely adopted for this purpose [13,41].

Intraoperative considerations

Preoperative planning of haemostatic coverage for surgery should incorporate a strategy for monitoring haemostatic response during surgery. However, this poses a challenge in CHwI as the major drawbacks of rFVIIa and aPCC are their unpredictable haemostatic effect, lack of laboratory assays to monitor efficacy and dosing frequency, as well as the potential risk of thrombosis. The utility of plasma-based coagulation assays such as PT and aPTT is limited, as these assays do not assess clot stability, the effect of platelets in haemostasis, or thrombin generation on the surface of platelets, which is thought to be a key component of the haemostatic mechanism of rFVIIa [43]. As previously mentioned, the use of TGT and TEG in this setting is still investigational.

The team must be prepared to manage any excessive breakthrough bleeding that may occur during surgery. In addition to adjustments in the primary haemostatic therapy in use, adjunctive haemostatic agents may be used. Despite concerns about potential thrombogenic risks and a lack of consensus related to the concomitant use of antifibrinolytic agents with bypassing agents to augment surgical haemostasis, this practice has been extensively employed in patients with CHwI [9,13,27,28,31,35,44]. To optimize haemostasis and prevent postoperative bleeding, the surgeon should attempt to minimize soft tissue dissection and should pay meticulous attention to primary haemostasis at the conclusion of surgery [30]. When feasible and especially for abdominal surgeries [45], a less invasive (e.g. laparoscopic) overall approach is preferable to open surgery; however, the potential risks of a less invasive approach, including limited access to the surgical field in the event of accidental vascular injury, must be weighed against potential benefits such as reduced postoperative pain and hastened recovery with a smaller incision [45]. Topical haemostatic agents, such as fibrin glue or topical thrombin, may be used as needed to augment systemic haemostatic treatments [13,27,28,30,36]. The potential for impaired wound healing in patients with haemophilia should also be considered in the technical approach to surgery [17]. Additional procedure-specific considerations of which the surgeon and OR team should have prior knowledge are outlined in Table 2.

General postoperative care

Pain management is a primary concern in the immediate postoperative period. Knowledge of the patient’s prior analgesic regimen may be critical for anticipating postoperative analgesic requirements, since patients receiving opioids before surgery may require higher-than-usual initial doses. Non-steroidal anti-inflammatory drugs should be avoided because they may induce platelet dysfunction and cause gastrointestinal bleeding [46]. Although highly effective and shown to be safe in patients with haemophilia without inhibitors after sufficient factor replacement [47,48], regional and neuraxial anaesthetic and analgesic techniques are contraindicated because of the risk for bleeding and a lack of evidence supporting their safety in these patients [8]. Given the limited options for delivering analgesia in patients with CHwI, consultation with the anaesthesiology or pain service may be especially helpful in this patient population.

Although bleeding is the primary complication of surgery in CHwI, thrombosis is also a concern, given postoperative immobility and exposure to potentially thrombogenic haemostatic treatments. This risk may be particularly increased in older patients and in the setting of overcorrected FVIII levels [49,50]. Whereas postoperative anticoagulation (e.g. low-molecular-weight heparin) has been advocated in specific groups of patients with haemophilia without inhibitors, namely older patients who have undergone major orthopaedic surgery [49] and patients with normal or near-normal trough factor levels following factor replacement [50], this practice is not generally recommended in patients with inhibitors [49,50]. Instead, non-pharmacological measures, such as intermittent pneumatic or graded compression methods, may be used [49]; however, pharmacological thromboprophylaxis may be considered in patients with underlying thrombophilia [46].

Infection may be especially catastrophic after joint replacement, potentially prompting prosthetic removal. Patients with haemophilia are at increased risk for delayed infection in particular [14]. The most likely source of delayed infection in this population is bacteraemia from a CVAD or during a dental procedure. Therefore, patients with CVADs or joint hardware should receive antimicrobial prophylaxis before any dental procedure. In addition, patients or their carers should be educated regarding the importance of using strict aseptic technique when caring for and accessing CVADs or PICCs or when attempting self-infusion.

Bleeding is perhaps the most serious concern after surgery in CHwI. Bleeding into the operative site after arthroplasty may lead to infection and loss of the prosthesis [51]. Therefore, in contrast to the traditional postsurgical approach, early mobilization of patients with inhibitors after arthroplasty is often discouraged because of the possibility of bleeding, even at the risk of compromising ultimate range of motion [51]. Once physical therapy is instituted, pretreatment with a bypassing agent is recommended before each
For most major surgeries reported in the literature, haemostatic therapy was continued for ca 10–14 days, with longer durations in cases complicated by postoperative bleeding. When unexpected postoperative bleeding occurs, several strategies may apply, including adjustment of dosing or replacement of the current haemostatic agent, cessation of rehabilitative measures, or platelet transfusion if there is thrombocytopenia or evidence of platelet dysfunction [13]. Consultation with the haematology team in the event of excessive postoperative bleeding is critical. Discharge planning for home, rehabilitative, or other facilities should be an integral part of preoperative assessment and should include an evaluation of the home environment and psychosocial support system by the HTC. To optimize outcomes, after discharge, ongoing communication with the HTC regarding home infusion therapy, physical therapy and coordination of care is crucial.

Conclusions

Comprehensive care and advances in haemostatic treatments have made it possible to safely perform a wide array of surgical procedures, specifically in patients with inhibitors, although restricted access to haemostatic treatments and comprehensive care in the developing world poses additional challenges in the surgical management of patients with CHwI. A coordinated series of peri- and intraoperative events carried out by the multidisciplinary HTC team will ensure optimal outcome in patients with CHwI undergoing surgery.

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Disclosures

Roshini Kulikarni is a consultant for Novo Nordisk, Baxter, Bayer, Octapharma and CSL Behring; is on the speakers’ bureau for Novo Nordisk and CSL Behring; and participates in clinical research protocols for Novo Nordisk, Baxter and Biogen Idec.

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