MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2017; 23: 129-137
DOI: 10.12659/MSM.899580

Received: 2016.05.16
Accepted: 2016.06.08
Published: 2017.01.09

Revision Knee Arthroplasty in Patients with Inherited Bleeding Disorders: A Single-Center Experience

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Manuscript Preparation E
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Source of support: Departmental sources

Background: The results of total knee arthroplasty (TKA) in patients with inherited bleeding disorders (IBDs) are poorer when compared with those in the general population, with a notably higher risk of complications and higher revision rates. Thus, revision procedures are becoming a growing concern in this group of patients. The aim of this study was to evaluate the results of revision TKA in patients with IBD.

Material/Methods: A retrospective cohort study with longitudinal assessment of hemophilia patients scheduled for revision TKA between January 2010 and September 2015 was performed. The clinical status of the patients was assessed based on the Knee Society Score, and the Numeric Rating Scale was used to assess knee pain severity and patient satisfaction with the surgery. Radiological examination, post-operative complications, and reinterventions were recorded and analyzed.

Results: Very good results were obtained in all patients treated for aseptic loosening of the implant. However, inferior results were found in cases with infection. All patients operated on for aseptic loosening required only single-stage TKA, whereas patients with infection underwent multiple interventions. Complications were observed only in cases with infection.

Conclusions: Our study clearly outlined the differences in results based on failure mode, with far inferior results obtained in cases with infection. Given the lack of data in this area as well as the high specificity of this population, further high-quality studies are needed.

MeSH Keywords: Arthroplasty, Replacement, Knee • Blood Coagulation Disorders • Reoperation

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/899580

3684 1 3 47

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Background

Inherited bleeding disorders (IBDs) constitute a group of rarely occurring coagulation disturbances caused by deficiency or improper function of blood clotting factors. The three most common IBDs are hemophilia A, hemophilia B (Christmas disease), and von Willebrand disease (VWD), which are triggered by the absence of coagulation factor VIII (FVIII), coagulation factor IX (FIX), and von Willebrand factor (VWF), respectively. The clinical course of IBD is dominated by spontaneous bleeding episodes, leading to irreversible destruction of affected joints. Severe arthropathy remains the major cause of morbidity for hemophilia, and the knee is the most commonly involved joint [1–6].

Total knee arthroplasty (TKA) is the only way to eliminate the progressive pain and improve the quality of life in end-stage arthropathy of the knee joint. According to previously published reports, it can offer satisfactory results in majority of hemophilia patients, with 10-year prosthetic survival rate of 83–92% [7–13]. Nevertheless, the results in this group of patients are poorer when compared with those in the general population, with a notably higher risk of complications and higher revision rates [1,7]. As a result, in the wake of the continuous increase in the number of primary TKA in hemophilia patients, revision procedures are becoming a growing concern.

The main goal of this study was to evaluate the results of revision TKA in patients with IBD. In this paper, we share our experience and outline our approach to the management of failed TKA in this difficult patient population. It should be emphasized that worldwide experience with this issue is very limited, and to the best of our knowledge, this is the first paper in the literature devoted to this compelling problem.

Material and Methods

This retrospective cohort study with longitudinal assessment of hemophilia patients scheduled to receive revision TKA was performed in the Department of Orthopedic Surgery and Traumatology of the Central Research Hospital of the Ministry of the Inferior in Warsaw, an orthopedic center for patients with IBD. All hemophilia patients operated on because of TKA failure between January 2010 and September 2015 were analyzed in this clinical series. The study was approved by the ethical review board, and informed consent for print and electronic publication of outcomes was provided by all patients.

The study group consisted of nine hemophilic men aged 41 to 62 years (mean age: 49.9 years). Eight patients had severe hemophilia A, and one patient had been diagnosed with a severe form (type 3) of VWD. There were no patients with clotting factor inhibitor in the study group. One patient required treatment in both knees, five patients underwent left-sided procedures, seven of the patients enrolled in this study were primarily operated on in other hospitals, and two patients underwent primary TKA in our department (cases 7 and 9). Four cases were operated on because of aseptic loosening of the implant, whereas periprosthetic joint infection was reported in five cases (six knees). In the study group, none of the patients were seropositive for human immunodeficiency virus (HIV), eight of nine patients were seropositive for hepatitis C virus (HCV), and two patients were seropositive for hepatitis B virus. The mean body mass index (BMI) was 25.48 kg/m^2, with three overweight (BMI: 25–29.9 kg/m^2) patients, one moderately obese (BMI: 30–34.9 kg/m^2) patient, and no underweight (BMI: <18.5) patients. Patient demographics and relevant comorbidities are presented in Table 1.

Before the operation, all patients were hospitalized at the Clinical Department of Hemostatic Disorders and Internal Diseases of the Institute of Hematology and Transfusion Medicine in Warsaw for preparation for the surgery, including appropriate replacement factor therapy [14]. They were only transferred to our department on the day of the surgery, where the respective surgeries were performed. The procedures were carried out with standard revision surgical techniques, through a medial parapatellar approach in all cases. The extensiveness of the treatment, including type of the prosthesis and degree of its constraint, depended on the level of intraoperatively assessed joint damage. In selected cases with periprosthetic joint infection, temporary cement-loaded spacers were implanted together with appropriate antibacterial treatment for at least 6 weeks [15,16]. A tourniquet was used in all patients, and suction drainage was applied post-operatively for 48 hours. During the operations, samples for histopathological and microbiological analysis were collected. All patients received peri-operative antibiotics in accordance with actual recommendations [17], and anti-thrombotic prophylaxis was administered in patients with risk factors [14,18,19]. All operations were performed by the same surgical team.

The patients were transported to the Institute of Hematology for further post-operative treatment and rehabilitation on the day of the surgery, following an evaluation of overall clinical status. After the operation, physical therapy was initiated. If not contraindicated, gradual patient verticalization and gait education were usually commenced from the second post-operative day, first with a walker and then with two elbow crutches with partial or full weight bearing. If necessary, generally, physical therapy was individually customized, depending on the status of the operated joint and the patient's general condition. To prevent bleeding complications, deficient factor supplementation was provided during the entire rehabilitation process [14]. All in-hospital patients were under the

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Table 1. Demographics and clinical characteristics of study participants.

	Case								
	1	2	3	4	5	6	7	8	9
Demographics									
Type of IBD	sHA	sHA	sHA	sHA	sHA	sHA	sHA	sHA	sVWD
Age (years)	41	45	49	54	40	49	62	48	61
Weight (kg)	72	65	88	64	81	74	92	73	83
Height (m)	1.76	1.70	1.75	1.64	1.78	178	168	183	173
BMI (kg/m^2)	23.24	22.49	28.73	23.80	25.56	23.36	32.60	21.80	27.73
Operated side	L	R	R	R	L	L	R	L	L	L
Co-morbidities									
HIV status	–	–	–	–	–	–	–	–	–
HCV status	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	–
HBV status	Positive	–	–	–	Positive	–	–	–	–
Others	Splenectomy and leg ulcers	–	Hypertension, diabetes mellitus, Mallory-Weiss syndrome, diverticulosis, peptic ulcer disease, and hiatal hernia	Cirrhosis, portal hypertension, esophageal varices, and splenomegaly	–	–	Hypertension, chronic kidney disease stage 1, and epigastric hernia	Hypertension and hypothyroidism	–
Clinical outcomes									
KSS pre-op/post-op knee function total	32/99 45/80 77/179	51/79 45/70 96/149	Awaiting reoperation	14/39 25/10 39/49	43/74 50/100 93/174	22/79 45/70 67/149	36/90 40/90 76/180	Awaiting reoperation	Lost to follow-up	Above-knee amputation
NRS Pain pre-op/post-op	4/1	5/0		7/5	5/0	6/1	6/1			
NRS Satisfaction	10	7	1	5	9	10	10	5		7
Follow-up (months)	15	21	24	42	26	30	53	23		40
Pathogen organism	–	–	*S. epidermidis* MRSE and *K. pneumoniae* ESBL	*S. aureus*	*S. aureus*	–	–	*S. epidermidis* MRSE	*S. aureus*	*A. otitis*, *E. coli*, and *P. rettgeri*
Time from primary TKA to first revision operation	8 years	13 years	8 years	12 years	16 years	11 years	10 years	2 years	2 months	6 weeks (1.5 months)

IBD – inherited bleeding disorder; sHA – severe hemophilia A; sVWD – severe von Willebrand disease; BMI – mean body mass index; HIV – human immunodeficiency virus; HCV – hepatitis C virus; HBV – hepatitis B virus; L – left; R – right; KSS – Knee Society Score; NRS – Numeric Rating Scale; *S. epidermidis* MRSE – methicillin-resistant *Staphylococcus epidermidis*; *K. pneumonia* ESBL – *Klebsiella pneumoniae* extended spectrum beta-lactamase; *S. aureus* – *Staphylococcus aureus*; *A. otitis* – *Alloiococcus otitis*; *E. coli* – *Escherichia coli*; *P. rettgeri* – *Providencia rettgeri*.

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strict care of a multi-disciplinary team, including orthopedists, hematologists, a physiatrist, and a psychologist. Owing to significant restrictions in range of motion typical for hemarthropathy, patients were discharged home after regaining the ability to walk independently with a walker or crutches regardless of the patients' ability to perform 90° of knee flexion, as in the general population [20]. Follow-up routinely took place at 6 weeks and at 3, 6, and 12 months after surgery and once a year in the following period.

The clinical status of the patients was assessed based on the Knee Society Score (KSS). The Numeric Rating Scale (NRS) was used to assess knee pain severity and the NRS Satisfaction subscale was used to assess patient satisfaction with the surgery [21,22]. Knee range of motion and axis were measured with a goniometer. Radiological examination included assessment of implant setting and possible evidence of its loosening, and was based on anteroposterior and lateral knee joint images. Finally, post-operative complications and reinterventions were recorded and analyzed in the study.

The results of patient evaluation performed before surgery and at latest follow-up visit were analyzed in this study. The length of follow-up ranged from 15 to 53 months, on average 30 months. The outcomes of the study were analyzed with descriptive statistics, and detailed description of selected cases is provided.

Results

Description of cases

Case 3 was patient K.Z., 49 years old, male, and with a severe form of hemophilia A. The previous course of treatment in other centers was determined based on an interview and on the patient's medical records. In 1999, the patient underwent simultaneous ipsilateral total hip and TKA at the right side. Eight years later, the knee joint prosthesis was removed, and an spacer was implanted because of septic loosening of the implant and periprosthetic fracture of the femoral shaft. After 6 years, the patient was admitted to our department for the first time and qualified for revision surgery. On admission, he was complaining of severe, intensifying pain for several months and significant reduction of right knee range of motion (0–40°). During the operation, the spacer was removed, and a rotating hinged total knee prosthesis was implanted (Figure 1A, 1B). The post-operative course and healing of the surgical wound were uneventful. For almost 2 years, the results were satisfactory, with significant improvement in terms of pain and knee function (KSS increased from 19 to 118, knee score increased from 9 to 63, and knee function increased from 10 to 55; the Visual Analogue Scale for Pain score decreased from 7 to 1). However, during the last follow-up examination, the patient complained of pain located in the mid-thigh area, and migration of the implant was revealed on the radiographs (Figure 1C). Currently, the patient is scheduled for reoperation.

Case 4 was patient G.W., 54 years old, male, and with a severe form of hemophilia A. In 1997, the patient underwent simultaneous bilateral TKA. In 2009, the right knee endoprosthesis was removed, and a cemented spacer was implanted because of septic loosening of the implant. A couple of months later, fracture of the right femur shaft occurred and was stabilized with nail and wire osteosynthesis. The patient reported to our clinic 2 years later for the first time, and in the first stage, the nail was removed. Then, after a couple of months, the spacer was removed, and rotating hinged revision knee replacement was performed (Figure 2A, 2B), complicated by delayed wound healing and profuse bleeding episodes in the post-operative period. As intensive replacement therapy was ineffective, ultrasound was performed, revealing high-pressure hematoma and formation of a pseudo-aneurysm in the popliteal fossa originating from a branch of the popliteal artery. In cooperation with a vascular surgeon, a decision was made to obliterate the pseudo-aneurysm using ultrasound-guided thrombin injection. A reduction in the volume of the pseudo-aneurysm was achieved, but the procedure failed to completely stop inflow of the blood. Thrombin injections were repeated three times within a few days, without complete success. Finally, arteriography and obliteration of the pseudo-aneurysm using endovascular coiling technique were performed. Complete obliteration was achieved, and no further blood inflow was observed.

In 2013, the patient's left knee endoprosthesis was removed, and a cemented spacer was implanted because of septic loosening of the implant. A couple of weeks later, the second stage of the procedure was performed with revision system and extension stems, without any complications. Good clinical and radiological outcomes were noted during the last follow-up examination of the patient (Table 1).

Descriptive statistics

Very good results have been obtained in all patients treated for aseptic loosening of the implant at mean follow-up of 2.5 years (range: 15-52 months). The mean KSS score increased from 79.0 pre-operatively to 164.25 post-operatively, and the pain level decreased from 5.25 pre-operatively to 0.75 post-operatively. All patients were highly satisfied with the surgical outcome, and the mean NRS Satisfaction score obtained in this group of patients was 9.75. No intra- or peri-operative complications occurred, and the healing of the surgical wound was uneventful in all cases. Radiological examination during the last follow-up showed correct position of the prosthetic components without any signs of loosening.

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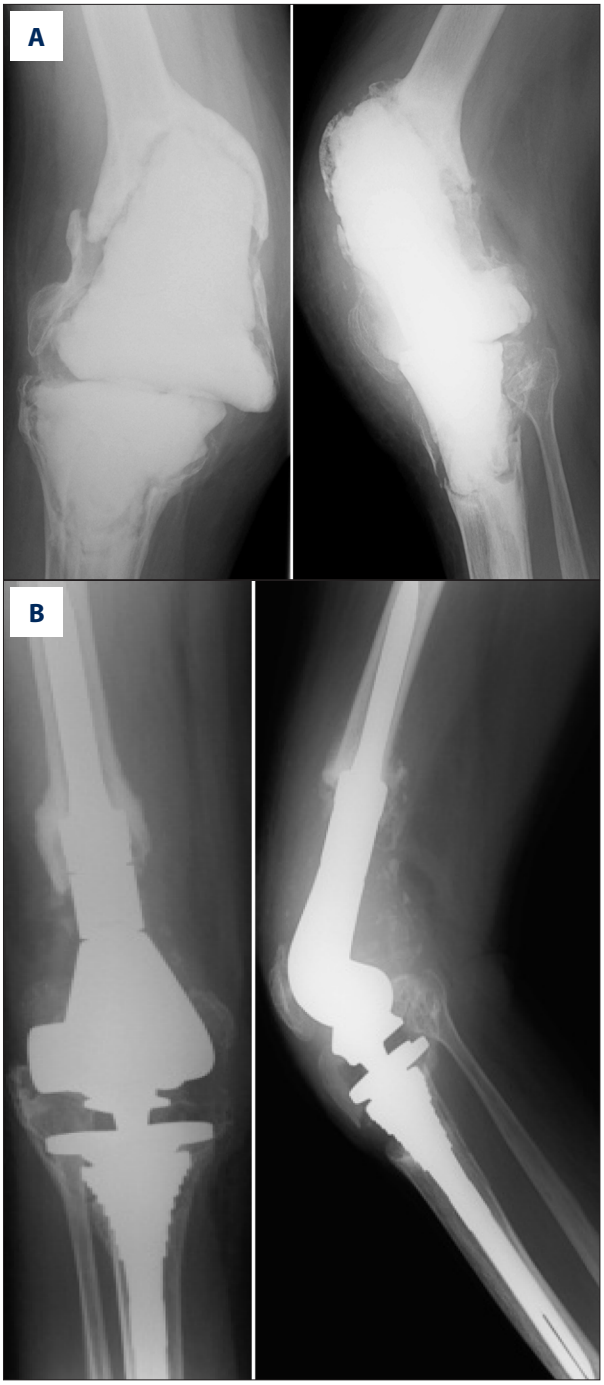

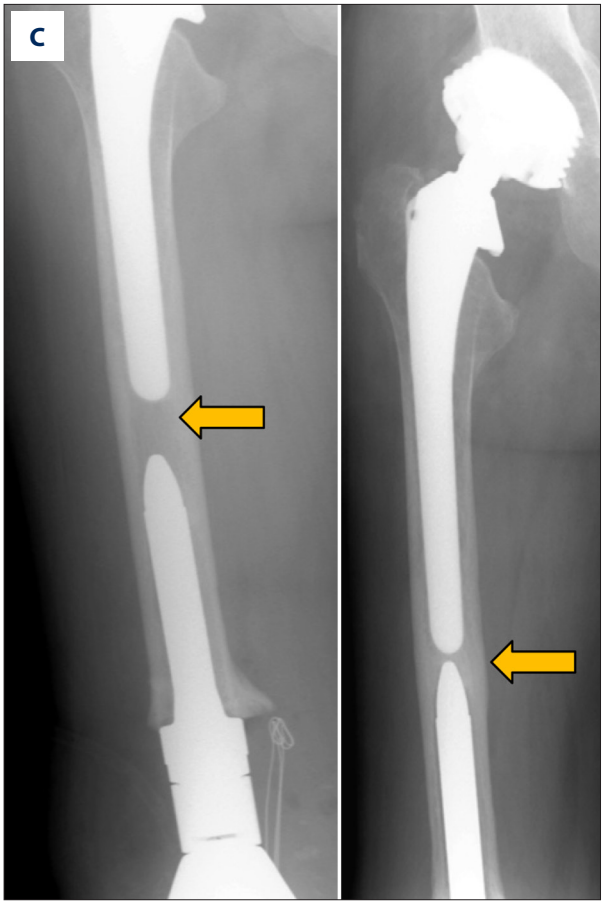

Figure 1. Case 3: (**A**) antibiotic-loaded knee spacer (pre-operative view), (**B**) post-operative radiograph 2 years after the operation, and (**C**) implant migration (arrows).

On the contrary, inferior results were obtained in the cases with infection at a comparable mean follow-up time (31 months, range: 23–42 months). One patient (case 8), treated for chronic periprosthetic joint infection, withdrew from further treatment in our department and was lost to follow-up. The treatment process of two other patients (cases 3 and 7) was not completed at the time of preparation of the manuscript. In the first patient (case 3), very good results were obtained for almost 2 years, but implant migration was revealed during the last follow-up examination. In the latter patient (case 7), two-stage revision allowed the infection process to subside, but 1.5 years later, the symptoms returned and another spacer had to be implanted. In one patient (case 9), above-knee amputation was performed. Only one patient (case 4) in this series underwent revision procedures on both knees. The left knee joint was operated on without any complications and with very good clinical outcome; the KSS score increased from 93 pre-operatively to 174 post-operatively, and the pain level decreased from 5 pre-operatively to 0 post-operatively. On the contrary, the clinical status of the right knee joint was very poor. The general satisfaction with performed treatment was low in this group of patients, with a mean NRS Satisfaction score of 5.4.

Complications were observed only in the cases with infection. Recurrent periprosthetic joint infection impeded treatment of three patients (cases 7–9). Impaired wound healing occurred in three patients (cases 4, 8, and 9), including sinus tracts with purulent discharge in two patients (cases 8 and 9) and vast necrosis of the skin and extensor mechanism in one patient (case 9, Figure 3); in the latter patient, above-knee amputation

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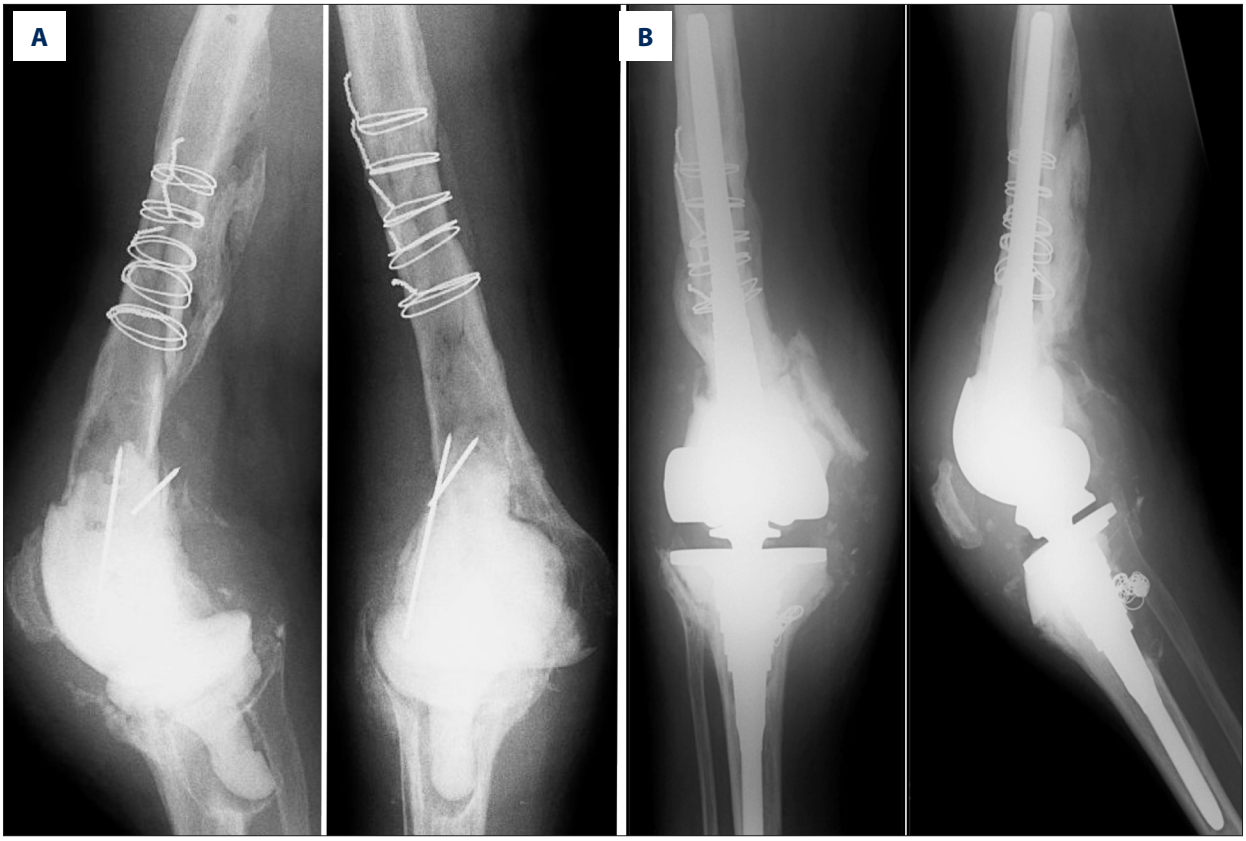

Figure 2. Case 4: (**A**) pre-operative and (**B**) post-operative (3.5 years) radiographs.

Figure 3. Case 9: vast skin damage with necrotic tissue at the anterolateral knee region.

had to be performed. Profuse bleeding episodes with recurrent hematoma occurred in one patient (case 4) because of pseudo-aneurysm formation. Lastly, aseptic loosening with implant migration disrupted the treatment process in one patient (case 3). No complications were observed in only one of the operated knee joints in this group of patients (case 4). In general, 13 orthopedic procedures were performed in the analyzed population over the study period (excluding removal of the intramedullary nail). All patients operated on because of aseptic loosening required only one single-stage TKA. On the contrary, patients with infection underwent multiple interventions.

The results obtained in this study are summarized in Table 1.

Discussion

The aim of this study was to present our experience in the treatment of failed TKA in patients with severe coagulation disorders. Given that IBDs are extremely rare and that joint replacement procedures in hemophilia patients are being conducted in only a few highly specialized orthopedics centers in selected countries, the worldwide experience and professional literature on this issue are very limited. This study is the first attempt to discuss the results of revision knee procedures in patients with IBD in the literature.

Patients with IBD comprise a unique and difficult-to-treat group of patients. They typically have multi-articular arthropathy with

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severe degeneration and contractures of the affected joints. The specificity of the coagulation disorders themselves as well as the existence of co-morbidities, including HIV and HCV infections, increases the risk of serious post-operative complications [14]. Hemophilia patients are usually young at the time of operation and therefore more likely to need further reoperations, but they expect normal activity with pain-free joints, functional independence, and participation in social activities without constraints. As a result, although TKA remains the treatment of choice in patients with advanced, painful, and disabling knee joint arthropathy, it carries a higher risk of complications in patients with co-occurrence of blood clotting disturbances, as confirmed by Cancienne et al. [1], who found significantly higher rates of infections, venous thromboembolism, transfusion of blood products, medical complications, and revision TKAs in patients with IBD when compared with a cohort of patients without bleeding disorder. In view of the above complications, revision procedures are becoming a growing concern in patients with IBD, as they contribute to the increasing number of revision TKAs being performed.

Despite limited data on the results of knee arthroplasty procedures in hemophilia patients, with the majority of available studies reporting only on small retrospective cohorts, the most perilous complications have been specified and discussed by several authors. Undoubtedly, the most common and devastating complication following TKA in this population is periprosthetic joint infection, which, according to Rodriguez-Merchan [7], has a mean infection rate of 6.2% (range: 1–11%); in contrast, the infection rate for non-hemophilia patients ranges from 1% to 2% [15,23,24]. Hemophilia patients are believed to be more prone to infection due to the possibility of recurrent hemarthroses, long-term intravenous self-substitution of deficient coagulation factor, HCV status, and HIV infection–associated immunodeficiency [1,8,25,26]. Interestingly, several recently published papers call into question the importance of HIV status, as similar rates of infection were found in HIV-positive and HIV-negative patient groups [7–9,27,28]. The two mechanisms by which the implant becomes septic include infection at the time of operation and hematogenous spread of bacteria from distant foci [29]. High-risk populations for the latter mechanism comprise patients with conditions such as diabetes mellitus, immunosuppression, rheumatoid arthritis, hemophilia, previous joint infections, and/or malnourishment; those taking corticosteroids; and those in their first 2 years after joint replacement, as specified by the American Dental Association and the American Academy of Orthopedic Surgeons [29,30]. In our study, one of the patients (case 7) had late infection and loosening of joint prosthesis caused by transient bacteremia during a dental procedure. Late infection of a TKA in a hemophilia patient after a dental procedure without any antibiotic prophylaxis was the subject of paper by Nadlacan et al. [29], who suggested serious consideration of antibiotic prophylaxis. Interestingly, our patient declared that he received antibiotic prophylaxis for all dental procedures, and in line with the quoted authors, precise information about high-risk procedures and appropriate recommendations for prophylaxis were provided for all of our patients.

Another predominant mode of TKA failure in hemophilia patients is aseptic loosening, which, according to Solimeno et al. [31], occurs in 6% of operated knees in hemophilia patients. Generally, the complex mechanism of aseptic failure after TKA include component loosening, osteolysis, instability, malposition of components, and polyethylene wear [32]. Figgie et al. [33] suggested development of a reactive and destructive bone-cement interface with local microhemorrhages as an explanation for the high incidence of aseptic loosening in patients with hemophilia, whereas Westberg et al. [13] and Hicks et al. [34] pointed to the role of polyethylene wear.

Apart from joint hemorrhages and wound healing problems commonly seen in hemophilia patients, other much less noted post-operative complications were observed in our series, including formation of aneurysm (case 4) and above-knee amputation (case 9). The treatment options for the first condition comprise intensive clotting factor replacement therapy, ultrasound-guided injection of thrombin, ultrasound-guided compression, selective angiographic embolization, and open vascular repair with resection of the pseudo-aneurysm and interposition grafting [35]. To our knowledge, to date, only eight cases of aneurysm following primary TKA [35–40] and one following revision TKA [41] have been reported in patients with hemophilia. Saarela et al. [38] applied local thrombin as treatment and obtained a satisfactory result, whereas in other reports, angiographic embolization was successfully performed. In one of our patients (case 4), thrombin injections were repeated three times without success, but complete obliteration was achieved with endovascular coiling technique. We therefore agree with Kickuth et al. [36] and Rodriguez-Merchan et al. [35] and recommend cost-effective early angiographic embolization as a treatment option. The role of prompt diagnostics and treatment was emphasized by some authors [35–42], and others [42,43] recommended routine pre-operative angiography or other diagnostics for the detection of vascular complications.

One patient (case 9), after a number of ineffective surgical interventions, including anterolateral thigh flap reconstruction, underwent transfemoral amputation. The number of papers addressing complication in the literature is scarce, and none of them addressed the hemophilia population. Sierra et al. [44] reported that the overall prevalence of amputation after TKA in the non-hemophilia population was 0.36%. Although most authors [44–47] state that above-the-knee amputation usually yields a poor functional result, Parvizi et al. [48] believe that it can provide a greater ability to reconstruct a functioning

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joint using an external prosthesis. Indeed, our patient accepted this treatment option and made a full recovery. Fitted with the prosthesis, he returned to full-time office work and regained his ability to walk long distances continuously without assistance. He is now able to perform most activities of daily living efficiently and declares he regained independence and would chose amputation procedure again if the need arises. Above-knee amputation should be always preceded by thorough history analysis, precise clinical examination, and, preferably, a series of interdisciplinary consultations, which were all discussed with the said patient. Pre-operative discussion with a detailed explanation of medical condition, indications, and possible further complications is obligatory, as it can facilitate the acceptance of limb amputation and the possibility of an unfavorable result. In our opinion, psychological consultations can be particularly beneficial and are recommended in such patients.

This study has several limitations, including its retrospective character, the lack of a control group, and the small number of cases, which is due to the considerable rarity of IBDs and revision knee procedures in this group of patients. Another shortcoming in the presented series is the lack of quality-of-life parameter analysis.

Revision knee arthroplasty in patients with IBD is an extremely complex and challenging procedure, burdened with a high risk of complications and an unpredictable outcome. Owing to the availability of deficient factor therapy, advances in surgical technique and implant design, and improvements in post-operative management, more primary TKAs are performed, which leads to an increase in the number of revision procedures. Although revision knee arthroplasty is becoming an increasingly important topic for orthopedic centers, surgeons, and clinicians involved in the treatment of hemophilia patients, none of the available articles addressed this issue specifically and only "in passing" remarks can be found in the literature [7,18,41]. In this context, the main reasons for this study were not only to analyze the results of revision knee procedures in this population or attempt to identify modifiable factors that might improve outcomes and decrease the incidence of re-revisions, but also to promote debate and discussion on this topic. Our study clearly outlined the differences in results based on failure mode, with far inferior results obtained in cases with infection. In light of the above results, avoidance of infection is paramount during primary surgery, and the role of the surgeons performing the initial operation should be emphasized. In our opinion, all TKA procedures in hemophilia patients should therefore be performed only by highly skilled surgeons, in close cooperation with hematological specialists. Consistent with past studies, we also believe that all patients should be educated on the importance of meticulous antisepsis with self-infusions, regular medical check-ups, immediate reporting of any signs of infection, and the use of prophylactic antibiotics before procedures with potential for contamination, including dental work, to avoid late-onset infections [1,7,8,29].

Our study confirmed the complexity of the issue as well as the considerable (surgical) difficulties of revision knee procedures in patients with IBD. Given the lack of data in this area as well as the high specificity of this population, further prospective controlled trials with bigger patient cohorts are needed to better verify the efficacy of currently used methods and to search for further solutions that will meet the challenges ahead and facilitate clinical decision making.

Conclusions

Revision knee arthroplasty in patients with IBD remains a demanding procedure with a high risk of post-operative complications. This study revealed the differences in results based on failure mode, with far inferior results obtained in cases with infection. Given the lack of data in this area as well as the high specificity of this population, further high-quality studies are needed.

Statement

The authors have no competing interests.

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