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SUPPLEMENT ARTICLE

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Invasive procedures in patients with haemophilia: Review of low-dose protocols and experience with extended half-life FVIII and FIX concentrates and non-replacement therapies

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Abstract

The performance of surgery and invasive procedures in patients with haemophilia is currently facing new challenges globally. The first is the appropriate application of low-dose protocols of clotting factor concentrates (CFC) achieving adequate perioperative haemostasis in resource constraint environments. The increasing availability of CFC through humanitarian aid programmes allows more invasive surgeries to be performed for which efficacy and safety data should be more widely collected and reported. Second, extended half-life CFC that are increasingly available in many countries represent valuable alternatives to standard half-life products in surgical patients allowing reduced number of infusions and lower consumption, in particular for extended half-life factor IX. Third, in the era of recently introduced non-factor prophylaxis, some minor surgical procedures can now be performed without additional haemostatic treatment, others with few low-dose administrations of CFC or bypassing agents. Additional factor VIII or bypassing treatment has proven to be safe and effective in association with emicizumab for major surgeries, and it was effectively given at low doses in association with fitusiran. No thrombotic complications have been reported in the surgical setting so far. A multidisciplinary team/facility remains crucial to manage major surgery in patients on prophylaxis with these new agents.

KEYWORDS

extended half-life concentrates, haemophilia, invasive procedures, limited resources, non-replacement therapies

1 | INVASIVE PROCEDURES IN PATIENTS WITH HAEMOPHILIA WITH LIMITED RESOURCES: AN ALTERNATIVE MODEL

1.1 | Introduction

Patients with haemophilia (PWH) may need surgical interventions or invasive procedures for haemophilia related complications or unrelated issues. Forty per cent of PWH reside in the developing world with limited resources. Invasive procedures on PWH with limited resources are difficult and challenging. Limited resources include availability and accessibility to Hemophilia Comprehensive Care Centers (HCCC) and clotting factor concentrates (CFC).

International guidelines for CFC prophylaxis for PWH undergoing surgical procedures are well established but are not practical in resource constraint settings.[1,2] These guidelines were indeed not established on the basis of clinical trials and aim to achieve normal levels of haemostasis with large margins of safety. They also fail to define safe lower limits of haemostasis for invasive procedures in PWH.[3] The need to define lower limits of haemostasis is crucial in limited resource setting so that resources can be used optimally.

There are limited data from developing world (with limited resources) with respect to PWH undergoing surgical/invasive procedures. We here try to map the efficacy of low-dose CFC protocols (lower than international recommendations) for surgical prophylaxis and invasive procedures. As summarized hereafter, the limited literature shows that low-dose protocols are effective, reduce CFC consumption by 30% and do not increase the risk of haemorrhage.

1.2 | Low-dose protocols for invasive procedures

The first series using low-dose protocol was reported in 1994 from India.[4] Thirty-seven haemophilia patients (32 HA and five HB)underwent orthopaedic, general surgical, neurosurgical and cardiothoracic invasive procedures. The postoperative trough levels were maintained at 20%-40% of factor VIII (FVIII) and between 15% and 30% for factor IX (FIX) for a minimum of 10 days. Haemostatic efficacy was well achieved. In 1998, another group from India described various kinds of surgery carried out with great success in 16 cases which included both severe and moderate haemophilia patients treated with modest amounts of factor concentrates and antifibrinolytic drugs.[5] This was further confirmed by Srivastava and colleagues who described the haemostatic management of 18 patients with severe haemophilia (11 HA and seven HB) undergoing 20 major surgery procedures using lower than usually recommended levels of CFC therapy.[6] Mathew and colleagues on the basis of their own experience and published data concluded in 2005 that low-dose protocols are effective, reduce factor consumption by one third and are not associated with a significantly increased risk of delayed haemorrhage.[3] The WFH Guidelines for Management of Haemophilia recommend similar replacement plan for limited resource situations using standard half-life products (Table 1).[1] This is a very important statement as it recognizes low-dose protocols for factor replacement for postoperative haemostasis. More recently, a study from Senegal involving 26 children showed that a treatment protocol using low quantity of CFC (mean amount FVIII of 1743 IU [810-2340]) was efficient in haemophilia patients who underwent circumcision.[7]

TABLE 1 Plasma factor peak level and duration of administration when there is significant resource constraint with standard half-life products (Ref.1)

	Haemophilia A	Haemophilia B
	Major surgeries/desired levels (IU/dL)	
Preoperative	60-80	50-70
Days 1-3	30-40	30-40
Days 4-6	20-30	20-30
Days 7-14	10-20	10-20
	Minor surgeries/desired plasma levels (IU/dL)	
Preoperative	40-80	40-80
Postoperative		
Days 1-5 depending on type of procedure	20-50	20-50

Orthopaedic surgeries are the most common surgeries for PWH in the developing world. Lee et al[8,9] reported their experience in patients with fractures and use of external fixators. Joint damage is very severe in PWH from developing world because of inadequate CFC availability for prophylaxis so that many PWH need total knee replacement (TKR) or total hip replacement (THR) at young age. Until now, one of our groups in India (SA in Maharashtra) has collected data on 42 patients who underwent 84 bilateral simultaneous TKR using low dose of Eloctate® (600 IU/kg over 14 days) (unpublished data). We have also performed nine coronary angioplasties in HA patients using a single dose FVIII 25 IU/kg at the time of arterial puncture and no further dose was given. None of the patient had excessive bleeding (unpublished data).

1.3 | Continuous infusion vs bolus infusions of CFC in resource constraint settings

Martinowitz et al showed that instead of intermittent bolus infusions of CFC, continuous infusion (CI) allows to achieve a 30% reduction in CFC requirements.[10,11] Although CI could be attractive, there are certain logistic issues like the stability of products, the need for expensive infusion pumps and disposables, and the requirement for more frequent factor assays that altogether increase the expenses. For these reasons, low-dose intermittent bolus replacement therapy appears easier and cheaper than CI and cost effective in resource constraint settings.

1.4 | Surgical procedures in haemophilia A patients with inhibitors

Very limited data are available in the literature from developing world on this topic. Bypassing agents are not available in enough quantities to allow surgery in this setting. The management of a patient with high-responding FVIII inhibitor using low doses of aPCC in the postoperative period was previously reported[12] but the literature on the use of bypassing agents in limited resources environments is scare. This could however likely change in the future with the availability of new agents such as emicizumab in the frame of donations programmes.

1.5 | Discussion

Surgery in PWH should be carried out in established HCCCs where trained teams are available with laboratory back up. In developing world, availability and accessibility of trained teams is an important issue. Slowly and definitely, the number of health professionals with an expertise in haemophilia is growing. Still, the limited availability

of CFC remains a major obstacle. It appears that adequate postoperative haemostasis can be achieved with lower doses of factor replacement protocols. There is however a need to collect more data in a systematic fashion as probably many surgical experiences from developing world are not published.

Low-dose protocols with an optimal use of the limited available CFC potentially increase by twofold compared to using standard replacement protocols the number of patients who can benefit from surgical procedures with a major impact on their quality of life than. The Humanitarian Aid Program of the WFH has definitely improved the CFC supply so that more surgical procedures can now be carried out throughout the developing world. Collecting and reporting these surgical data appears critically important.

Available but limited data suggest that there is no great difference in surgical haemostasis and outcomes using low dose as compared with standard recommended protocols. These observations raise a fundamental and so far unanswered question for both developed and developing countries: 'What is the minimum factor level required for adequate surgical haemostasis and wound healing?'

2 | INVASIVE PROCEDURES WITH EXTENDED HALF-LIFE CONCENTRATES

In patients with haemophilia, surgery and other invasive procedures represent a major challenge as they are inherently associated with the potential for excessive and uncontrolled bleeding. Most invasive procedures require intensified FVIII or FIX replacement to achieve and maintain haemostasis and adequate factor levels until wound healing is complete. Because of their relatively short half-life (approximately 12 hours for standard half-life FVIII [SHL-FVIII] and 18 hours for standard half-life FIX [SHL-FIX]), standard formulations of FVIII and FIX require frequent administrations in the peri- and postoperative periods.

Recent major treatment advances in haemophilia include the development of new recombinant extended half-life (EHL) FVIII (EHL-rFVIII) and FIX (EHL-rFIX) products with improved pharmacokinetic (PK) properties that aim to reduce the burden of prophylaxis. Four EHL-rFVIII products have recently been approved, 3 obtained by pegylation (BAY 94-9027 [Jivi®], BAX 855 [Adynovate®] and N8-GP [Esperoct®]) and one by Fc-fusion (Elocta®/Eloctate®). With respect to EHL-rFIX, three are currently approved, one obtained by pegylation (Refixia®), one by albumin fusion (Idelvion®) and one by Fc-fusion (Alprolix®). Pharmacokinetic studies in adults have shown a 1.2- to twofold increase in half-life of EHL-rFVIII compared to full-length factor VIII and a 4 to 6-fold increase in half-life for EHL-rFIX.[13] For prophylaxis, EHL-rFVIII and to a much greater extent EHL-rFIX products can be used to prolong the dosing interval or provide higher factor trough levels for longer periods.

The safety, efficacy and consumption of all EHL in limited numbers of patients undergoing surgery and invasive procedures have recently been evaluated in several pivotal trials including pegylated EHL-rFVIII,[14-16] Fc-fused EHL-rFVIII,[17] Fc-fused EHL-rFIX,[18] albumin-fused EHL-rFIX[19] and pegylated EHL-rIX.[20]

As reviewed hereafter, the use of EHL concentrates impacts on the haemostatic management of surgery and invasive procedures compared SHL-FVIII/FIX. In all published studies, the levels of FVIII and FIX targeted pre- and postoperatively when using EHL concentrates were not different from the guidelines-recommended ranges that have previously been defined with the use of SHL-FVIII/FIX.[1]

2.1 | EHL-rFVIII and surgery

Studies performed with the different EHL-rFVIII have demonstrated that these products are effective and well tolerated for the prevention and treatment of bleeds during major orthopaedic and non-orthopaedic surgeries as well as for other minor invasive procedure.[14-17] The efficacy and safety results were consistent with those previously reported for unmodified FVIII. No FVIII inhibitor, thromboembolic events or clinically significant safety issues were detected and reported in published studies.

Most patients received a median bolus between 50 and 60 IU/kg preoperatively. Very few patients needed intraoperative infusion. The total number of infusions on the day of the surgery varied between 1 (most patients) and 3 (minority of patients). Haemostatic control was assessed as good or excellent in most reported cases. In the immediate postoperative period, most patients required one infusion of EHL-rFVIII per day.

These studies demonstrated that less frequent infusions and reduced factor consumption were needed to cover surgery with EHL-rFVIII compared to SHL-FVIII. Considering the wide variability in the types of surgeries, differences in local practices as well as distinctive ways information about FVIII usage was collected across studies, it is challenging to make comparisons across different products regarding FVIII consumption and frequency of infusions. However, there is no objective reason to suspect that the different EHL-rFVIII that show a very similar half-life prolongation would have different properties in this setting.

The ability to measure FVIII activity is of paramount importance for the preparation and management of major surgeries. Considering the high intraindividual variability in pharmacokinetics, all patients candidate for surgery should undergo preoperatively PK evaluation in order to measure their incremental recovery as well as their half-life. Preoperative PK testing enables an accurate prediction of the dose required and helps to predict the FVIII levels that would be achieved to provide perioperative bleed protection. Also, FVIII should be measured daily postoperatively to adapt the treatment regimen.

Compared to adult and adolescents subjects, dosing on the day of surgery appeared to be higher (higher initial dose or greater need to provide a second infusion to prevent bleeding) in paediatric patients reflecting the well-known shorter half-life of FVIII in children compared to adults.[17]

2.2 | EHL-rFIX and surgery

Studies performed with the different EHL-rFIX have demonstrated that these products are effective and well tolerated for the prevention and treatment of bleeds during major orthopaedic and non-orthopaedic surgeries as well as for other minor procedure.[18-20] The efficacy and safety results were consistent with those previously reported for unmodified FIX. No FIX inhibitor, thromboembolic events or clinically significant safety issues were detected and reported in published studies.

Most patients received a median bolus between 80 and 90 IU/kg preoperatively. Most patients require one to three doses of EHL-rFIX on the day of surgery. Haemostatic control was assessed as good or excellent in most cases. In the postoperative period, the majority of patients were dosed approximately every 2 days to maintain the desired FIX activity level. This is in contrast with SHL-FIX which is required to be dosed at least daily to maintain haemostasis. As a result, EHL-rFIX concentrates allow major surgical interventions in patients with HB with significantly reduced concentrate consumption and infrequent injections as reported with SHL-FIX.

2.3 | EHL-rFVIII and continuous infusion

Conventional FVIII and FIX are often administered via CI during surgery and the postoperative period in order to maintain the appropriate factor levels. Since EHL-rFIX products have a much longer half-life than EHL-rFVIII, bolus infusions represent the treatment modality of choice in patients with HB since they can maintain adequate and stable FIX levels with bolus injections.

Regarding EHL-rFVIII, there has been a report of the successful use of CI of Fc-fused rFVIII.[21] The lower rate of continuous infusion during steady state at 3 IU/kg/h of Fc-fused rFVIII vs 5 IU/kg/h on SHL-FVIII suggested a trend towards lower FVIII consumption, likely reflecting the accumulation of EHL-rFVIII in comparison with SHL-FVIII. The clinical advantages of CI are maintenance of constant FVIII levels and the ability to monitor levels at any time, rather than having to test just before bolus infusions. The disadvantages are the need for extra intravenous access for blood sampling. These aspects are similar for SHL-FVIII and EHL-rFVIII concentrates. There might be some concerns about the stability of the different EHL-rFVIII when administered by CI.

2.4 | Non-severe haemophilia and haemophilia carriers

The use of EHL-rFVIII and EHL-rFIX has mainly been studied and reported in patients with severe haemophilia undergoing surgery or invasive procedures. However, although evidence is still limited, the use EHL-rFIX in particular could be beneficial in patients with non-severe HB undergoing invasive procedures who could reach and maintain prolonged haemostasis with a very limited number of infusions. Similarly, successful use of EHL-rFIX has been recently reported in carriers of HB with FIX deficiency requiring invasive procedure (delivery, surgery).[22]

2.5 | Developing countries

Through the WFH humanitarian aid programme, an increasing number of patients in less developed countries have now access to EHL-rFVIII and rFIX concentrates that are used for surgery. Data on the use of these concentrates are currently being collected in the frame of the World Bleeding Disorders Registry of the WFH.

2.6 | Conclusions

The use of EHL-rFVIII and EHL-rFIX in patients undergoing surgery is effective, safe and well tolerated. These concentrates enable in most patient fewer infusions and reduced consumption and potentially allow earlier patient discharge, in particular for patients with HB.

Close monitoring of FVIII and FIX levels is however mandatory, certainly in the peri- and immediate postoperative period using the appropriate assays, as patients might require repeated bolus. More real-life data should be collected using standardized protocols to better define the ideal modalities of use of EHL-rFVIIII and FIX in both developed and developing countries.

3 | INVASIVE PROCEDURES IN THE ERA OF NON-FACTOR REPLACEMENT THERAPY

3.1 | Introduction

Innovative therapies able to enhance the haemostatic potential independently of replacement factor administration have recently been developed for bleeding prevention in inhibitor and non-inhibitor PWH and are at advanced stages of clinical investigation or already approved.[23]

These agents are similarly administered by the subcutaneous route however they act differently by enhancing coagulation (ie emicizumab) or inhibiting anticoagulant pathways (ie fitusiran inhibiting antithrombin and concizumab inhibiting TFPI).[23,24]

Another important aspect of these novel therapeutics is that they cannot completely prevent any breakthrough or perioperative bleeding making the association with bypassing agents (BPAs: activated prothrombin complex concentrate [aPCC]) or recombinant activated factor VII (rFVIIa) or FVIII or FIX products sometimes required,[23,24] therefore, changing treatment modalities during bleeding and surgery.

Due to the specific mechanism of action and characteristics, each of these novel drugs has its own profile in terms of safety and efficacy, consequently the use in the perioperative setting should be

investigated for each agent. The surgical setting represents a challenge due to the concomitant risk of bleeding and thrombotic complications, especially in inhibitor patients in whom bypassing therapy is usually required. So far, limited information on surgical management of PWH treated with fitusiran is available from clinical trials[25] and no surgical experience has been reported with concizumab. Surgical data have been more extensively collected in the trial programme with emicizumab,[26] and few surgical cases treated with emicizumab in the real-world setting were recently published.[27,28]

3.2 | Perioperative management of PWH treated with fitusiran

Fitusiran is a RNA interference agent developed to suppress antithrombin (AT) synthesis in hepatocytes in order to rebalance haemostasis in PWH A or B with and without inhibitors.[29] In the phase 2 study, monthly subcutaneous injections of fitusiran led to a durable, dose-dependent AT reduction with improved thrombin generation and decreased bleeding frequency.[30]

A fatal cerebral sinus vein thrombosis occurred in a non-inhibitor PWH A following FVIII treatment for a breakthrough bleed and the programme was put on hold until the development of a risk-mitigation strategy. After the implementation of protocol guidelines on the use of low doses of FVIII/FIX and BPAs to treat breakthrough bleeds, the programme reopened[31] and no further thrombotic events have been reported.

A single preliminary report of five surgical operations done in four PWH A receiving fitusiran in the phase 2 extension trial is available.[25] All patients had AT levels <20%, and no thromboprophylaxis was administered. One inhibitor patient was treated with rFVIIa (90 μg/kg, three times) for a bleeding complication after dental extraction. The other inhibitor patient underwent thoracotomy and was treated with FVIII (42-84 U/kg/d for 7 days) followed by BPAs (aPCC, 74-216 U/kg/d for 4 days and rFVIIa, 93 μg/kg/d for 3 days). Two non-inhibitor patients had tooth extractions, endoscopic cholecystectomy and nasal septoplasty and were managed with low-dose FVIII (14-28 U/kg/d). These results seem promising but they are preliminary and obtained in a limited surgical series. Additional experiences are required to support these strategies and/or to suggest alternative approaches.

3.3 | Perioperative management of PWH treated with emicizumab

Emicizumab is a bi-specific, humanized monoclonal antibody which bridges FIX/activated FIX and FX/activated FX and leads to activation of FX, thus mimicking the physiologic function of activated FVIII.[32] The drug has been approved internationally for prophylaxis in PWH A of all ages with and without inhibitors. Overall, the clinical trial programme showed that a large proportion of patients receiving emicizumab weekly, biweekly or monthly remained bleed-free: in particular, 63% of adults and 77% of children with inhibitors treated weekly[33,34] and more than half of the patients with or without inhibitors treated up to once per month.[35]

During the phase 3 study, thrombotic microangiopathy (TMA) and thrombotic events (3 and 2 cases, respectively) were observed with concomitant therapy of emicizumab and high doses of aPCC (>100 U/kg per day, >24 hours) to treat breakthrough bleeds.[33] Therefore, guidelines have been implemented to recommend rFVIIa use and avoid aPCC or, if not possible, using the lowest aPCC doses for the management of bleeding.

Across the HAVEN studies, 215 minor and 18 major surgeries were performed.[15] Most minor interventions were dental and central venous access device (CVAD) procedures which were primarily managed without the use of prophylactic coagulation factor, with 90% not requiring treatment for postoperative bleeds. Of the 34% procedures managed with prophylactic coagulation factor, 88% did not result in treated postoperative bleeds. Overall, bleeding complications occurred most commonly following dental procedures.

Of the 18 major surgeries, 83% were managed with prophylactic coagulation factor and no postoperative bleed occurred in 80%. The three major surgeries managed without prophylactic coagulation factor were not complicated by bleeding. No thrombotic complication was reported.[26] With respect to perioperative treatment with prophylactic coagulation products across these surgeries, FVIII was given at usual doses in non-inhibitor patients while rFVIIa was the BPA used in all inhibitor patients, but one case who underwent laparoscopic appendectomy after a single dose of aPCC (49.7 U/kg).[26,36]

Two detailed reports of arthroplasty performed in inhibitor patients during the trial programme were published.[37,38] One patient received a low-dose rFVIIa regimen (100 mcg/kg preoperatively followed by 80 mcg/kg every 3 hours) for hip replacement and had a bleeding on postoperative day 1 which was controlled by FVIII treatment (115 IU/kg by bolus followed by continuous infusion at 3.3-4 IU/kg/h; inhibitor titre: 2 BU/mL).[37] The other case underwent knee replacement and was successfully treated with higher doses of rFVIIa (200 mcg/kg preoperatively followed by 100 mcg/kg every 2 hours on postoperative day 1, subsequently tapered to every 3, 4 and 6 hours on days 2, 3 and 4, respectively).[38]

Real-world cases from United States have shown the surgical practice in inhibitor PWH receiving emicizumab. In this series,[28] minor procedures were completed with observation alone and the remaining were successfully managed with standard doses of rFVIIa (90 mcg/kg). Recently, a hip replacement was performed administering rFVIIa 180 mcg/kg preoperatively, 90 mcg/kg every 3 hours on postoperative days 1-3, every 6 hours on days 4-7, every 8 hours on days 8-11 and every 12 hours on days 12-14 without any bleeding complication.[27]

3.4 | Laboratory monitoring

The availability of reliable laboratory assays to assess haemostasis during non-factor replacement therapy is a requirement for the

management of severe breakthrough bleeds and major surgery. In these settings, FVIII monitoring is often required during replacement therapy. Inhibitor testing is also needed, particularly to guide the therapeutic decision of using BPAs or FVIII products. Furthermore, in these conditions, laboratory monitoring may be helpful for early detection of prothrombotic markers in patients treated with FVIII/FIX or BPAs.

It is important to be aware that emicizumab interferes with all aPTT-based assays and, therefore, neither the inhibitor titre nor the FVIII activity should be measured using the conventional clotting assays. Suitable solutions are to assess the inhibitor titre or FVIII activity by chromogenic assays employing bovine reagents that are insensitive to emicizumab.[39] According to the mechanism of action of fitusiran or concizumab, it appears possible to measure FVIII activity and inhibitor titre using the conventional aPTT-based assays in the presence of these therapeutic agents.

3.5 | Discussion

The introduction of emicizumab in our practice has required specific practical guidelines for the management of bleeding and surgery.[40,41] Once more, the relevance of the multidisciplinary team supported by specialized coagulation laboratory has been highlighted. All specialists locally involved in the emergency care should also be informed and keep updated on these new therapeutic strategies. The rapidly growing experience on emicizumab and the other non-factor replacement agents will necessitate timely and consistent adaptation to the available data.

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