Evidence based management of the knee in Hemophilia

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Introduction

Hemophilia is an x-linked condition which results in a deficiency of coagulation factors, either factor VIII (in hemophilia A) or factor IX (in hemophilia B)[1]. In moderate and severe cases, the factor deficiency leads to recurrent spontaneous hemarthroses, which in turn lead to contractures and early degenerative joint disease. The knee is the commonest joint to be affected by hemophiliac arthropathy, and there is now a large body of evidence to guide us in the management of such patients. The aim of this article is to assess the current evidence for surgical interventions in patients with hemophilia, with a special focus on the knee.

General concepts in hemophilia and its treatment

Hemophilia is one of the commonest bleeding disorders encountered in orthopedic surgery. It is an X-linked recessive condition affecting one in 5000 men. Hemophilia is a disorder of the initiation of coagulation, and is due to reductions in the concentrations of, or the presence of a less active version of, one of two coagulation factors, factor VIII and factor XI. The deficiency of these factors results from a defect in one of two genes on the X chromosome, F8 (which codes for factor VIII) and F9 (which codes for factor XI). Hemophilia A, the commonest form, is a deficiency of factor VIII, and hemophilia B (previously known as Christmas disease) is a deficiency of factor XI[1].

The severity of hemophilia is graded according to the amount of the deficient coagulation factor present in the circulation. This is expressed as a percentage (with normal being 100%): mild disease results from a concentration of between 5-40% of normal; moderate disease from 1-5% and those with severe disease have a concentration of less than 1%[2]. Those with severe disease bleed

spontaneously, whilst in mild and moderate disease, excessive bleeding is observed after minor trauma, surgery or dental work.

In developed countries (20-30% of the world population), the orthopedic problems of hemophilia have reduced since the introduction of prophylaxis using concentrates of the deficient coagulation factor[3]. The use of prophylaxis has the effect of turning serious hemophilia into a milder form by maintaining the factor level above 1% permanently; doses are titrated to the concentration of factors and the incidence of bleeds[4]. This in turn has led to a reduction in the number of orthopedic procedures performed for hemophilia – Tobasse *et al* report a dramatic decline in orthopedic interventions in the first decade of this century in a study of patients enrolled in the US Universal Data Collection program; whilst 7.2% of patients underwent an orthopedic intervention in 2000, this fell to just 1.7% in 2010[3]. However, the huge economic cost of primary prophylaxis means that 70-80% of the world's hemophiliac population does not have access to such treatment; indeed, some regions of the world do not even have access to treatment with factor concentrate when bleeding occurs. Even in developed countries, while children with hemophilia have an excellent prognosis from the point of view of their musculoskeletal health, there remain a cohort of older adults who continue to face the musculoskeletal consequences of the hemarthroses that they suffered before the advent of modern therapies.

The major complication of treatment with coagulation factor concentrates is the generation of inhibitors. These are antibodies which are raised against the coagulation factor concentrate, decreasing the efficacy of treatment and necessitating the use of higher doses of factor concentrate[5]. Whilst inhibitors are rare in hemophilia B (affecting around 3% of patients), they are found in 13% of patients with hemophilia A and up to a third of patients when the disease is severe[6]. A proportion of these patients can be treated with immune tolerance induction (ITT) which involves exposing the patient to prolonged high concentrations of coagulation factors in order to induce peripheral tolerance[5].

While improvements in medical prophylaxis and treatment for hemophilia have improved outcomes and reduced the need for orthopedic interventions in developed countries[3], musculoskeletal problems remain common in hemophiliacs. Such is the complexity of managing such patients that they are best approached in the context of a multidisciplinary team, with members from hematology, orthopedic surgery, physical medicine and rehabilitation, pediatrics, psychology, physiotherapy and nursing. The correct periprocedure management of these patients is perhaps as important as the procedure itself.

The musculoskeletal disease in hemophilia is a result of an inflammatory response to the presence of hemoglobin-derived iron in the knee joint. The inflammation leads to a severe, destructive arthropathy with cartilage destruction and bony erosions (Fig. 1). A major feature of the disease is stiffness; over time, severe arthrofibrosis forms leading to progressive contractures of the joint[7] (Fig 2). The principle of treatment of hemophiliac arthropathy is to prevent hemarthroses (which is largely performed through medical means), to treat the hemarthroses (in order to prevent the inflammatory response), to treat the synovitis which results from this inflammation, and finally, in cases of severe joint destruction, to effectively reconstruct the joint to facilitate the relief of pain and the restoration of function.

Pediatric orthopedic management of the knee in hemophilia

Treatment of acute hemarthroses

Symptom control in hemophiliac arthropathy is best prevented by the prevention and prompt treatment of hemarthroses and the synovitis that results. In the acute setting, hemarthroses should be treated with a single dose of factor concentrate; the European Hemophilia Therapy Standardization Board have recommended a dose of 25-40IU/kg of factor VIII in patients with hemophila A without inhibitors, with an increased dose in patients with post-traumatic bleeds[8]. Analgesia and non-steroidal anti-inflammatories are helpful but corticosteroids are not

recommended[8]. The use of ice may provide symptomatic relief but is controversial as it may impair coagulation, prolonging the bleeding episode[9]. The orthopedic surgeon is most likely to be called upon to perform arthrocentesis, which merits inclusion in this article as a simple but very effective procedure, which can be performed as an out-patient. It allows the effective drainage of a painful tension hemarthrosis, and may have a prognostic benefit in preventing the inflammatory response associated with the hemarthrosis[10]. Arthroscopy in the acute setting is not recommended[8]. Physiotherapy is useful for rehabilitation after the acute bleed.

Synovectomy

After recurrent hemarthrosis, the hemophiliac patient's knee reaches a state of chronic synovitis (synovial hypertrophy), which in turn perpetuates the tendency towards new bleeding. Under these circumstances, this hypertrophic synovium must be resected using non-surgical (radiosynovectomy and chemical synovectomy) or surgical procedures (arthroscopic or open synovectomy). The aim of all of these methods is to reduce the frequency and intensity of the hemarthrosis in patients in whom solely medical management has failed. Synovectomy has the effect of improving knee function, reducing the frequency of hemarthroses, reducing the incidence of flexion contractures and therefore improving quality of life. Whichever means is used to perform synovectomy, it should be accompanied by physiotherapy and continuous passive motion may be used to maintain range of movement following intervention.

In radiosynovectomy, a beta-emitting colloidal radionucleotide is introduced into the joint by injection. Whilst a number of agents are used, usually yttrium-90 is used for the knee and rhenium-186 is used for the ankle and the elbow as the synovium is thicker in the knee and yttrium-90 has a greater therapeutic penetration power than rhenium-186 (although no clinical difference has been demonstrated between the two agents in practice)[11]. In the USA and other countries phosphorus-32 (P-32) is used. The radionucleotides are taken up by cells within the synovium, and the exposure to the radiation results in reduction in the rate of proliferation of these inflammatory cells, and leads to necrosis and subsequent fibrosis of the synovium itself[12]. In chemical synovectomy an oxidant such

as osmic acid or rifampicin is introduced into the joint by multiple weekly injections[13]. In arthroscopic or open synovectomy, the synovium is excised directly. Given the tendency of synovium to bleed, surgical synovectomy necessitates good perioperative hemostasis, and the control of coagulation factors intra-operatively using infusions of the deficient factor (either continuous or bolus).

There is now good evidence that synovectomy is an effective procedure for the prevention of recurrent hemarthroses in hemophilia although there is little evidence that it prevents the development of secondary arthritis[14]. This latter point is surprising: whilst it might be expected to slow the development of degenerative change by limiting the exposure of the joint to the high levels of hemosiderin which are thought to be the cause of degenerative change in hemophilia, all series show the development of degenerative change in spite of synovectomy. The progression of degenerative change may be slowed: none of these studies are comparative and, whilst degenerative change is reported in all, it is not clear what degree of degeneration would be expected had synovectomy not been performed. In addition to removing the need for treatment of symptomatic hemarthroses, synovectomy improves knee pain and function and slows the reduction in range of movement and the development of flexion contractures[13,15]. The reduction in the incidence of hemarthroses and need for subsequent treatment renders synovectomy highly cost-effective[16].

There are extensive published results to support the use of radiosynovectomy and it is in widespread use across Europe. The largest such study is a retrospective review of 500 cases with a mean follow-up of 18.5 years (0.5-38)[17]. Both yttrium-90 (^{90}Y, in 64% of cases) and rhenium-186 (^{186}Re, in the remaining 36%) were used. The series involves 192 knees as well as ankles and elbows, and the results are presented for the group overall rather than being classified by joint; however, the size and length of follow-up merits this study's inclusion here. Overall, there was a marked and statistically significant decrease in the incidence of hemarthrosis, from a median of 6 per six months

to a median of 1.9, together with statistically significant reductions in pain and clinical signs of synovitis. There was no indication that radiographic progression was slowed. One fifth of patients required two injections and around one tenth required three; only 6.3% required surgery, either arthroscopic synovectomy or TKA.

The largest series examining the results of radiosynovectomy for knees alone is that of Turkmen *et al*[18] who examined 82 patients undergoing radiosynovectomy with ^{90}Y. As with the Rodriguez-Merchan study, all cases were performed under a continuous infusion of coagulation factors. Again, there was a significant reduction in bleeds, from 12.7 per six months to 0.6 following treatment. No radiographic outcomes are given. Many smaller studies exist which report similar results for radiosynovectomy (Table 1).

Radiosynovectomy has been in use for forty years and few major complications have been reported[19]. However, in particular given the pediatric population who are most likely to receive radiosynovectomy, there have been concerns regarding the dose of ionizing radiation which patients are being exposed to[19]. There has been a single report of two cases of acute lymphocytic leukemia in children who with hemophilia who had received P-32 radiosynovectomy, but causation is not clear[20]. More recently, Infante-Rivard *et al* have demonstrated no evidence of a dose-response relationship between exposure to radiosynovectomy and risk of malignancy[21]. Whilst some authors have reported the presence of reversible chromosomal aberrations following radiosynovectomy, others have found no evidence of an effect[19]. In fact, the dose of radiation involved in radiosynovectomy is low at around 0.74 millisieverts (mSv); normal environmental exposure is around 2mSv per year. A recent systematic review has suggested no evidence of an increase in malignancies related to radiosynovectomy[19]. Other complications of radiosynovectomy are rare; a recent case report has documented two cases of cutaneous ulceration after radiosynovectomy but this is the first time this has been reported[22]. There is no clinical evidence that radiosynovectomy has any negative effects on

articular cartilage; an animal study has demonstrated only transient fibrillation of cartilage with no underlying structural changes and a return to normal within a year[23].

There are fewer studies on chemical synovectomy. One study (Table 1) reports the outcomes of 22 knees using rifampicin, whilst another study reports the outcomes of 72 knees treated with osmic acid although knees are not reported separately rendering detailed analysis impossible[24,25]. Chemical synovectomy has been described in cases where radiosynovectomy is not available or contraindicated (for instance, in countries where the use of these agents is disallowed in children)[13]. Agents used include osmic acid and rifampicin; in all published reports it is noted that a painful inflammatory response takes place following chemical synovectomy and a period of immobilization with analgesia is required[13,24,25]. On the basis of limited evidence, chemical synovectomy appears effective but less so than radiosynovectomy[24]. For this reason, together with the need for immobilization and the degree of postprocedure pain, we do not use it in our practice.

Several series exist of arthroscopic synovectomy in patients with hemophilia, although many are small series with short follow-up, or include synovectomy in joints other than the knee; these are excluded from this review[26]. De Almeida *et al* have published five year results of two-portal arthroscopic synovectomy in nine knees of patients with severe hemophilia A[14]. The primary outcome was the number of bleeding episodes in the operated joint each year in the five years following surgery, compared to the year before synovectomy; clinical scores (IKDC, WOMAC and SF-36), range of movement and radiological outcomes were collected as secondary outcome measures. Mean number of bleeding episodes reduced significantly from 20 (SD 8.3) in the first year to between 0.8 and 3.7 over subsequent years. Significant improvements were reported in clinical scores (for instance, the median WOMAC score improved from 42 to 11); however, there was radiographic progression of disease over the five year follow-up period.

Yoon *et al* report similar results after six-portal arthroscopic synovectomy (anterolateral, anteromedial, superolateral, superomedial, posteromedial and transeptal portals were used)[27].

Clinical and radiological results from a total of 28 knees in 26 patients with a mean age of 18 years, all but one of whom had hemophilia A, were reported at a mean of six years. Hospital for Special Surgery (HSS) knee score improved from a mean of 56.4 points to a mean of 71.5 (range: 41-89) at latest follow-up with little change in range of movement. Little radiographic change was noted, with radiographs being stable in 25 cases, and deteriorating in three. Eickhoff reported the results of 10 patients following arthroscopic synovectomy, reporting significant improvement in eight with no improvement in two, with improvement in flexion deformity in six of the ten cases[28]. Wiedel's series of nine knees in eight patients followed-up for 10-15 years reported a marked decrease in the incidence of bleeding even at long follow-up intervals, although again, radiographic progression of disease was noted[29]. In hemophilia, arthroscopic synovectomy is considered a major surgical procedure due to the risk of bleeding.

Rampal *et al* reported their experience of open synovectomy, through a medial parapatellar approach, in 23 knees with a median follow-up of 8.8 years and a minimum follow-up of five years[30]. They again report improvements in clinical scores, along with range of movement, but progressive deterioration of radiological parameters. Teigland reported on nine open synovectomies at a mean follow-up of 12 years[31]. A radical approach was used with complete medial and lateral meniscectomies; while there were no recurrent bleeds, there was significant progression of disease and six of the nine cases had resulted in either ankylosis or arthroplasty. Rodriguez-Merchan *et al* report on 27 synovectomies in 27 patients, of which 18 were open and 9 were arthroscopic[32]. Groups were not matched and the arthroscopic group had significantly shorter follow-up. In both groups, the rate of post-operative bleeding was low (four of the 27 patients reported any bleeding) and none reported any pain or functional impairment as a result of postoperative hemarthrosis. However, there was radiographic progression in both groups: in the open group; using the 13 point scale of Petterson and Gilbert[33], there was a median deterioration of five points in the open group and one point in the arthroscopic group, reflecting the shorter follow-up of the latter.

There are few studies directly comparing surgical synovectomy with radiosynovectomy, and the choice of first-line therapy differs by unit and treating physician. An expert review, based on 354 cases over 38 years being treated with radiosynovectomy (295 knees) or arthroscopic synovectomy (66 knees; some received both treatments) suggests that, if medical management has failed, radiosynovectomy should be preferred as a first-line treatment, but that arthroscopic synovectomy should be used in recalcitrant cases[34]. The only other comparative study is that of Triantafyllou *et al* comparing open with arthroscopic synovectomy in 13 cases, finding that both procedures reduced the incidence of hemarthrosis. Comparing the two procedures, open synovectomy was found to be more likely to result in a decreased range of movement when compared to the arthroscopic procedure, and patients left hospital more quickly and required less coagulation factor infusion with the arthroscopic technique.

In the authors' experience, it is recommendable to perform a radiosynovectomy before any type of surgical synovectomy, given that the nonsurgical method is much simpler and easier, and has similar results. Although radiosynovectomy can be performed at any age, for practical reasons we use radiosynovectomy with yttrium-90 in children over 12 years of age, and we prefer arthroscopic synovectomy in children under that age (in this age group, both methods would require anesthesia, removing one of the principal advantages of radiosynovectomy). The dose we use for knee radiosynovectomy is 185 megabequerels (MBq). Yttrium-90 is a pure beta-emitter, with therapeutic penetration power of 2.8 mm and an average half-life of 2.8 days. We do not perform chemical synovectomy because of the need for repeated weekly painful injections.

Management of flexion contractures

As a result of repeated hemarthroses, the inflamed synovium of the knee becomes fibrotic leading to arthrofibrosis, shortening of the muscles surrounding the joint, and progressive and severe contractures[7]. Contractures are common (affecting up to 95% of individuals with hemophilia) and

can be disabling, even if the joint surfaces themselves remain intact[35]. Contractions can either be acute (neoflexum - <30 days following an episode of hemarthrosis); semiacute (paleoflexum, >30 days, <1 year); or chronic (archiflexum, >1 year with established arthropathy)[36]. Limitation of the range of movement can occur at either end of the range, but flexion contractures are most disabling. These can be treated with a number of surgical and nonsurgical techniques.

Physical therapy is the mainstay of preventative treatment for joint contractures[37]. For minor contractures, physiotherapy may be an effective form of treatment, with techniques including manual traction, muscle strengthening, joint stability and gait training being helpful[38]. Serial casting is a well-established treatment to improve the state of flexion contractures. Fernandez-Palazzi *et al* reported a series of 58 patients, undergoing serial casting over four to six weeks[39]. They describe an improvement in flexion deformity from a mean of 42.5º to a mean of 9.1º. In the same way, orthoses and splints have been used for the correction of minor deformities[40].

More severe deformities require soft tissue procedures such as release of hamstrings or posterior capsule to allow full extension[41]. Wallny *et al* in 1999 reported a series of 27 patients undergoing hamstrings release with or without capsulotomy, describing immediate improvements post-operatively and reporting no complications (with most patients demonstrating full resolution of the contracture). However, long-term results (at a mean follow-up of 12.5 years) only eleven patients maintained their range of movement with a mean loss of 10º and five patients deteriorating to the extent that they were worse than before the operation[42]. The authors recommend the technique in patients with severe deformities but essentially normal joint surfaces; total knee arthroplasty (TKA) is recommended in cases with joint degeneration. An alternative to surgical release is injection of botulinum toxin into affected muscles. Daffunchio *et al* report their experience of the use of botulinum toxin in 21 patients with at least a flexion contracture of 10º, refractory to physiotherapy[36]. Both paleoflexum and archiflexum cases were included, and contractures ranged from 10º to >46º. In mild to moderate contractures (those <45º), statistically significant

improvements are described of between 44 and 46%. In severe cases, there was a mean improvement of 30%, but this did not reach statistical significance. Botulinum toxin is commonly used in patients with muscle spasticity. Therefore, for us its role in muscle contractures like those seen in hemophiliacs is controversial.

Soft tissue releases can be used in conjunction with an external fixator for progressive extension[43] to address severe deformities. In the severest deformities, distal femoral osteotomies have been used to correct sagittal plane deformities, although the published data on such procedures in this patient population are limited. Caviglia *et al* describe the use of extension supracondylar osteotomies to correct flexion deformities in 19 patients[44]. Whilst the procedure does not increase the absolute range of movement, it improves function by returning the range that does exist into a more functionally useful position. It should be borne in mind that introducing a deformity to the distal femur will render future TKA more challenging. In most cases, these patients have severe joint degeneration and it is likely that these patients are more suitably treated with TKA.

Total knee arthroplasty in hemophilia

Patients with hemophilia who deteriorate to the extent of requiring TKA pose particular challenges to the arthroplasty surgeon, anesthetist and other clinical teams. Such patients should be managed by a multidisciplinary team in a center with experience of managing the perioperative care of patients with hemophilia[45]. Generally, any major surgery in patients without inhibitors is performed under hemostatic cover with bolus or continuous infusion of the relevant factor concentrate to prevent major perioperative bleeding[45]. Patients with inhibitors are more likely to bleed and have a higher rate of potential complications such as infection; until relatively recently, major orthopedic procedures were only rarely performed in this group due to the potential for major bleeding but new products and protocols have rendered such procedures safer in such patients[46]. Prior to surgery, patients with inhibitors should be treated with ITT (immunotolerance induction) or other

agents such as rituximab or plasmapheresis to reduce the antibody titer as low as possible to allow emergent treatment with coagulation factors in the event of intraoperative or postoperative bleeding[47]. Bypassing agents such as recombinant factor VII activated (rFVIIa) or activated prothrombin complex concentrates (aPCCs) are given as repeated boluses intra- and postoperatively to prevent bleeding complications. In common with TKA performed for other reasons, the use of a multimodal bleeding prevention approach including intra-articular or oral tranexaminc acid has been introduced to cases performed for hemophilia[48].

In addition to hematological management, the principal challenges of TKA in hemophiliac patients are technical challenges (in particular, dealing with severe deformities and the need for constrained devices); prevention of venous thromboembolism; and managing the risk of prosthetic joint infection (PJI)[49]. In existing series, many of these problems are exacerbated by high rates of uncontrolled HIV infection secondary to the use of pooled blood transfusions in the 1980s. As the effect of this diminishes over time, we will have a truer idea of the rate of success of TKA in this population. However, several series exist which report excellent results in the medium to long term following TKA in such patients.

Rate of complications following TKA in hemophilia

The most important study of the rate of complications after TKA in hemophilia is the database study of Cancienne *et al*[50]. They compared the outcomes of 3,396 patients with hemophilia to a matched cohort of 427,132 patients without bleeding disorders, reporting a small but statistically significantly higher rate of perioperative infection at three and six months (with odds ratios of 1.5 (2.0% v 1.3%, 95% CI 1.2-2.0) and 1.6 (3.5% v 2.2%, 95% CI 1.4-2.0) respectively) in the hemophilia cohort. Patients with hemophilia had a significantly higher risk of venous thromboembolism (VTE, OR 2.2, 95% CI 1.8-2.7), medical complications (OR 1.3, 95% CI 1.2-.15) and blood transfusion (OR 1.3, 95% CI 1.2-1.4). Revision was more likely in patients with hemophilia at all time points from six months to eight years (with odds ratios of between 1.4 and 1.5 at each time point). Hemophilia patients were no more likely to report stiffness than controls. In other published series, the rate of infection in hemophilia is

consistently higher than that expected from TKA in OA; however, the situation appears to be improving, with later series reporting lower levels of infection (Table 2). It is not clear whether this is due to a lower proportion of patients with HIV, or whether it is solely due to an increased awareness of the risk of infection and improvements in prophylaxis. A separate meta-analysis of 336 TKAs report a rate of infection of 7.1% and hemarthrosis in 7.7%[51].

Venous thromboembolism (VTE) is of particular interest in patients with hemophilia as the bleeding disorder itself may represent a contra-indication to thromboprophylaxis[52]. Several smaller studies have failed to determine a higher risk of deep vein thrombosis (DVT) or pulmonary embolism (PE) in hemophilia patients undergoing TKA, although the thromboprophylaxis regime varies. Buckner *et al* report a multicenter observational study of 46 patients with a variety of thromboproxhylaxis regimens (calf compression in 23/46 patients, with a further four patients having chemical thromboprophylaxis with low molecular weight heparin)[53]. They report one symptomatic lower leg DVT (in a patient who had received calf compression), and one symptomatic PE (in a patient who had used compression stockings). No asymptomatic DVTs were diagnosed on ultrasound examination of the remaining patients. A total of 18/46 patients had major bleeding during the study (defined as any intracranial or intraarticular bleed, or resulting in a drop in hemoglobin of ≥2g/dL or requiring two units of blood), including two of the four patients who received heparin prophylaxis. A Japanese study of 38 patients undergoing ultrasound examination following TKA reported no patients with subclinical VTE[54], whilst a study of 71 cases of hip and knee arthroplasty reported one case of symptomatic VTE on a patient who was receiving thromboprophylaxis[55]. This third study, of Perez Bortero *et al,* includes a review of the existing literature, encompassing 1,107 joint replacements in 843 patients. Not including two asymptomatic VTEs detected on screening ultrasound, they report symptomatic VTE in six cases, giving an incidence of 0.5% (95% CI 0.1-0.9%)[55]. Overall, the evidence on VTE is inconsistent, and further studies are necessary to define the optimal form of VTE prophylaxis in this group of patients.

Implant survival and functional outcome

Table 2 gives details of all studies of TKA in hemophilia comprising at least ten patients and performed since 2000; a total of 1,029 TKAs are reported. In the eight studies reporting revision rates at ten years, implant survival ranges from 81% to 89%, which is substantially lower than that expected for TKA overall (the National Joint Registry for England, Wales and Northern Ireland reports a rate of survival of 96.6% (95% CI 96.5-96.7) for cemented TKA, irrespective of diagnosis[56]). However, the cohort of patients with hemophilia undergoing TKA are younger (with a mean age of 40 years in the studies referenced) and the vast majority are male. The ten year survival figure given in the same National Joint Registry report for males under the age of 55 is 91.8% (90% CI 89.4-91.3), with which the figures for hemophilia compare rather more favorably. Survival in later studies appears to be no better than in previous studies; however, the higher mortality rate in earlier studies due to HIV infection may give a falsely high figure for implant survival.

In studies reporting functional outcomes, significant improvements in range of movement, Knee Society Score (objective and functional subsections, KSS-O and KSS-F) and Hospital for Special Surgery (HSS) score are reported in all studies. A meta-analysis of 336 TKAs undertaken in patients with hemophilia supports these findings, with significant improvements achieved in functional scores and range of movement following TKA[51].

Conclusions

The widespread availability of coagulation factor concentrates has improved the long-term function of the knee in patients with hemophilia in the developed world. However, in many countries and communities, severe musculoskeletal complications of hemophilia remain a substantial problem for orthopedic surgeons; even in developed countries, we continue to treat patients with the long-term consequences of years of hemophilic arthropathy.

There is now a significant evidence base for the treatment of the consequences of hemophilia in the knee. In the presence of synovitis, the use of radiosynovectomy appears to be safe with excellent results in terms of short term symptomatology, although no form of synovectomy has been demonstrated to improve long-term outcomes in terms of progression to symptomatic degenerative arthropathy of the knee. The use of conservative and surgical measures to treat contractures can improve the quality of life of patients with hemophilia, whilst TKA can provide equivalent functional results in hemophilic arthropathy to those reported in degenerative or inflammatory arthritides. The results of TKA in hemophilia will be further improved by the development of better perioperative care, in particular concerning prophylaxis for VTE and prosthetic joint infection.

Figure 1: Radiographs of a patient with bilateral end-stage arthrosis secondary to hemophilia.

a – bilateral anteroposterior radiographs; b- bilateral lateral radiographs

Figure 2: Fixed flexion contracture and synovitis in a patient with hemophilia

References

1. Fijnvandraat K, Cnossen MH, Leebeek FW, Peters M. Diagnosis and management of haemophilia. *BMJ 2012;344:e2707.*

2. White GC, 2nd, Rosendaal F, Aledort LM, Lusher JM, Rothschild C, Ingerslev J, Factor V, Factor IXS. 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;85-3:560.*

3. Tobase P, Lane H, Siddiqi AE, Ingram-Rich R, Ward RS, Universal Data Collection Joint Outcome Working Group HTCNSI. Declining trends in invasive orthopedic interventions for people with hemophilia enrolled in the Universal Data Collection program (2000-2010). *Haemophilia 2016;22-4:604-14.*

4. Blanchette VS. Prophylaxis in the haemophilia population. *Haemophilia 2010;16 Suppl 5:181-8.*

5. Kempton CL, Meeks SL. Toward optimal therapy for inhibitors in hemophilia. *Blood 2014;124-23:3365-72.*

6. Eckhardt CL, van Velzen AS, Peters M, Astermark J, Brons PP, Castaman G, Cnossen MH, Dors N, Escuriola-Ettingshausen C, Hamulyak K, Hart DP, Hay CR, Haya S, van Heerde WL, Hermans C, Holmstrom M, Jimenez-Yuste V, Keenan RD, Klamroth R, Laros-van Gorkom BA, Leebeek FW, Liesner R, Makipernaa A, Male C, Mauser-Bunschoten E, Mazzucconi MG, McRae S, Meijer K, Mitchell M, Morfini M, Nijziel M, Oldenburg J, Peerlinck K, Petrini P, Platokouki H, Reitter-Pfoertner SE, Santagostino E, Schinco P, Smiers FJ, Siegmund B, Tagliaferri A, Yee TT, Kamphuisen PW, van der Bom JG, Fijnvandraat K, Group IS. Factor VIII gene (F8) mutation and risk of inhibitor development in nonsevere hemophilia A. *Blood 2013;122-11:1954-62.*

7. Solimeno L, Goddard N, Pasta G, Mohanty S, Mortazavi S, Pacheco L, Sohail T, Luck J. Management of arthrofibrosis in haemophilic arthropathy. *Haemophilia 2010;16 Suppl 5:115-20.*

8. Hermans C, De Moerloose P, Fischer K, Holstein K, Klamroth R, Lambert T, Lavigne-Lissalde G, Perez R, Richards M, Dolan G, European Haemophilia Therapy Standardisation B. Management of acute haemarthrosis in haemophilia A without inhibitors: literature review, European survey and recommendations. *Haemophilia 2011;17-3:383-92.*

9. Forsyth AL, Zourikian N, Valentino LA, Rivard GE. The effect of cooling on coagulation and haemostasis: should "Ice" be part of treatment of acute haemarthrosis in haemophilia? *Haemophilia 2012;18-6:843-50.*

10. Manners PJ, Price P, Buurman D, Lewin B, Smith B, Cole CH. Joint Aspiration for Acute Hemarthrosis in Children Receiving Factor VIII Prophylaxis for Severe Hemophilia: 11-year Safety Data. *J Rheumatol 2015;42-5:885-90.*

11. Rodriguez-Merchan EC, De la Corte-Rodriguez H. Radiosynovectomy in haemophilic synovitis of elbows and ankles: Is the effectiveness of yttrium-90 and rhenium-186 different? *Thromb Res 2016;140:41-5.*

12. Das B. Role of radiosynovectomy in the treatment of rheumatoid arthritis and hemophilic arthropathies. *Biomed Imaging Interv J 2007;3-4:e45.*

13. Rivard GE. Chemical synovectomy in haemophilia: status and challenges. *Haemophilia 2001;7 Suppl 2:16-9.*

14. de Almeida AM, de Rezende MU, Cordeiro FG, Villaca PR, D'Amico EA, Hernandez AJ, Camanho GL. Arthroscopic partial anterior synovectomy of the knee on patients with haemophilia. *Knee Surg Sports Traumatol Arthrosc 2015;23-3:785-91.*

15. Alioglu B, Ozsoy H, Koca G, Sakaogullari A, Selver B, Ozdemir M, Dallar Y. The effectiveness of radioisotope synovectomy for chronic synovitis in Turkish paediatric haemophiliacs: Ankara experience. *Haemophilia 2010;16-6:932-6.*

16. Tamurian RM, Spencer EE, Wojtys EM. The role of arthroscopic synovectomy in the management of hemarthrosis in hemophilia patients: financial perspectives. *Arthroscopy 2002;18-7:789-94.*

17. Rodriguez-Merchan EC, De la Corte-Rodriguez H, Jimenez-Yuste V. Radiosynovectomy in haemophilia: long-term results of 500 procedures performed in a 38-year period. *Thromb Res 2014;134-5:985-90.*
18. Turkmen C, Kilicoglu O, Dikici F, Bezgal F, Kuyumcu S, Gorgun O, Taser O, Zulfikar B. Survival analysis of Y-90 radiosynovectomy in the treatment of haemophilic synovitis of the knee: a 10-year retrospective review. *Haemophilia 2014;20-1:e45-50.*
19. Rodriguez-Merchan EC, Valentino LA. Safety of radiation exposure after radiosynovectomy in paediatric patients with haemophilia. *Haemophilia 2015;21-4:411-8.*
20. Dunn AL, Busch MT, Wyly JB, Abshire TC. Radionuclide synovectomy for hemophilic arthropathy: a comprehensive review of safety and efficacy and recommendation for a standardized treatment protocol. *Thromb Haemost 2002;87-3:383-93.*
21. Infante-Rivard C, Rivard GE, Derome F, Cusson A, Winikoff R, Chartrand R, Guay JP. A retrospective cohort study of cancer incidence among patients treated with radiosynoviorthesis. *Haemophilia 2012;18-5:805-9.*
22. Garcia-Colmenero L, Martin-Ezquerra G, Monfort J, Pujol RM. Persistent cutaneous ulcers after Yttrium-90 synovectomy, an unusual complication: two case reports and a review of the literature. *Int Wound J 2016 (epub ahead of print).*
23. Makela OT, Lammi MJ, Uusitalo H, Hyttinen MM, Vuorio E, Helminen HJ, Tulamo RM. Analysis of lapine cartilage matrix after radiosynovectomy with holmium-166 ferric hydroxide macroaggregate. *Ann Rheum Dis 2003;62-1:43-9.*
24. Molho P, Verrier P, Stieltjes N, Schacher JM, Ounnoughene N, Vassilieff D, Menkes C, Sultan Y. A retrospective study on chemical and radioactive synovectomy in severe haemophilia patients with recurrent haemarthrosis. *Haemophilia 1999;5-2:115-23.*
25. Fernandez-Palazzi F, Rivas S, Viso R, de Bosch NB, de Saez AR, Boadas A. Synovectomy with rifampicine in haemophilic haemarthrosis. *Haemophilia 2000;6-5:562-5.*
26. Dunn AL, Busch MT, Wyly JB, Sullivan KM, Abshire TC. Arthroscopic synovectomy for hemophilic joint disease in a pediatric population. *J Pediatr Orthop 2004;24-4:414-26.*
27. Yoon KH, Bae DK, Kim HS, Song SJ. Arthroscopic synovectomy in haemophilic arthropathy of the knee. *Int Orthop 2005;29-5:296-300.*
28. Eickhoff HH, Koch W, Raderschadt G, Brackmann HH. Arthroscopy for chronic hemophilic synovitis of the knee. *Clin Orthop Relat Res 1997-343:58-62.*
29. Wiedel JD. Arthroscopic synovectomy of the knee in hemophilia: 10-to-15 year followup. *Clin Orthop Relat Res 1996-328:46-53.*
30. Rampal V, Odent T, Torchet MF, Rothschild C, Elie C, Glorion C, Padovani JP. Surgical synovectomy of the knee in young haemophiliacs: long-term results of a monocentric series of 23 patients. *J Child Orthop 2010;4-1:33-7.*
31. Teigland JC, Tjonnfjord GE, Evensen SA, Charania B. Synovectomy for haemophilic arthropathy: 6-21 years of follow-up in 16 patients. *J Intern Med 1994;235-3:239-43.*
32. Rodriguez Merchan EC, Galindo E, Ladreda JM, Pardo JA. Surgical synovectomy in haemophilic arthropathy of the knee. *Int Orthop 1994;18-1:38-41.*
33. Petterson H, Gilbert MS. Classification of the hemophilic arthropathy. In: *Diagnostic imaging of hemophilia*. New York: Springer, 1985.
34. Rodriguez-Merchan EC. Hemophilic synovitis of the knee: radiosynovectomy or arthroscopic synovectomy? *Expert Rev Hematol 2014;7-4:507-11.*
35. Atkins RM, Henderson NJ, Duthie RB. Joint contractures in the hemophilias. *Clin Orthop Relat Res 1987-219:97-106.*
36. Daffunchio C, Caviglia H, Nassif J, Morettil N, Galatro G. Knee flexion contracture treated with botulinum toxin type A in patients with haemophilia (PWH). *Haemophilia 2016;22-1:134-41.*
37. Buzzard BM. Physiotherapy for the prevention of articular contraction in haemophilia. *Haemophilia 1999;5 Suppl 1:10-5.*

38. Heijnen L, de Kleijn P. Physiotherapy for the treatment of articular contractures in haemophilia. *Haemophilia 1999;5 Suppl 1:16-9.*
39. Fernandez-Palazzi F, Battistella LR. Non-operative treatment of flexion contracture of the knee in haemophilia. *Haemophilia 1999;5 Suppl 1:20-4.*
40. Nelson IW, Atkins RM, Allen AL. The management of knee flexion contractures in haemophilia: brief report. *J Bone Joint Surg Br 1989;71-2:327-8.*
41. Rodriguez-Merchan EC, Magallon M, Galindo E, Lopez-Cabarcos C. Hamstring release for fixed knee flexion contracture in hemophilia. *Clin Orthop Relat Res 1997-343:63-7.*
42. Wallny T, Eickhoff HH, Raderschadt G, Brackmann HH. Hamstring release and posterior capsulotomy for fixed knee flexion contracture in haemophiliacs. *Haemophilia 1999;5 Suppl 1:25-7.*
43. Balci HI, Kocaoglu M, Eralp L, Bilen FE. Knee flexion contracture in haemophilia: treatment with circular external fixator. *Haemophilia 2014;20-6:879-83.*
44. Caviglia HA, Perez-Bianco R, Galatro G, Duhalde C, Tezanos-Pinto M. Extensor supracondylar femoral osteotomy as treatment for flexed haemophilic knee. *Haemophilia 1999;5 Suppl 1:28-32.*
45. Carcao M, Hilliard P, Escobar MA, Solimeno L, Mahlangu J, Santagostino E. Optimising musculoskeletal care for patients with haemophilia. *Eur J Haematol 2015;95 Suppl 81:11-21.*
46. Solimeno LP, Mancuso ME, Pasta G, Santagostino E, Perfetto S, Mannucci PM. Factors influencing the long-term outcome of primary total knee replacement in haemophiliacs: a review of 116 procedures at a single institution. *Br J Haematol 2009;145-2:227-34.*
47. Teitel JM, Carcao M, Lillicrap D, Mulder K, Rivard GE, St-Louis J, Smith F, Walker I, Zourikian N. Orthopaedic surgery in haemophilia patients with inhibitors: a practical guide to haemostatic, surgical and rehabilitative care. *Haemophilia 2009;15-1:227-39.*
48. Rodriguez-Merchan EC, Romero-Garrido JA, Gomez-Cardero P. Multimodal blood prevention approach including intra-articular tranexamic acid in primary total knee arthroplasty for patients with severe haemophilia A. Haemophilia 2016;22:e318-20.
49. Rodriguez-Merchan EC. Special features of total knee replacement in hemophilia. *Expert Rev Hematol 2013;6-6:637-42.*
50. Cancienne JM, Werner BC, Browne JA. Complications After TKA in Patients With Hemophilia or Von Willebrand's Disease. *J Arthroplasty 2015;30-12:2285-9*
51. Moore MF, Tobase P, Allen DD. Meta-analysis: outcomes of total knee arthroplasty in the haemophilia population. *Haemophilia 2016;22-4:e275-85.*
52. Hermans C. Venous thromboembolic disease in patients with haemophilia. *Thromb Res 2012;130 Suppl 1:S50-2.*
53. Buckner TW, Leavitt AD, Ragni M, Kempton CL, Eyster ME, Cuker A, Lentz SR, Ducore J, Leissinger C, Wang M, Key NS. Prospective, multicenter study of postoperative deep-vein thrombosis in patients with haemophilia undergoing major orthopaedic surgery. *Thromb Haemost 2016;116-1:42-9.*
54. Takedani H, Ohnuma K, Hirose J. Deep venous thrombosis was not detected after total knee arthroplasty in Japanese patients with haemophilia. *Haemophilia 2015;21-5:585-8.*
55. Perez Botero J, Spoon DB, Patnaik MS, Ashrani AA, Trousdale RT, Pruthi RK. Incidence of symptomatic venous thromboembolism in patients with hemophilia undergoing joint replacement surgery: a retrospective study. *Thromb Res 2015;135-1:109-13.*
56. National Joint Registry for England, Wales and Northern Ireland 12th Annual Report. *2015.*
57. Kavakli K, Aydogdu S, Omay SB, Duman Y, Taner M, Capaci K, Memis A, Balkan C, Karapinar D. Long-term evaluation of radioisotope synovectomy with Yttrium 90 for chronic synovitis in Turkish haemophiliacs: Izmir experience. *Haemophilia 2006;12-1:28-35.*
58. Li P, Chen G, Zhang H, Shen Z. Radiation synovectomy by 188Re-Sulfide in haemophilic synovitis. *Haemophilia 2004;10-5:422-7.*
59. Triantafyllou SJ, Hanks GA, Handal JA, Greer RB, 3rd. Open and arthroscopic synovectomy in hemophilic arthropathy of the knee. *Clin Orthop Relat Res 1992-283:196-204.*

60. Kim KI, Kim DK, Juh HS, Khurana S, Rhyu KH. Robot-assisted total knee arthroplasty in haemophilic arthropathy. *Haemophilia 2016;22-3:446-52.*
61. Rodriguez-Merchan EC. Total Knee Arthroplasty in Hemophilic Arthropathy. *Am J Orthop (Belle Mead NJ) 2015;44-12:E503-7.*
62. Strauss AC, Schmolders J, Friedrich MJ, Pflugmacher R, Muller MC, Goldmann G, Oldenburg J, Pennekamp PH. Outcome after total knee arthroplasty in haemophilic patients with stiff knees. *Haemophilia 2015;21-4:e300-5.*
63. Mortazavi SM, Haghpanah B, Ebrahiminasab MM, Baghdadi T, Hantooshzadeh R, Toogeh G. Simultaneous bilateral total knee arthroplasty in patients with haemophilia: a safe and cost-effective procedure? *Haemophilia 2015 (epub ahead of print).*
64. Panotopoulos J, Ay C, Trieb K, Schuh R, Windhager R, Wanivenhaus HA. Outcome of total knee arthroplasty in hemophilic arthropathy. *J Arthroplasty 2014;29-4:749-52.*
65. Westberg M, Paus AC, Holme PA, Tjonnfjord GE. Haemophilic arthropathy: long-term outcomes in 107 primary total knee arthroplasties. *Knee 2014;21-1:147-50.*
66. Cho KY, Kim KI, Khurana S, Cho SW, Kang DG. Computer-navigated total knee arthroplasty in haemophilic arthropathy. *Haemophilia 2013;19-2:259-66.*
67. Chevalier Y, Dargaud Y, Lienhart A, Chamouard V, Negrier C. Seventy-two total knee arthroplasties performed in patients with haemophilia using continuous infusion. *Vox Sang 2013;104-2:135-43.*
68. Zingg PO, Fucentese SF, Lutz W, Brand B, Mamisch N, Koch PP. Haemophilic knee arthropathy: long-term outcome after total knee replacement. *Knee Surg Sports Traumatol Arthrosc 2012;20-12:2465-70.*
69. Atilla B, Caglar O, Pekmezci M, Buyukasik Y, Tokgozoglu AM, Alpaslan M. Pre-operative flexion contracture determines the functional outcome of haemophilic arthropathy treated with total knee arthroplasty. *Haemophilia 2012;18-3:358-63.*
70. Rahme M, Ehlinger M, Faradji A, Gengenwin N, Lecocq J, Sibilia J, Bonnomet F. Total knee arthroplasty in severe haemophilic patients under continuous infusion of clotting factors. *Knee Surg Sports Traumatol Arthrosc 2012;20-9:1781-6.*
71. Wang K, Street A, Dowrick A, Liew S. Clinical outcomes and patient satisfaction following total joint replacement in haemophilia--23-year experience in knees, hips and elbows. *Haemophilia 2012;18-1:86-93.*
72. Feng B, Weng XS, Lin J, Qian WW, Wei W, Sheng L, Zhai JL, Bian YY, Qiu GX. Outcome of total knee arthroplasty combined patelloplasty for end-stage type A hemophilic arthropathy. *Knee 2012;19-2:107-11.*
73. Goddard NJ, Mann HA, Lee CA. Total knee replacement in patients with end-stage haemophilic arthropathy: 25-year results. *J Bone Joint Surg Br 2010;92-8:1085-9.*
74. Chiang CC, Chen PQ, Shen MC, Tsai W. Total knee arthroplasty for severe haemophilic arthropathy: long-term experience in Taiwan. *Haemophilia 2008;14-4:828-34.*
75. Innocenti M, Civinini R, Carulli C, Villano M, Linari S, Morfini M. A modular total knee arthroplasty in haemophilic arthropathy. *Knee 2007;14-4:264-8.*
76. Silva M, Luck JV, Jr. Long-term results of primary total knee replacement in patients with hemophilia. *J Bone Joint Surg Am 2005;87-1:85-91.*
77. Bae DK, Yoon KH, Kim HS, Song SJ. Total knee arthroplasty in hemophilic arthropathy of the knee. *J Arthroplasty 2005;20-5:664-8.*
78. Legroux-Gerot I, Strouk G, Parquet A, Goodemand J, Gougeon F, Duquesnoy B. Total knee arthroplasty in hemophilic arthropathy. *Joint Bone Spine 2003;70-1:22-32.*
79. Norian JM, Ries MD, Karp S, Hambleton J. Total knee arthroplasty in hemophilic arthropathy. *J Bone Joint Surg Am 2002;84-A-7:1138-41.*
80. Cohen I, Heim M, Martinowitz U, Chechick A. Orthopaedic outcome of total knee replacement in haemophilia A. *Haemophilia 2000;6-2:104-9.*

First author	Year	Knees (patients)	Mean f/u (yrs)	Age (yrs)	Type of synovectomy	Substrate	ROM (pre)	ROM (post)	Radiographic score used	Radiographic score		Clinical score used	Clinical outcome		Bleeds per month		Other outcome
										Pre	Post		Pre	post	Pre	Post	
Turkmen[18]	2014	82 (67)	16.8	16.8	Radio	Y-90	-	-	Arnold-Hilgartner	II	-	None	-	-	2.1	0.1	63% 5yr survival
Rodriguez-Merchan[19]	2014	192	18.5*	23.7*	Radio	Y-90	-	-	WFH	4.4	4.3	WFH	4.9	4.1	1.0	0.3	
Alioglu[15]	2010	18 (13)	1.8	12.5	Radio	Y-90	-	-	None	-	-	None	-	-	3.83	0.62	
Kavakli[57]	2006	56 (42)	2	13.9	Radio	Y-90			Denver (MRI)	7.9	8.3	None	-	-	1.36	-	
Li[57]	2004	29 (29)	0.5-1.5‡	26.1	Radio	Re-188	-	-	None	-	-	None	-	-	3.2	0.9	
De Almeida[14]	2015	9 (8)	5	16.1	Arthroscopic	-	103	113	Arnold-Hilgartner	III	IV	IKDC	40.2	63.4	1.7	<0.1	
Yoon[27]	2005	28 (26)	5.9	17.8	Arthroscopic	-	106	102	Arnold-Hilgartner	III	III	HSS	56.4	71.5	5	1	
Wiedel[29]	1996	9 (8)	10-15‡	16	Arthroscopic	-	115.5	111	Arnold-Hilgartner	III	IV	None	-	-	-	-	
Rampal[30]	2010	23 (21)	8.8	13.5	Open	-	45†	80†	Petterson	1	4	Petrini	13	5†	-	-	
Teigland[31]	1994	9 (8)	12.7	17.8	Open	-	61	53	WFH	5.3	8.4 ♦	-	-	-	-	-	
Rodriguez-Merchan[32]	1994	27 (27)	13	11.9	Arthroscopic / open	-			Petterson	3.3	6.4	WFH	2.6	1.2	-	-	
Triantafyllou[59]	1992	13 (11)	6.7	10.9	Arthroscopic/open	-	95	109.8	Arnold-Hilgartner	III	IV	None	-	-	1-4‡	0.38	-
Fernandez-Palazzi[25]	2000	22	1.8*	18	Chemical	Rifampicin	-	-	None	-	-	'excellent' patient-reported result in 11/22.					

Table 1: Synovectomy. Only studies with outcomes reported separately for knees are included. IKDC – international knee documentation committee; WFH – World Federation of Hemophilia. *mixed study population (includes other joints), follow-up and age are for whole group inclusive of other joints. †figures given only in graph form in paper so numbers estimated. ‡No mean given in paper so range given here. ♦ surgical procedure included complete medial and lateral meniscectomy.

First author	Year	Pts (knees)	Mean f/u	Age (yrs)	Survival given at	Survival % (95% CI)	% deep infection	ROM pre	ROM post	KSS-O pre	KSS-O post	KSS-F pre	KSS-F post	HSS pre	HSS post
Kim[60]	2016	32 (29)	5	38.4	5	100 (-)	3.1	70.8	84.7	27.1	82.8	34.2	80.2	-	-
Rodriguez-Merchan[61]	2015	74 (88)	8	38.2	8	90 (-)	6.8	-	-	21	64	37	77	-	-
Strauss[62]	2015	21 (23)	8.3	51	-	-	4.3	26.7	73	22.9	72.9	40.2	62.6	-	-
Mortazavi[63]	2015	27 (35)	-	35.5	-	-	-	61.3	93.9	28.3	88.8	37.3	90.1	-	-
Pantopoulos[64]	2014	32 (45)	7.4	40.7	10	86.4 (-)	4.4	-	-	-	-	-	-	45	85
Westberg[65]	2014	74 (107)	11.2	41	10	88 (80-94)	6.5	70	79	-	-	-	-	-	-
Cho[66]	2013	25 (27)	3.4	36.5	-	-	0	-	-	34	85.3	62	83	-	-
Chevallier[67]	2013	51 (72)	7.8	41	10	88 (77-100)	4.1	-	-	-	-	-	-	-	-
Zingg[68]	2012	30 (43)	8.6	44	10	86 (-)	7.0	-	-	36	73	62	83	-	-
Atila[69]	2012	21 (21)	5.7	34	-	-	2.9	37.6	57.1	-	-	-	-	37.9	79.4
Rahme[70]	2012	14 (20)	5.5	36.5	-	-	15	-	-	-	-	-	-	31.5	
Wang[71]	2012	31 (40)	11.8	48.6	10	83 (-)	13	45	70	-	79.7	-	57.1	-	-
Feng[72]	2012	19 (25)	3.4	33.4	-	-	4	55	82	-	-	-	-	51	91
Goddard[73]	2010	57 (70)	9.2	43	15	80 (60-98)	1.4	-	-	-	-	-	-	-	82
Solimeno[46]	2009	92 (116)	7	39	7	81 (-)	8	75	90	-	-	-	-	38	91
Chiang[74]	2008	26 (35)	6.9	34.2	10	85 (-)	11.4	63.2	79.8	-	-	42	77.1	-	-
Innocenti[75]	2007	20 (24)	4.4	36	4.4	100 (-)	0	47	89	23	84	32	75	-	-
Silva[76]	2005	68 (90)	7.8	40.1	10	83 (72-90)	16	-	-	-	81.3	-	88.7	-	-
Bae[77]	2005	21 (25)	6.2	35.8	6.2	100 (-)	0	73.4	92.2	18.6	82.8	41.4	75.8	-	-
Legroux-Gerot[78]	2003	12 (17)	4.5	39	4.5	100 (-)	0	66	89	37.6	86.0	42.3	81.1	-	-
Norian[79]	2002	38 (53)	9.2	33.7	5	90 (78-96)	13.2	-	-	-	-	-	-	-	-
Cohen[80]	2000	16 (21)	5.6	39.6	-	-	9.5	-	-	-	-	-	-	24.1	77.5
Overall		801 (1026)	7.8	39.5			7.0	63	83	30*	86*	48*	89*	40*	88*

Table 2: Outcome studies of total knee arthroplasty in hemophilia. CI – confidence intervals; ROM – range of movement. KSS-O – knee society score, objective component; KSS-F – knee society score, functional component; HSS – Hospital for Special Surgery knee score. *means are given only when both pre- and post-operative scores are given (and in the case of the KSS, where both functional and objective scores are given).