A standardized treatment regimen for patients with severe haemophilia A undergoing orthopaedic or trauma surgery: a single centre experience

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Recommendations on the administration of clotting factor concentrates in patients with severe haemophilia undergoing surgery are usually determined by monitoring target clotting factor levels. In this retrospective cohort study, we enrolled patients with severe haemophilia A who underwent major orthopaedic or trauma surgery. We wanted to evaluate the feasibility and the safety of a standardized medical treatment procedure. Further on, we wanted to assess whether our standardized treatment regimen enables surgical procedures in certain situations in which measuring clotting factor VIII (FVIII) activity is not available. We created a standardized medical treatment procedure that included a medical protocol and close cooperation with the Haemophilic Treatment Centre. Thirteen surgical procedures in nine patients were examined. The feasibility and safety of this standardized treatment concept were assessed by identifying perioperative complications and by means of a questionnaire. Depending on the surgery, the amount of FVIII administered within the first 10 days ranged between 653 and 1027 units/kg body weight. No allogeneic blood transfusion was required. The measurement of FVIII activity was performed repeatedly in five patients. In all patients activated partial thromboplastin time monitoring was performed during the hospital stays. The surgeons and patients were satisfied with our treatment concept and adhered to the medical regimen protocol. By means of a detailed, standardized medical protocol and by ensuring close cooperation between the patient, the surgeons and the Haemophilic Treatment Centre, we could show that elective and emergency operations can be safely performed even in situations in which FVIII activity could not be monitored. *Blood Coagul Fibrinolysis* **26:396–402**

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Introduction

Haemophilia A is a rare X-linked recessive coagulation disorder that is caused by a deficiency of coagulation factor VIII (FVIII). According to plasma coagulant levels, haemophilia A can be classified into severe (<1% clotting factor activity), moderate (1–5% clotting factor activity) and mild (5–30% clotting factor activity) forms [1]. Joint bleedings predominantly affect elbows, knees and ankles, and less often shoulders and hips. Recurrent bleeding episodes into the same joint lead to synovial inflammation. Chronic haemarthrosis finally results in joint destruction and the development of haemophilic arthropathy [2].

Primary prophylaxis initiated during the early years of life can markedly reduce the risk of subsequent arthropathy and improve the quality of life and has, therefore, replaced episodic treatment in many haemophilic patients [3]. Currently, modified FVIII and IX concentrates with extend half-life are becoming available [4]. Haemophilic adults who have not been treated with primary prophylaxis and have developed haemophilic arthropathy can be treated with secondary prophylaxis to delay joint destruction and to maintain and improve mobility [5,6].

Arthropathy, however, is still one of the most common complications of haemophilia, especially in older haemophilic patients. After conservative therapies have failed, orthopaedic surgery is often the last choice to reduce pain and disability and to achieve stability [7,8]. Total knee replacement (TKR) and total hip replacement (THR) are most frequently used, whereas total joint replacement of the shoulder, elbow and ankle remain controversial. Furthermore, muscular atrophy, instability of the joints and osteoporosis due to immobilization predispose haemophilic patients to bone fractures [9]. In haemophilic patients, orthopaedic procedures are demanding. Surgery is technically challenging due to concomitant soft-tissue fibrosis, osteoporosis and muscle contractures. Therefore, close cooperation with the haemophilia team must be ensured to avoid bleeding complications.

Although orthopaedic procedures are being performed more often, published studies concerning haemophilic patients are limited. Country-specific recommendations for substitutive therapy in patients undergoing surgery are used in cases wherein clotting factor activity monitoring is possible [10]. However, joint replacements are increasingly performed in endoprosthetic specialized

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hospitals in which continuous measurement of clotting factor activity and a specialist in coagulation disorders are not always available.

In this retrospective analysis, we enrolled patients of our Haemophilic Treatment Centre (HTC) with severe haemophilia A in whom major orthopaedic or trauma surgery was performed under the following two different conditions: the haemophilic patients either had planned for elective joint replacement or were admitted to the emergency department due to bone fracture. We evaluated the feasibility and safety of our standardized medical treatment procedure, which specified a standardized medical protocol for substitutive therapy and close cooperation with the surgeon. Based on these results, it was our aim to evaluate a standardized treatment regimen that can be safely used in haemophilic patient undergoing major orthopaedic surgery under elective and emergency conditions even in rare situations when monitoring FVIII activity is not possible.

Material and methods

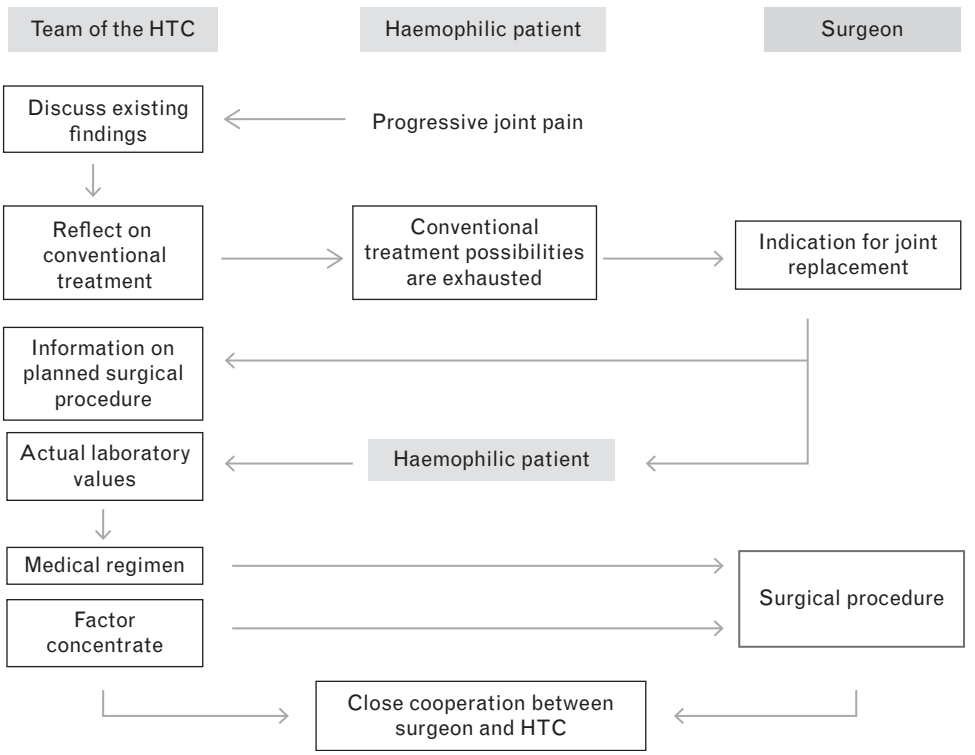
In the HTC of the University of Munich, Munich, Germany, we treat adult haemophilic patients who suffer from severe, moderate or mild forms of either haemophilia A or B.

In this observational cohort study, we retrospectively analyzed data from all patients with severe haemophilia A who underwent major orthopaedic and trauma surgery in 2010 or 2011. The surgical procedures were either performed at the University of Munich (department of trauma surgery) or in an external hospital that specialized in artificial joint replacements. In each of the above-mentioned hospitals, surgeons with experience operating on patients with haemostatic disorders were present. However, FVIII activity measurement in the external hospital was not always possible within a reasonable timeframe.

The analyzed patients underwent either elective artificial joint replacement or urgent osteosynthesis due to a fracture of the femur.

In haemophilic patients scheduled for elective artificial joint replacement, we use a standardized procedure that comprises the following steps (Fig. 1). First, the patient, who may suffer from progressive joint pain, arranges an appointment in our HTC. The existing findings are discussed with the patient and the colleagues of the department of trauma surgery. If conventional treatment possibilities (e.g. physiotherapy, adequate medical pain treatment, synovectomy, RSO) are exhausted, the patient will be sent to a department of our university hospital or an external hospital that is specialized in complex orthopaedic and trauma surgery. Second, after the surgeon confirms the indication for artificial joint replacement therapy, an inpatient admission appointment is planned.

Fig. 1



Standardized procedure for an elective artificial joint replacement. HTC, Haemophilic Training Centre.

To obtain current laboratory values, including blood count, liver and kidney values, prothrombin time, activated partial thromboplastin time (aPTT), fibrinogen, FVIII activity, inhibitor status to exclude the existence of an inhibitor and, if necessary (e.g. in patients suffering from HIV or chronic hepatitis C), measurement of viral load and $CD4^+$ cell count, the patient is advised to consult us once more. Third, after receiving the laboratory values and information from the surgeon concerning the planned surgical procedure, we prepare a standardized medical protocol (Appendix, http://links.lww.com/BCF/A12). This protocol provides essential information concerning the patient's medical history, the planned surgery, the patient's clotting factor concentrates, as well as the dose and time intervals of clotting factor substitution that should be administered before and during the first day after the surgical procedure. In addition, the protocol includes recommendations meant to minimize blood loss. For example, we recommend the avoidance of painkillers that interfere with platelet function [e.g. aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs)] and discourage the administration of colloids. We generally do not recommend the use of medical thromboprophylaxis in patients with haemophilia A unless the patient exhibits specific risk factors (i.e. obesity, several comorbidities, and prolonged immobility). The medical protocol is sent to the department in which the surgical procedure is performed and to the patient. Fourth, upon hospital admission, the responsible surgical colleague requests the amount of clotting factor concentrate required for the inpatient stay from our HTC, and the clotting factor concentrate is sent to the hospital immediately. In the course of the first postoperative day and on the following days until discharge, we contact the responsible surgeon. We obtain information concerning the surgical procedure and the postoperative course, bleeding complications and current laboratory values, in particular the aPTT and, if possible, FVIII activity. Subsequently, the medication regimen is adjusted according to the clinical and laboratory findings.

In cases of emergency, for example, severe bleeding, bone fracture or indication for urgent abdominal surgery, our team is usually consulted via a 24-h emergency call number. In cases of suspected major trauma, we receive information from the doctor in charge of the emergency department. In such a case, we first recommend the amount of clotting factor that should be administered immediately. Clotting factor concentrates are always available from the department of transfusion medicine of our hospital (Fig. 2). Second, after the diagnosis of major orthopaedic trauma is made and the indication of trauma surgery is confirmed by the surgeon, we provide oral information on the perioperative substitution regimen. Third, the written medical protocol (Appendix, http://links.lww.com/BCF/A12) will be provided to the doctor who is responsible for further treatment as soon as possible. Further procedures are analogous to that mentioned above.

The dose of recommended clotting factors mainly depends on the body weight as well as the type of the surgical procedure and takes into account the personal bleeding history and previous demand on factor substitution. It is calculated as follows: the initial substitution (directly before the operation) is 50–70 units/kg body weight followed by 30–40 units/kg body weight every 8–12 h for days 1–3 and 20–30 units/kg body weight every 8–12 h for days 4–10. Thereafter, the substitution is continued in a dosage of 20–30 units/kg body weight every 24 h until the end of intensive postoperative rehabilitation/physiotherapy [11].

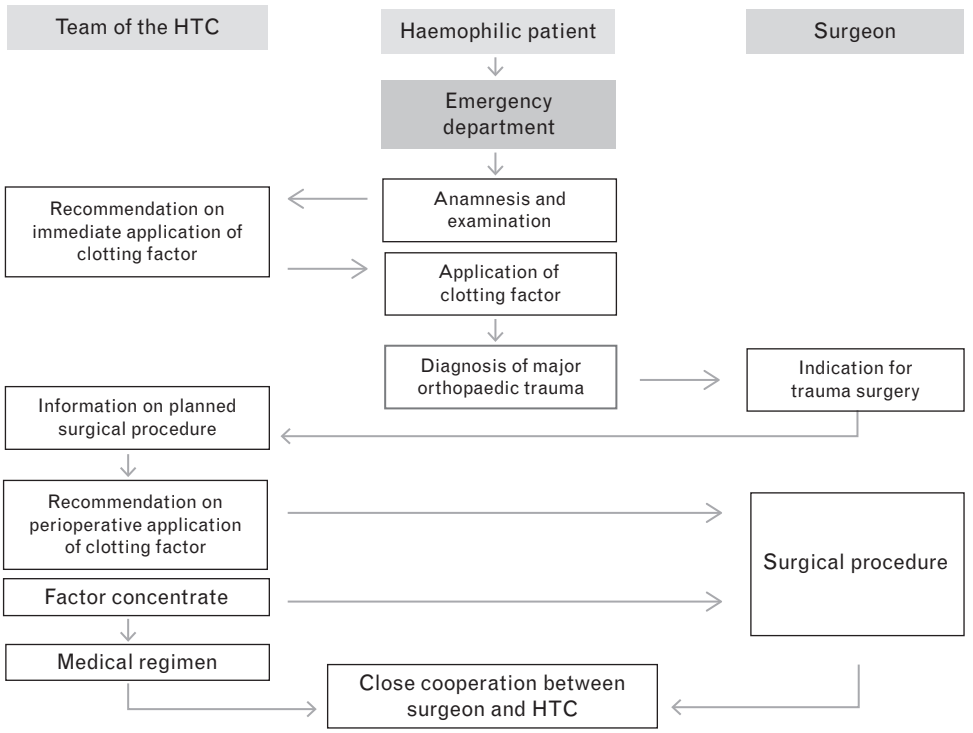
To evaluate the safety of our standardized treatment regimen, even when FVIII activity monitoring is not available, we focus our retrospective analysis on the amount of intraoperative and postoperative blood loss, need for allogeneic blood units and occurrence of complications (i.e. thrombosis). To determine whether our recommendations were implemented by the treating doctor, we documented whether colloids or NSAIDs were administered in the perioperative setting, if medical thromboprophylaxis was provided and whether our recommendations on the administration of clotting factor concentrate were followed. By means of a questionnaire, we investigated opinions regarding the practicability and feasibility of our concept among the treating surgeons who are specialized in complex orthopaedic and trauma surgery and the patients (rating scale: 10 = very good and 1 = poor). The questionnaire for the surgeons focused on the comprehensibility and feasibility of the medical protocol, an adequate clotting factor concentrate supply and cooperation with the HTC during the perioperative period. The questionnaire sent to the patients concerned the preoperative haemostatic preparation for the surgical procedure, clotting factor concentrate supply and cooperation with the HTC during the inpatient stay.

Results

In 2010 and 2011, nine patients suffering from severe haemophilia A with a mean age of 47 ± 9 years underwent major orthopaedic or trauma surgery. Four haemophiliacs were on secondary prophylaxis, whereas the remaining five patients received on demand therapy. Plasma-derived clotting factor concentrates were administered in the majority of the patients; three patients were treated with recombinant FVIII concentrate. Six patients had concomitant hepatitis C infections, and two patients were HIV infected. The patients had no type of thromboembolic event recorded in their personal history.

Procedural data are summarized in Table 1. Ten artificial joint replacements [i.e. eight TKR, one re-TKR and one total ankle replacement (TAR)] and three urgent osteosyntheses due to femur fracture were performed. Two

Fig. 2



Standardized procedure in case of an emergency operation. HTC, Haemophilic Training Centre.

patients underwent bilateral TKR; in one patient, a revision was required due to infectious complications during a 1-year period.

Recurrent monitoring of FVIII activity was performed in five patients; aPTT measurements (normal range: 25–42 s) were performed repeatedly in all patients and stayed within the normal limits on postoperative day 1. In all patients, FVIII concentrate was administered exactly according to the medical protocol. Depending on the type of surgery, the total amount of FVIII administered within the first 10 days ranged between 42 000 and 86 000 units in total (653–1027 units/kg body weight). The documented total blood loss during and after surgery ranged between 500 and 2000 ml in TKR and 300 and 700 ml after femur osteosynthesis. There was no need for a

Table 1 Procedural data of elective orthopaedic surgery and urgent osteosynthesis performed in patients with severe haemophilia A

Patient (No.)	Type of surgery	Hospital stay postop (days)	Amount of FVIII applied until POD 10 (units [units × KG kg])	aPTT on POD 1 (s)	Haemoglobin on POD 1 (mg/dl)	Estimated total blood loss (ml)	Application of colloids, NSAID or heparin prophylaxis	Application of FVIII according to the regimen
Elective orthopaedic surgery								
1	TKR (left side)	17	77 000 [1027]	34	11.8	1100	No	Yes
2	TKR (right side)	12	68 000 [1000]	39	10.6	Not measured	Yes	Yes
	TKR (left side)	12	66 000 [970]	40	10.5	1900	Yes	Yes
3	TKR (left side)	17	86 000 [1075]	31	10.9	1450	Yes	Yes
	TKR revision (left side)	9	65 000 [813]	21	10.6	600	Yes	Yes
4	TKR (left side)	11	86 000 [935]	34	12.1	500	Yes	Yes
5	TKR (left side)	14	67 000 [838]	38	11.6	1000	No	Yes
	TKR (right side)	9	59 000 [738]	41	10.0	800	No	Yes
6	TKR (left side)	9	69 000 [885]	41	9.1	2000	No	Yes
7	TAR (left side)	15	69 000 [767]	26	13.3	300	No	Yes
Urgent osteosynthesis								
8	Osteosynthesis (right side)	6	59 000 [737]	38	11.8	300	No	Yes
1	Osteosynthesis (left side)	8	49 000 [653]	32	13.4	500	No	Yes
9	Osteosynthesis (left side)	27*	42 000 [677]	37	12.6	700	Yes	Yes

NSAIDs, nonsteroidal anti-inflammatory drugs; POD, postoperative day; Postop, postoperatively; TAR, total ankle replacement; TKR, total knee replacement.
* Prostatic hyperplasia, voiding disorder; waiting for a short-term care option.

transfusion of allogeneic blood units in any of the patients in the perioperative period. The haemoglobin level on the first postoperative day was more than 9 mg/dl in all of the patients.

Against our recommendation minor protocol violations occurred. In particular, colloids were administered to three patients and NSAIDs were given to six patients. One patient was treated with medical thromboprophylaxis (i.e. low molecular heparin) for a short period of time. No significant blood loss, however, was found in this patient. There were no clinical signs of thromboembolic events in any of these patients.

All treating surgeons and seven out of nine patients responded to the questionnaire. As Fig. 3 indicates, the majority of the patients were satisfied with the medical haemostatic care in advance of the operation, the clotting factor supply and cooperation with the haemophilia team during the perioperative period. The surgeons easily adhered to the medical protocol as well as the clotting factor supply. All surgeons appreciated the collaboration with the coagulation disorder specialist. The HTC team was not contacted via the emergency number in any of the elective cases.

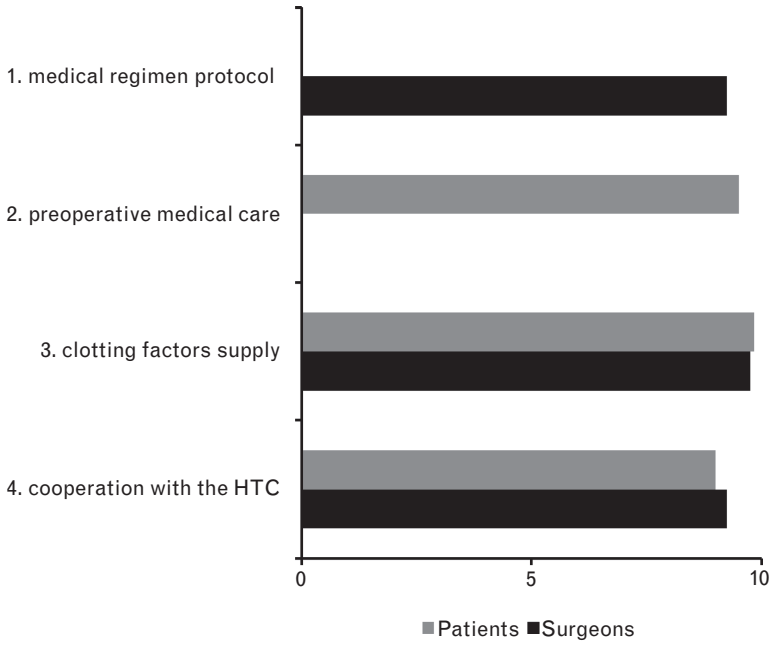
Discussion

In recent decades, major advances have been made in the management of haemophiliac patients. The improved safety of plasma derived as well as the development of recombinant products and treatment of HIV and chronic hepatitis have resulted in an increased life expectancy. Haemophilic patients are aging; therefore, the need for artificial joint replacements in haemophiliacs who have not been on primary prophylaxis is increasing. It has been shown that TKR is an effective treatment in haemophilic arthropathy to obtain pain relief and functional improvement [12–14].

Because the catchment area of our HTC is over 200 km and hospitals specialized in joint replacements have recently emerged, surgical procedures in our haemophilic patients are sometimes performed in external hospitals. In most of these hospitals, a laboratory that is capable of performing FVIII activity measurements and an on-site doctor who specializes in controlling haemostasis are not available. To ensure good patient-centred care, we have developed a standardized medical treatment procedure for the most frequent major surgical procedures that compose elective orthopaedic and trauma surgery and have created a detailed, standardized medical protocol.

According to the World Federation of Haemophilia, it is recommended that clotting factor level monitoring should be performed in the preoperative and postoperative periods (www.wfh.org). Haemophilia A patients scheduled to undergo major surgery should be supplemented to achieve a FVIII plasma activity of 80–100% prior to surgery; after surgery, the substitution should be continued in decreasing dosages for 14 days [10]. If

Fig. 3



An evaluation of our standardized treatment regimen by means of a questionnaire (rating scale: 10 = very good, 1 = poor). The evaluated concepts are as follows: 1. comprehensibility and feasibility of the medical protocol; 2. complete and contemporary preoperative haemostatic preparation; 3. availability and a supply of clotting factor; and 4. accessibility, expertise and communication with the Haemophilic Training Centre (HTC).

clotting factor activity monitoring is not available within a reasonable time, performing aPTT measurements are recommended. The disadvantage is that higher clotting factor consumption may result. In our study, FVIII monitoring could be performed only in five patients, whereas aPTT measurements were routinely performed. The aPTT measurements were within the normal range for all of the patients on the first postoperative day. However, it must be taken into account that the aPTT does not only reflect FVIII activity, but is also influenced by a number of other factors. The clotting factor concentrate that was administered in our study was in accordance with our patient recommendations and (i.e. during the first 10 days) ranged between 653 and 1027 units/kg body weight. This is concomitant with or slightly lower than data that were presented by Srivastava [11].

TKR in nonhaemophilic patients is usually associated with a total blood loss that ranges within 800–1200 ml [15]. In three of our patients, the documented blood loss was higher, but there was no need for an allogeneic blood transfusion. In addition, the blood loss after TKR was primarily in the range that was reported by Heeg *et al.* [16] in haemophiliac patients who had undergone total knee or hip replacement. In osteosynthesis of the femur, we found a lower blood loss than recently reported in published studies [17].

In patients undergoing major orthopaedic surgery, the prevalence of deep venous thrombosis is between 41 and 85% when bilateral venography is used. Therefore, routine pharmacological thromboprophylaxis is strongly recommended [18]. Currently, no evidence-based studies address if and, consequently, when medical thromboprophylaxis should be performed in patients with severe haemophilia. Because FVIII activity after surgery is usually not as high in patients with haemophilia A compared with nonhaemophilic patients, there are varying opinions concerning whether patients with haemophilia should have medical thromboprophylaxis [10]. Based on our regimen, we did not regularly recommend medical thromboprophylaxis in patients with severe haemophilia A, and in the course of the hospital stay, there were no clinical signs of a thrombosis in any of these patients. In one patient, low molecular weight heparin was administered against our recommendation, but no bleeding complication occurred.

To reduce bleeding complications, we did not recommend treatments with colloids and painkillers that may affect haemostasis. We discovered that non-steroidal anti-inflammatory drugs and colloids were administered to half of our patients, but no negative effects related to bleeding were observed. Nevertheless, as alternative possibilities regarding pain medications and fluids exist, we still would not recommend the use of colloids perioperatively or the intake of painkillers that affect haemostasis in the first postoperative days.

This study has several main limitations. The study is retrospective and involves only a small number of patients. Moreover, our results are from a heterogeneous orthopaedic patient population.

According to the results of the questionnaire, we can state that our standardized treatment regimen is well received by the patients and surgeons.

Due to the diverse biochemical characteristics of the new modified FVIII and IX clotting factor concentrates, routine laboratory monitoring is disturbed by the modified FVIII and IX products. Up to now, there is not enough experience on how to handle surgery procedures in haemophilic patients treated with these new products. The half-life extension may lead to a prolongation of the application interval in the postoperative setting [19].

In conclusion, our data indicate that our standardized medical treatment procedure and standardized medical protocol for patients with severe haemophilia are safe and have proven feasibility in elective orthopaedic operations and trauma surgery. We emphasize that the treatment of haemophilic patients who undergo surgery is best performed with an interdisciplinary approach. Defining algorithms may improve therapy quality. In certain situations in which monitoring coagulation factor activity cannot be ensured within a reasonable timeframe, it may still be possible to perform orthopaedic and trauma surgery in patients with haemophilia if aPTT measurements are established. In addition, a reliable consultation of a haemophilic specialist must be assured. Therefore, close cooperation between a surgeon who has a familiarity with bleeding disorders and a haemostatic department with 24-h availability is required before and after the surgical procedure.

Acknowledgements

Conflicts of interest

M.S. received speaker and consultant honoraria from Baxter (Vienna, Austria), Bayer (Leverkusen, Germany), Biotest (Dreieich, Germany), CSL Behring (Marburg, Germany), Novo Nordisk (Bagsvaerd, Denmark), Octapharma (Lachen, Switzerland), and Pfizer (New York, New York, USA). M.S. worked on an advisory board for Biotest and Pfizer. S.L. received speaker honoraria from CSL Behring (Marburg, Germany), Biotest (Dreieich, Germany), Novo Nordisc (Bagsvaerd, Denmark) and Bayer (Leverkusen, Germany), and received study support from CSL Behring and The Medicines Company GmbH (Leipzig, Germany). B.H. and C.H. have no interests which might be perceived as posing a conflict or bias.

References

1 White GC 2nd, Rosendaal F, Aledort LM, Lusher JM, Rothschild C, Ingerslev J. Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. *Thromb Haemost* 2001; **85**:560.

2 Valentino LA. Blood-induced joint disease: the pathophysiology of hemophilic arthropathy. *J Thromb Haemost* 2010; **8**:1895–1902.
3 Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R, *et al.* Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med* 2007; **357**:535–544.
4 Oldenburg J, Albert T. Novel products for haemostasis: current status. *Haemophilia* 2014; **20 (Suppl 4)**:23–28.
5 Hay CR. Prophylaxis in adults with haemophilia. *Haemophilia* 2007; **13 (Suppl 2)**:10–15.
6 Collins PW, Blanchette VS, Fischer K, Björkman S, Oh M, Fritsch S, *et al.* Break-through bleeding in relation to predicted factor VIII levels in patients receiving prophylactic treatment for severe hemophilia A. *J Thromb Haemost* 2009; **7**:413–420.
7 Rodriguez-Merchan EC, Quintana M, De la Corte-Rodriguez H, Coya J. Radioactive synoviorthesis for the treatment of haemophilic synovitis. *Haemophilia* 2007; **13 (Suppl 3)**:32–37.
8 Rodriguez-Merchan EC. Haemophilic synovitis: basic concepts. *Haemophilia* 2007; **13 (Suppl 3)**:1–3.
9 Rodriguez-Merchan EC. Aspects of current management: orthopaedic surgery in haemophilia. *Haemophilia* 2012; **18**:8–16.
10 Hermans C, Altisent C, Batorova A, Chambost H, De Moerloose P, Karafoulidou A, *et al.* Replacement therapy for invasive procedures in patients with haemophilia: literature review, European survey and recommendations. *Haemophilia* 2009; **15**:639–658.
11 Srivastava A. Dose and response in haemophilia: optimization of factor replacement therapy. *Br J Haematol* 2004; **127**:12–25.
12 Cohen I, Heim M, Martinowitz U, Chechick A. Orthopaedic outcome of total knee replacement in haemophilia A. *Haemophilia* 2000; **6**:104–109.
13 Sheth DS, Oldfield D, Ambrose C, Clyburn T. Total knee arthroplasty in hemophilic arthropathy. *J Arthroplasty* 2004; **19**:56–60.
14 Bae DK, Yoon KH, Kim HS, Song SJ. Total knee arthroplasty in hemophilic arthropathy of the knee. *J Arthroplasty* 2005; **20**:664–668.
15 Cushner FD, Friedman RJ. Blood loss in total knee arthroplasty. *Clin Orthop Relat Res* 1991;98–101.
16 Heeg M, Meyer K, Smid WM, Van Horn JR, Van der Meer J. Total knee and hip arthroplasty in haemophilic patients. *Haemophilia* 1998; **4**:747–751.
17 Kajja I, Bimenya GS, Eindhoven B, Jan Ten Duis H, Sibinga CT. Blood loss and contributing factors in femoral fracture surgery. *Afr Health Sci* 2010; **10**:18–25.
18 Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, *et al.* Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; **133 (Suppl 6)**:381S–453S.
19 Kitchen S, Gray E, Mertens K. Monitoring of modified factor VIII and IX products. *Haemophilia* 2014; **20 (Suppl 4)**:36–42.