CURRENT CONCEPTS REVIEW

Total Knee Arthroplasty in Patients with Hemophilia: What Do We Know?

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Abstract

Total knee arthroplasty is considered as the treatment of choice for those with end stage hemophilic arthropathy. Compared to other patients undergoing TKA, these patients have specific features such as bleeding tendency, younger age, pre-operative restricted range of motion (ROM), altered anatomy, and increased complications. This narrative review of literature is going to investigate several issues regarding the TKA in hemophilic patients including indications, perioperative factor replacement, surgical challenges, postoperative rehabilitation, outcomes, and complications.

Level of evidence: I

Keywords: Hemophilia, Hemophilic arthropathy, TKA, Total knee arthroplasty

Introduction

Total knee arthroplasty (TKA) is known as the gold standard treatment for end stage hemophilic arthropathy. Due to particular features of these patients compared to primary osteoarthritis of the knee, such as bleeding tendency, younger age, pre-operative restricted range of motion (ROM), altered anatomy, and increased complications, it is necessary to consider several important issues during TKA in patients with hemophilia preoperatively, intraoperatively, and postoperatively.

This manuscript is a narrative review of the current literature available about TKA in hemophilic patients.

Indications

Pain is the most common indication for total knee arthroplasty. In advanced hemophilic arthropathy of the knee, there is a limitation in joint range of motion and weight bearing can be extremely painful. Treatment of the knee arthropathy depends on the stage of the disease, impact on quality of life, severity of symptoms, previous treatment, and available resources (1). Surgical procedures such as TKA are reserved for patients in whom conservative methods have already failed (2-4). Solimeo et al. mentioned incapacitating pain and impaired function as indications for TKA (5). Radiographic findings in hemophiliacs are far worse than clinical findings and physicians must be aware that they should treat the patient not the X-ray (6). Despite good result of TKA, surgeons must keep this reality in mind that this procedure holds the risk of prosthesis loosening and late joint infections in immunologically compromised persons (7). According to the current literature, there is no defined criteria for TKA in hemophiliacs. It seems that common practice is knee replacement in patients who fail to respond to analgesics, orthotics, and physical therapy (1, 6).

Perioperative factor replacement

Perioperative factor replacement for TKA in hemophilic patients plays an important role in prevention of hematoma, hemarthrosis, and related problems. The debate on the definition of major or minor surgeries
in hemophilia is continuing; however, TKA is always accounted as a major surgery (8). There are different protocols for factor replacement in patients undergoing TKA. Some scholars have suggested the level of 120% for factor VIII and factor IX during induction of anesthesia, extra 40% after 4 hours in operating room, level of 60-80% for 72 hours postoperatively, 50% for 14 days, 30-40% for 3-4 weeks and 40% before each physical therapy session up to 6 weeks after surgery (9). The guideline of World Federation of Hemophilia recommends a desired preoperative factor level of 80-100% for major surgeries in hemophilia A and a level of 60-80% for hemophilia B, with postoperative levels gradually tapering to approximately 50% until the wound is healed (typically over a period of 10 to 14 days). This guideline has also recommended to divide the level of factor in major surgeries based on the level of access to resources (Table 1) (1). The half-life of different factor VIII and factor IX differ, the standard types of factor VIII and IX have half life of 8-12 and 18-24 hours, respectively. There are two options for factor replacement; first: the initial dose (patient’s weight (in kg) multiplied by the desired rise in factor VIII level (as a whole number, such that a desired level of 100 percent is entered as 100) multiplied by the volume of distribution (for factor VIII and factor IX, this equals 0.5 and 1, respectively)) and subsequent doses are given at intervals of approximately one half-life of the infused product for that patient, which is based on the peak and trough levels as described below. These subsequent doses are usually half of the first dose and are given at almost one half-life of the product. This will be guided by the patient’s measured factor level and the desired peak level. Second: Initial dose (that is calculated similar to the previous option) followed by continuous infusion of 4 IU/kg/h and 6 IU/kg/h for factor VIII and factor IX, respectively. Although monitoring the factor level is required less frequently in the second option, factor activity levels should be checked periodically, with the interval determined by the previous level, dose adjustments, and clinical bleeding. The factor half-life and ultimate hemostasis could be significantly affected due to the individual pharmacokinetic variations, so, monitoring is needed to determine the subsequent doses in both methods (10, 11).

Factor replacement is challenging in the presence of inhibitors (neutralizing alloantibody against infused factor), as inhibitors bind to the infused factor and render it ineffective (12). It is very important to find the inhibitor in preoperative assessments. For a patient with a titer >5 Bethesda unit with a high responding inhibitor and need for major surgery like TKA, a bypassing product is the choice. These products include recombinant activated factor VII (rFVIIa) and activated prothrombin complex concentrates (aPCCs) such as FEIBA (factor eight inhibitor bypassing agent) that contain an activated form of a downstream clotting factor in the coagulation cascade. For inhibitor positive hemophilia A patients, both of these products could be selected, however rFVIIa is the preferred agent for hemophilia B as it does not contain factor IX when some individuals with hemophilia B with an inhibitor may have the experience of reactions or anaphylaxis upon exposure to factor IX. Both of these bypassing agents are prothrombotic, so, caution about venous thromboembolism (VTE) should be taken especially about aPCCs (FEIBA) (13). When rFVIIa is administered 90 to 120 mcg/kg every 2-3 hours until hemostasis is achieved and then at three- to six-

| Table 1. Suggested plasma factor peak level and duration of administration for TKA as a major surgery |
|-------------------------------------------------------------|---------------|-----------------|-------------|
| Major surgery | Hemophilia A | Desired level (IU/DL) | Duration (days) | Hemophilia B | Desired level (IU/DL) | Duration (days) |
| Pre-op | 80-100 | Duration (days) | 60-80 | 1-3 |
| | 60-80 | 4-6 | 30-50 | 7-14 |
| Post-op | 30-50 | 7-14 | 20-40 | 7-14 |

WHEN THERE IS SIGNIFICANT RESOURCE CONSTRAINT

| Major surgery | Hemophilia A | Desired level (IU/DL) | Duration (days) | Hemophilia B | Desired level (IU/DL) | Duration (days) |
| Pre-op | 60-80 | 1-3 | 30-40 | 1-3 |
| Post-op | 20-30 | 4-6 | 10-20 | 10-20 | 1-3 | 4-6 | 7-14 |
hour intervals after hemostasis has been restored, FEIBA is given 50 to 100 units/kg every 6 to 12 hours, not to exceed 100 units/kg/dose or 200 units/kg/day. Dosing of these products is adjusted by the clinical response instead of laboratory testing. This protocol continues at least 48-72 hours for major surgeries and is followed by taper in by gradual increasing the dosing intervals. When the bleeding could not be controlled by one of these agents the other one may be effective. Plasmapheresis is another option for inhibitor positive hemophilic patients (>5 Bethesda unit) with life threatening bleeding when bypassing agents are ineffective (12, 14).

**Surgical challenges**

TKA in hemophiliac patients is a challenging and technically demanding process due to altered anatomy, marked and prolonged bony deformity and defects, diffused osteopenia, soft tissue contracture, and muscle atrophy. Indeed, the surgeon should be familiar with the revision TKA techniques and special implants (15-19). Preoperatively, a whole musculoskeletal system examination including both knees, hips, and ankles are mandatory because of multiple joint involvements that may alter the surgical plan. AP, lateral, sunrise, and notch view of both knees are necessary. Adding 3 joint view of both lower limbs and CT scan may be needed to complete the evaluation of the anatomy and bony defects (20).

Although some authors have reported using cruciate retaining (CR) prosthesis, others discuss a better deformity management and more favorable outcomes by sacrificing PCL and using posterior stabilizing (PS) prosthesis (21-26). According to a systematic review by Moore et al. (18) PS was used in 41% of the patients, consequently considered as the most commonly used prosthesis. Due to the prolonged axial bony deformity (varus or valgus) and muscle atrophy, the risk of intraoperative joint instability is much more than primary TKA in OA patients. In order to manage the instability, it seems CCK and even hinge prosthesis are necessary to be obtained (27). Physéal overgrowth in early age, widening of the femoral intercondylar notch, and huge osteophytes are characteristic features in this group of patients. Huge osteophytes may mislead the surgeon on the determination of the correct joint limits leading to misaligned prosthesis (28, 29). Wider medial-lateral diameter, higher medio-lateral to antero-posterior size aspect ratio, and larger patella are important characteristics of these patients in contrast to OA patients (30). Bony defects are common in these patients due to prolonged deformity, poor bone quality and large subchondral bone cysts. The operating surgeon need to consider them in preoperative planning and manage them as the same in non-hemophilic patients.

The use of prophylactic antibiotic is not different between hemophilic and non-hemophilic patients. First generation cephalosporin is the antibiotic of choice, however, in case of allergy to cephalosporins vancomycin or clindamycin are good alternatives (21, 23, 30-32). The use of antibiotic-loaded cement is recommended by many authors and is our own practice as well (2, 20, 27, 30, 33). The use of tourniquet during TKA in hemophiliacs is largely recommended. However, most authors have emphasized that meticulous hemostasis after deflating tourniquet is necessary at the end of TKA before the closure to avoid postoperative hematoma (21, 34). Kubes et al. believe in limited use of tourniquet just before cementing of the implant. They argue that meticulous hemostasis, immediate diagnosis of popliteal vessel injury and sufficient time for this time-consuming complicated soft tissue and bone management are benefits of not using tourniquet during the main procedure (35). According to our practice, the tourniquet must be kept inflated during the whole operation course and deflated after the dressing and bandage is done (32).

Standard midline incision is the preferred approach (2, 22, 30, 32, 34, 36, 37). In some cases with previous surgery such as open synovectomy or corrective osteotomies, previous scars are utilized with accepted rules of revision surgeries (38). Also, while some authors prefer midvastus approach, majority of studies have used medial parapatellar approach (15, 21-23, 32, 33, 35). Because of the marked adhesions, arthrofibrosis, and decreased ROM in hemophilic patients, patellar subluxation is restricted and makes the exposure difficult in some patients. Therefore, using extensile approaches are indicated in some patients to avoid patellar-avulsion. Quadriceps snip, V-Y quadricepsplasty, and tibial tubercle osteotomy are frequently used (21, 22, 30, 33, 36, 39). Although tubial tubercle osteotomy is biomechanically superior to other mentioned extensile approaches, it has not been widely used in the literature for hemophilic patients. Strauss et al. stated that thin soft tissue coverage in proximal tibia due to muscle atrophy, difficulty in osteotomy site fixation because of probable stemmed tibial component, and inability to extensor mechanism lengthening are the reasons to avoid TTO (21). Post-operative extension lag is a complication of V-Y quadricepsplasty, though it should be performed restrictive (21). We have a very low threshold for quadriceps snip in patients with hemophilia to improve the exposure and believe that this procedure will give enough exposure in almost all hemophilic patients who receive TKA (2).

Synovectomy is part of TKA in patients with hemophilia and should be done in all patients. It is helpful in exposure and may reduce the chance of bleeding in the replaced joint in the future (21, 22, 34, 39). In addition, most of hemophilic patients who are candidates for TKA suffer from limited ROM in the knee. They usually present with flexion contracture of the knee, however, some patients have stiffness and even ankylosis in the affected joint. Additional soft tissue release to address the contractures is an integral part of operation as it was shown that inadequate soft tissue release, will compromise the end result (15, 26, 34, 39). Some authors have recommended additional bone cut to be done either from distal femur or both distal femur and proximal tibia, if the flexion contracture still exists after adequate soft tissue release (15, 30, 32, 39). Atilla et al. also reported open hamstring release and posterior capsulotomy in 2 cases with residual flexion contracture after additional bone cut (15). In spite of all above measures, in some patients with
long-standing knee arthropathy and flexion contracture, there is remaining flexion contracture at the end of the surgery. Feng et al. suggested long leg cast immobilization to correct this flexion contracture (39). We have shown in our series that flexion contracture after TKA in patients with hemophilia is different from flexion contracture in patients with TKA for osteoarthritis. We do not accept any flexion contracture at the end of TKA in patients with knee osteoarthritis. However, we have previously shown that the remaining flexion contracture in patients with hemophilia usually would be resolved in 6 months with physical therapy and splints (40). We prefer not to cut from distal femur or proximal tibia if possible as it will lead to more bone deficiency in these patients.

Most authors prefer patella resurfacing, but, it is not doable in some cases due to osteoporosis and thin patella (15, 27, 30, 32, 33, 36). Some authors prefer patelloplasty in spite of patella resurfacing in hemophilic patients. They have argued that due to lower level of activity, less anterior knee pain and thin osteoporotic patella, patelloplasty is preferred and patella resurfacing is not needed. They have reported good results after patelloplasty (39).

Kim et al. reported 32 robot-assisted TKA in 29 hemophilic patients. They reported good functional outcomes without any complications (23). They hypothesized that considering the younger age in hemophilic patients better long-term outcomes may be reached by restoring a neutral mechanical axis. They also emphasized that long-term follow-ups are needed to clinically investigate the hypothesis. Using suction drain following TKA has been recommended by many authors (15, 20, 21, 23); however, Mortazavi et al. investigated the use of suction drain in patients with hemophilia following TKA and compared the complication rate and functional outcomes between patients with and without suction drain (30). They found no difference regarding the complications or functional outcomes between the two groups and concluded that there is no rationale for the use of drain after primary TKA.

In a retrospective case-control study Rodriguez-Merchan et al. recommended the use of a standardized multimodal blood loss prevention method (MBLPM) that includes intra-articular tranexamic acid (TXA) (MBLPM-TXA) in patients with hemophilia A who underwent TKA because it was effective in reducing the transfusion rates (41).

Post-operative rehabilitation

Majority of studies in TKA arthroplasty in hemophiliacs did not express any data about post-operative rehabilitation. Lobet et al. believe that improvement in postoperative management following TKA is one of the factors that makes TKA the treatment of choice for end stage hemophilic arthropathy (42). The use of rehabilitation services is one of the least studied aspects of TKA (42). Most studies suggest the initiation of postoperative rehabilitation in hospital at the early phase after surgery. In Rodriguez-Merchan practice the intensive rehabilitation was started in the 3rd postoperative day and continued twice daily during hospital stay. The discharge protocol in his report was continuing the rehabilitation for 6 to 8 weeks, 5 days a week (43). In 2011 klein et al. published a guideline for multiple joint procedure in persons with hemophilia (44). Mortazavi et al. started rehabilitation on the same day of surgery (2). In their rehabilitation protocol, patients start walking and knee range of motion on the same day of surgery. It is unclear if CPM (Continuous Passive Motion) machine is useful following TKA in hemophiliacs (42). It is well documented that proper hemostatic coverage during rehabilitation is crucial; however, there is some controversy between the authors in defining the proper hemostasis (45).

Outcomes

The functional outcomes and survival rate of TKA in patients with hemophilia is generally inferior to TKA in osteoarthritis patients (24, 26, 46). However, they are improving as a result of better implant designs and more proper factor replacement (2, 21, 22). In a systematic review including 10 papers, Moore et al. found significant improvement in the post-operative range of motion and clinical and functional knee scores (31). However, the mean post-operative ROM was from 6.07 to 82 degrees, which is less than ROM after TKA in non-hemophilic patients (0-129 degrees). Pre-operative ROM, which is one of the main determinants of postoperative ROM is usually more restricted in patients with hemophilia. Although the average final functional score after TKA is higher in patients without hemophilia, the average improvement in KSS and HSSKS in non-hemophilic patients (41 and 36) is similar to hemophiliacs (37, 9).

There is a similar trend regarding the survival rate. In the most promising report, Goddard et al. reported 20-year survival rate of 94.0%, similar to non-hemophilic population, during the 9.2-year follow up; additionally, the rate of infection and aseptic loosening were the same as the normal population (47). Zingg et al. reported 10-year prosthetic survival rate of 88% (48). Based on a study with longest follow-up interval by Wang et al., 83% of excellent results was reported; moreover, 86% of patients were willing to have the same surgery (49). The main reasons for patient satisfaction had been the pain relief and increased quality of life due to better ROM, especially in extension. These promising outcomes make TKA a much more valuable option in end stage hemophilic arthropathy; however, complications remain as a major concern.

Complications

The overall complication rate following TKA in hemophiliacs is relatively high. In a meta-analysis by Moore et al., they reported 106 complications among 336 performed TKA (31.5%). They included infection and revision for infection as two rather than one complications; however, the rate of complications was still high (31). The bleeding diathesis of hemophilic patients along with local factors such as poor bone quality, bone loss, soft tissue fibrosis, muscle atrophy, axial deformity and flexion contracture are the potential reasons for higher
complications (50). Infection, periprosthetic fracture, bleeding, neurovascular injury, inhibitor development, loosening, patellar clunk syndrome and subluxation, anterior knee pain, component removal, and loosening are some but not all reported problems after TKA in hemophiliacs. Initial reports have shown extremely high complication rates. Ten of 13 patients in the study of Goldberg et al. had serious complications; postoperative bleeding in three knees led to arthrodesis or revision, five superficial wound infection and three peroneal and/or posterior tibial nerve palsies were reported. Two patients had patellofemoral pain that needed further patella resurfacing (51). Figgie et al. followed Goldberg's study. Six of 19 patients had poor results at the end follow-up. Among seven patients with under 80% factor replacement cover, four failed and six had complications (24). However, improvement in surgical technique and implant designs as well as access to factor concentrate has decreased the complication rate after TKA in hemophiliacs (23).

Infection is the most devastating complication after TKA. The risk of periprosthetic joint infection (PJI) after TKA in general population is less than 1%, however, the average rate of infection after TKA in patients with bleeding disorders is 7.1% (31). Some authors reported the infection rate as high as 17% (25, 47, 50, 52, 53). It is very important to consider that late infection is more common in this patient population and the longer the follow up, the higher rate of the complication has been reported in the literature. Cancienne et al. reported 3.5% infection rate at six months; while, Silva and Luck reported only 77% implant survival rate free of infection at 10 years (50, 53).

There are several explanations for higher infection rate in these patients including button limited to higher rate of HIV and HCV infection, frequent intravenous aches for infusion of coagulation factors which increase the risk of bacteremia, and high incidence hematoma which is the known risk factor for PJI (50).

The role of chemical thrombophylaxis after TKA in patients with hemophilia has yet to be determined. Cancienne et al. demonstrated 3.2% venous thromboembolism (VTE) rate after TKA in hemophilic patients which is surprisingly higher than the 1.4% rate in general population (P<0.0001) (50). In contrary, Botero et al. reviewed 35 studies of hip and knee arthroplasty in 1017 hemophilic patients and found a VTE rate of 0.9% (54). In a survey of 140 federally funded hemophilia treatment centers in the US, 67% of the surgeons felt that knee and hip arthroplasty in hemophilic patients is high risk enough to warrant some form of thromboprophylaxis and only 55% of them provided some type of prevention (55). However, both AAOS and ACCP guidelines recommend no chemoprophylaxis in patients with bleeding diathesis, as the bleeding diathesis in hemophilic patients and disrupted coagulation pathway may obviate the necessity of administration of anticoagulant agents after TKA (56, 57). At our institution, we follow AAOS and ACCP guidelines and do not use any chemoprophylaxis in patients with hemophilia following TKA; however, we emphasized on early ambulation and mechanical prophylaxis. We have not observed any symptomatic VTE after TKA in our hemophilic patients (2).

Stiffness is another potential complication of TKA in patients with hemophilia. While range of motion usually improves significantly after TKA in hemophiliacs, sometimes manipulation under anesthesia or even lysis of adhesions for stiffness may be required (25, 34). The incidence of stiffness after TKA in hemophilic patients has been reported between 1-48% (50, 58). We believe that this variability in the rate of stiffness is due to the postoperative protocols. We apply a very disciplined rehabilitation protocol at our institution and start the knee range of motion active and active assisted on the same day of surgery. Since the time we have implied this protocol, we did not have any manipulation under anesthesia for stiffness even in patients with very limited range of motion preoperatively (2).

Blood loss is a known complication of TKA in patients with bleeding diathesis. The reported frequency of blood transfusion following TKA in hemophilia is 29.1% to 58%, which impose all inherent complications of blood transfusion including antibody production, infection, allergic reaction and prolonged hospital stay and rehabilitation time (50, 59). However, in our institution, we develop a protocol, which has decreased the rate of blood transfusion to less than 1%. We perform TKA under tourniquet control and do not deflate the tourniquet until the complete wound closure, dressing, and bandage of the operated leg. In addition, we inject a cocktail into the joint space after watertight closure of the capsule. The cocktail includes transamine, ketorloc, marcaine, epinephrine, and morphine. As mentioned previously, we do not use any suction drain after the surgery.

The rate of medical complications following TKA is higher in patients with hemophilia. Cancienne et al. demonstrated significantly higher rate of medical complications like myocardial infarction, respiratory failure, urinary tract infection, acute renal failure and acute cholecystitis 3 months after TKA in hemophilic patients compared to general population (6.5% vs 4.9%) (50).

The higher rate of aseptic loosening after TKA in hemophilic patients (about 6%) in relation to general population could be attributed to their younger age at the time of operation (39 years) and therefore, higher demand placed on the prosthesis and more wear (50, 59).

**Simultaneous bilateral TKA**

Simultaneous bilateral TKA in patients with hemophilia is an attractive option for several reasons. First, bilateral involvement is common in these patients and correction of both knees deformity and pain at the same time makes the rehabilitation process faster and less complicated. In addition, the involvement of the other knee in unilateral TKA puts an overload on the prosthesis, which theoretically makes it more vulnerable to aseptic loosening. Secondly, patients have one admission and one operating room visit which leads to less hospital stay and earlier return to daily living activity. Third, it is a cost saving surgery. The cost of simultaneous bilateral TKA was 45% less than staged bilateral TKA (37). The
main reason for decrease in the cost was reduction in factor consumption. This in turn results in diminished probability of developing inhibitors. Finally, it was shown that the functional outcome and rate of complication following simultaneous bilateral TKA are not significantly different from staged bilateral TKA (37).

Simultaneous bilateral TKA in patients with hemophilia have been reported by several authors, however, there is always a concern safety of this procedure (15, 25, 26, 33, 35, 60).

The literature is controversial with regard to simultaneous bilateral versus unilateral TKA in patients without hemophilia. Some showed inferior results and more complication rates (61-63) and some other revealed no increased complications and even better results (64-69). Hu et al. included 14 studies (15,563 patients, 4320 simultaneous bilateral and 11243 staged bilateral) and found a significantly higher mortality rate in 30 days after surgery and a higher neurological complication rate; however, they did not find any higher infection, pulmonary thromboembolism, deep vein thrombosis, and cardiac complications in simultaneous bilateral patients (70). They concluded that the higher mortality and neurological problems were based on only two studies and they questioned these results. Fu et al. included 18 articles in their systematic analysis (107,318 patients, 28,760 simultaneous bilateral, and 78,558 staged bilateral) and found that the simultaneous bilateral group has a significantly higher mortality rate in 30 days after surgery, a higher rate of pulmonary thromboembolism (PTE) and transfusion. Interestingly, they found lower revision and infection rates in simultaneous bilateral group. They did not find any differences in the neurological complications, DVT, cardiac complications, and superficial infection. They concluded that higher mortality rate due to PTE can be managed properly by perioperative anticoagulation and simultaneous bilateral TKA is an appropriate option in selected patients (71).

The same controversy exists in simultaneous bilateral TKA in patients with hemophilia. Some authors believe that the procedure dose not increase the rate of complications, as most of hemophilic patients are young and have no medical comorbidities. They concluded that this practice will decrease the cost, hospital stay, and time of sick leave, besides the better rehabilitation and faster return to work (37). Some other authors have questioned the safety of this approach due to the lack of acceptable qualified evidence and recommended more prospective studies to answer the question more confidently (72).

However, simultaneous bilateral TKA could be considered as a good and reasonable option at least in selected hemophilic patients, as lower costs, increased quality of life, and better rehabilitation program are advantages, without any reported adverse outcome (37, 72).

Rodriguez-Merchan has recently reported that the mean infection rate with TKA in people with hemophilia is 7%, and local infiltration analgesia (LIA) and intraarticular tranexamic acid (TXA) are also recommended to control postoperative pain after TKA (41, 73).

In conclusion, TKA in patients with hemophilia is a successful operation with good functional outcome. However, this operation is not without complications. Applying specialized preoperative, operative, and postoperative rehabilitation protocols will help surgeons to overcome technical difficulties and avoid complications, which in turn are associated with good functional outcome and acceptable patient satisfaction. In this regard, this surgery is better to be done in selected referral centers with high volume surgeries on hemophilic patients.

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