

Integrative Approach in Haemophilic Arthropathy of The Knee: a Case Report

**Andri Maruli T. Lubis¹, Kurniadi Husodo¹, Lugyanti Sukrisman²,
Djajadiman Gatot³**

¹ Department of Orthopaedic and Traumatology, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia

² Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta

³ Department of Pediatrics, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta.

Correspondence mail:

Department of Orthopaedic and Traumatology, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital. Jl. Diponegoro No. 71, Jakarta 10430, Indonesia. email: andri_lubis@yahoo.com.

ABSTRAK

Haemophilic arthropathy adalah kelainan sendi yang paling sering dijumpai pada penderita hemofili. Kelainan tersebut terdiri dari sinovitis kronik dan kerusakan progresif tulang rawan sendi. Pada laporan kasus ini disajikan laporan mengenai sinovektomi secara artroskopi pada haemophilic arthropathy untuk mengurangi frekuensi perdarahan sendi. Pasien adalah seorang anak laki-laki berusia 15 tahun dengan Haemophilic arthropathy pada lutut kiri. Kami melakukan arthroscopic synovectomy disertai dengan terapi penggantian faktor VIII yang dimonitor intensif. Intraoperatif ditemukan hipertrofi sinovial yang membentuk vili pada seluruh bagian sendi, defek tulang dan tulang rawan multipel, serta defisiensi anterior cruciate ligament (ACL) dan posterior cruciate ligament (PCL). Pada tindak lanjut 6 bulan pascaoperasi, keluhan subjektif dan frekuensi perdarahan jauh berkurang. Visual analog scale (VAS) membaik dari 5-6 menjadi 1-2 pascaoperasi dan skor International Knee Documentation Committee meningkat dari 49 menjadi 66. Frekuensi hemartrosis berkurang dari 4-8 kali per bulan menjadi kurang dari 1 kali per bulan. Arthroscopic synovectomy yang dilakukan pada kasus ini mengurangi rasa nyeri, menurunkan frekuensi hemartrosis, dan meningkatkan luaran fungsional.

Kata kunci: *arthroscopic synovectomy, haemophilic arthropathy, hemofilia, anterior cruciate ligament, posterior cruciate ligament.*

ABSTRACT

Haemophilic arthropathy is the most prevalent joint disorder in haemophilia. This disorder is characterized by chronic synovitis and progressive destruction of joint cartilage. We report a case of arthroscopic synovectomy to reduce bleeding frequency in haemophilic arthropathy of the knee. Patient was a 15 years old male with haemophilic arthropathy of the left knee. We performed an arthroscopic synovectomy under tightly regulated factor VIII replacement therapy. There were villous synovial hypertrophy at all part of the joint, multiple bone and cartilage defect, and also anterior cruciate ligament (ACL) and posterior cruciate ligament (PCL) deficiency found intraoperatively. After 6 month follow up, subjective complain and bleeding frequency decreased significantly. The visual analog scale improved from 5-6 to 1-2, and the International Knee Documentation Committee Score increased from 49 to 66. Bleeding frequency decreased from 4-8 times per month to less than 1 time per month.

Arthroscopic synovectomy performed in this case could reduce the pain, decrease the frequency of bleeding, and improve patient's functional outcome.

Key words: arthroscopic synovectomy, haemophilic arthropathy, haemophilia, anterior cruciate ligament, posterior cruciate ligament.

INTRODUCTION

Haemophilia is an X-linked recessive blood coagulation disorder caused by deficiency of coagulation factor VIII (haemophilia A) or IX (haemophilia B).¹ Worldwide prevalence of haemophilia A and B is estimated 1 in 10,000 males and 1 in 25,000 males respectively.² Clinical manifestation of haemophilia A and B is similar. Bleeding in the joints (haemarthrosis) is the most frequent musculoskeletal manifestation in people with haemophilia. Acute haemarthrosis is characterized by sudden swelling of the joints which may be preceded by prodromal symptoms such as stiffness and pain. With adequate treatment, acute haemarthrosis usually will subside. After repeated bleeding (chronic haemarthrosis) particularly in patients with severe haemophilia, joint abnormalities will progress to chronic synovitis, inflammatory arthritis, and progressive arthropathy.³ This article reports an arthroscopic synovectomy performed in haemophilic arthropathy of the knee with anterior and posterior cruciate ligament deficiency in a 15-year old teenager with haemophilia A.

CASE ILLUSTRATION

A fifteen-year old teenager came to our outpatient clinic with complaint of swelling on his left knee since 2 years before. He was diagnosed as haemophilia A at the age of 5 months, when he had bruises at the skin spontaneously without history of trauma. Since then, the patient came routinely to the haematology clinic in our hospital to get factor VIII replacement therapy (Koate®). Factor VIII was only given when there was bleeding (on demand), once to twice a month. Since 2 years ago, there was slowly progressive swelling on his left knee. The knee was warm, tense, and tender. The swelling subsided after factor VIII replacement therapy was given. The frequency of swelling occurred once a month at the beginning,

but became more frequent afterward. The patient was given factor VIII replacement therapy only when there was swelling. Since 6 months before, the frequency of swelling increased to 1-2 times a week and did not completely resolve after factor VIII replacement therapy. The knee was more tense, tender, and stiff, the International Knee Documentation Committee (IKDC) score was 49. Patient had a history of intracranial haemorrhage and bleeding from both ears 3 years ago. There was no history of haemophilia in his family.

On physical examination, the patient's body mass index was 16 kg/m². There was effusion at the left knee with muscle atrophy at the left thigh and lower leg. The knee was warm and tender, with range of motion 10-135° (**Figure 1**). The haemoglobin level was 7 g/dL, activated partial thromboplastin time (APTT) was 84.4 seconds (control: 30.1 seconds). At plain X-ray there were osteoporotic bones with erosion on lateral femoral condyle and the articular surface of patella, subchondral cyst at femoral epiphysis, tibial epiphysis, and medial surface of patella (**Figure 2**).

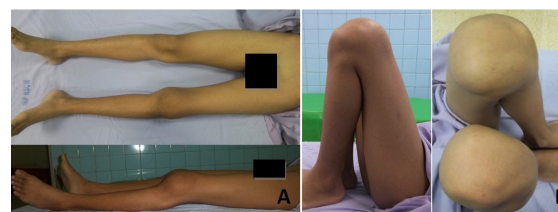


Figure 1. Preoperative clinical picture of the knee; (A) maximum extension, (B) maximum flexion.

Our working diagnosis was haemarthrosis with haemophilic arthropathy of the left knee. We performed arthroscopic synovectomy under tightly regulated factor VIII replacement therapy. Factor VIII (Koate®) at the dose of 40 U/KgBW (1,440 unit) was given intravenously 12 hours before surgery, followed by 25 U/KgBW/24hours



Figure 2. Plain X-ray of the left and right knee; (A) sunrise view, (B) weight bearing anteroposterior view, (C) lateral view.

(900 unit/day) until the bleeding stops. The patient received 450 cc packed cell transfusion before surgery and preoperative haemoglobin level was 10.0 g/dl. After anaesthesia, we performed an intraoperative physical examination, range of motion was 10-135°, varus and valgus stress test was negative, anterior and posterior drawer test was positive, Lachman test was +3 (more than 10 mm).

During surgery, standard anterolateral, anteromedial, and superolateral arthroscopic portal was created. There was haemarthrosis at the left knee, so an irrigation procedure was performed. We found villous synovial hypertrophy at all parts of the joint (**Figure 3**), Anterior cruciate ligament (ACL) and posterior cruciate ligament (PCL) deficiency at the intercondylar notch (**Figure 4A**), 4x5 cm bone defect on the lateral femoral condyle (**Figure 4B**), 1x3 cm International Cartilage Repair Society (ICRS) grade IV defect at the medial femoral condyle (**Figure 4C**), 4x4 cm ICRS grade II defect at tibial plateau (**Figure 4D**). We shaved the synovium until there was no villous synovial hypertrophy left on the joint area (**Figure 4E**).

There was unremarkable during postoperative care. On the next day the patient started to move his left knee, although still felt pain (VAS 6-7), range of motion was 45-55°, on sixth day, the pain was decreasing, range of motion was 30-60°, and the patient started to walk using

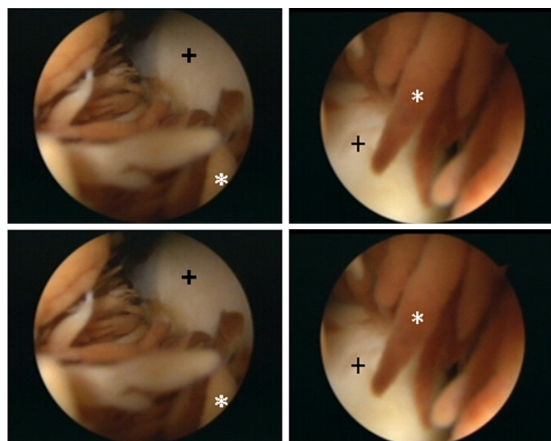


Figure 3. Synovial hypertrophy at all part of the joint; villous synovial protrusion (asterisk sign), surface of the joint cartilage (plus sign).

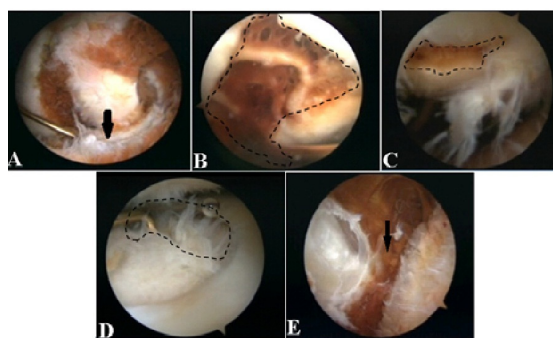


Figure 4. (A) Intercondylar notch with ACL and PCL deficiency (arrow), (B) Bone defect sized 4x5 cm at lateral femoral condyle, (C) ICRS grade IV cartilage defect size 1x3 cm at medial femoral condyle, (D) ICRS grade II cartilage defect size 4x4 cm at tibial plateau, (E) after synovectomy, synovial membrane without villous hypertrophy.

bilateral crutches. On the next day, patient was discharged. Patient routinely came to The Haematology Clinic every three days to get factor VIII replacement therapy.

Three weeks after the surgery patient came to our clinic, pain at the left knee has decreased significantly (VAS 2-3) and could walk with a unilateral crutch, range of motion was 20-90° (**Figure 5**). The patient got factor VIII replacement therapy 15 U/KgBW twice a week. At the sixth week after the operation pain at the left knee was minimal (VAS 1-2), he walked without crutch, range of motion was 10-125° (**Figure 6**). Postoperative plain X-ray of the left knee taken at 6th week showed similar result to preoperative plain X-ray, that there was effusion, epiphyseal enlargement, osteoporosis, erosion at the lateral



Figure 5. Clinical picture of the knee 3 weeks after surgery; (A) maximum extension, (B) maximum flexion, range of motion was 20-90°.



Figure 6. Clinical picture of the knee 6 weeks after surgery; (A) maximum extension, (B) maximum flexion, no sign of inflammation, range of motion of left knee was 10-125°.



Figure 7. Plain X-ray 6 weeks after surgery; (A) anteroposterior standing view, (B) lateral view.

femoral condyle, and subchondral cysts (**Figure 7**). The patient underwent physiotherapy twice a week in our hospital's medical rehabilitation center. Six months after the operation, pain was minimal (VAS 1-2), patient walked without crutch, range of motion was 0-125°, IKDC score

was 66. Frequency of bleeding was less than once a month. Patient got factor replacement therapy routinely twice a week.

DISCUSSION

Haemophilia is classified as mild, moderate, or severe according to the activity of factor VIII/IX in the circulation. In patients with severe haemophilia the levels of factor VIII/IX in circulation is less than 1%, moderate haemophilia 1% to 5%, and mild haemophilia 5% to 40%.¹⁻² Patients with severe haemophilia will experience spontaneous bleeding, especially in the joint, muscles, soft tissues, and other life-threatening location (eg. in the brain), other than minor bleeding from mucous membranes, nose, and eyes. Patients with moderate haemophilia rarely experience spontaneous bleeding; bleeding usually occurs after mild trauma. Patients with mild haemophilia usually bleed after surgery or major trauma.¹

Joint bleeding (haemarthrosis) is the most common musculoskeletal manifestation in haemophilia.³ After repeated bleeding, joint disorder will progress into haemophilic arthropathy, a disorder characterized by chronic synovitis and progressive articular cartilage destruction.³⁻⁴ In this case, the knee was warm, tense, tender without history of trauma 2 years ago, patient never complained pain at the knee before. This history of swelling in the left knee was thought to be the initial haemarthrosis. Afterward swelling in the left knee occur more frequently, the affected knee was tender and stiff, and never completely subside after coagulation factor replacement therapy. It shows that joint disorders have progressed into haemophilic arthropathy, the pain never subsided completely because of chronic synovitis and progressive articular cartilage damage. The joint was also seen enlarged because of swelling, chronic synovitis, and epiphyseal enlargement.⁵⁻⁶ When he moved, there was pain and palpable crepitus indicating damage of the joint cartilage. This finding was confirmed by the presence of blood, and also bone and cartilage defects found at arthroscopy. The anterior drawer sign, posterior drawer sign, and Lachman test also showed positive results. This finding was confirmed by

the absence of the ACL and PCL in the left knee at the time of arthroscopic procedure.

Haemophilic synovitis is caused by chronic accumulation of blood in the joint. Blood is not a normal element found in the synovial fluid. When intraarticular bleeding occurs, the degradation product of blood will be absorbed by synovial membrane. Iron contained in the blood will cause severe inflammatory reaction of the synovial membrane. The normal synovial membrane has the capacity to absorb blood after an episode of haemarthrosis. Therefore, initial haemarthrosis will only lead to nonspecific inflammatory reaction of the synovial membrane which will soon subside.⁵ After repeated bleeding occurred in the same joints, the amount of degradation products to be absorbed exceeds the absorbing capacity of synovial membrane, resulting in hypertrophy and chronic inflammation of the synovial membrane. Increased vascularization is required to improve the ability of the synovial membrane to absorb the degradation product of blood into circulation more effectively. Therefore, the synovial membrane becomes hypertrophic, villous, and the blood vessels dilate and form sinusoids. These hypertrophied, villous, and hypervascular synovial membrane are vulnerable to be entrapped between joint surfaces and cause recurrent bleeding.^{3,5,7}

Iron as a degradation product of haemoglobin will catalyze the formation of destructive oxygen metabolites that would cause apoptosis in chondrocytes. The iron was also thought to cause chronic synovitis and proliferation of synovial cell and vascular tissue at subsynovial membrane.⁸ This hypervascular, villous, and fragile synovial tissue will bleed easily, thus forming vicious cycle.⁸⁻⁹ Therefore, synovectomy is a way to prevent recurrent bleeding by removing the hyperplastic, villous, and hypervascular synovial membrane.¹⁰

Granulation tissue (pannus) formed will grow over the cartilage surface and prevent diffusion of nutrition to articular cartilage.¹¹ Cartilage destruction is also caused by enzymes and proinflammatory cytokines produced by cells infiltrating the synovial membrane, and by mechanical distension of the joint due to extravasation of blood which cause

increased intraarticular pressure. This might lead to chondrocyte apoptosis and inhibition of proteoglycan synthesis that will cause permanent joint cartilage destruction.⁸⁻⁹ Subchondral bleeding will cause erosion at the subchondral bone and result in collapse of the articular surface. These changes will cause irreversible damage to joint and lead to end stage arthropathy (severe arthritis and permanent deformity) in people with haemophilia.^{7,11}

Anteroposterior, lateral, and skyline projection of plain X-ray of the left knee showed effusion, osteoporosis, epiphyseal enlargement, erosion on the lateral femoral condyle and the articular surface of patella, and subchondral cyst at femoral epiphyses, tibial epiphyses, and medial side of patella. Those characteristic was classified as Arnold-Hillgartner stage IV and Petterson score 9.¹²⁻¹³ The Arnold Hillgartner system is a progressive scale, with the worst radiological findings determine the stage of a haemophilic arthropathy. Petterson score is an additive scale, any abnormality found was given a value of 0, 1, or 2. Lowest score is 0 and the highest 13. Arnold-Hillgartner scale is simpler and easier to use, but Petterson score is more precise and may distinguish various stages of haemophilic arthropathy better. Therefore, World Federation of Haemophilia in 1981 recommended the Petterson score to be widely used, but the Arnold Hillgartner scale is still commonly used.¹² Although early abnormalities in the joint, such as synovial hyperplasia, cartilage surface irregularity and mild narrowing of joint space is not visible on plain X-ray, when joint disorder has reached an advanced stage, the disease course can be monitored adequately by plain X-ray.¹²

The key in the treatment of haemophilic arthropathy is aggressive management at the time of initial haemarthrosis. These can be done with factor replacement therapy, joint aspiration, physiotherapy, and close clinical observation.⁵ If chronic synovitis have already set in, synovectomy may be done to slow the progression of haemophilic arthropathy and to prevent end stage arthropathy.^{5,7}

Before surgery, the patient was given on-demand coagulation factor therapy, i.e. only

when there was bleeding. Based on research conducted by Fischer et al,¹⁴ on-demand therapy use less coagulation factors compared to primary or secondary prophylaxis, which are 1260 IU/kg/year (on-demand) and 1550 IU/kg/year (primary or secondary prophylaxis). These two values are not statistically significantly different, but the on-demand group experiences 3.2 times higher joint bleeding, 2.7 times higher clinical severity, and 1.9 times higher Petterson score compare to group given prophylactic therapy.¹⁴ It explains the rapid progression of disease in this case. It is also mentioned that the progression of haemophilic arthropathy can be slowed or even prevented by administering the coagulant factor as primary prophylaxis.¹

During arthroscopy procedure, we also found ACL and PCL deficiency. This finding was consistent with the physical examination (anterior drawer sign, posterior drawer sign, and Lachman test). Until now, we have not found a report or literature describing cruciate ligament damage in haemophilic arthropathy. We hypothesized that it was caused by bone destruction at the origin or insertion of those ligaments, causing the ligaments to detach and being reabsorbed along with the haemarthrosis. A study in rabbits showed that a model haemarthrosis created by injecting autologous blood into rabbit knee joint daily for 7 days caused synovial proliferation and iron deposition in synoviocytes, but no abnormality found in the ACL. Total collagen content, collagenase activity, and biomechanical properties of ACL in the knee that had haemarthrosis was no different from contralateral knee as the control.¹⁵ Further study which aims to explain this ACL and PCL deficiency may be conducted in the future. In the normal knee, the function of ACL and PCL is restrain anterior and posterior translation of the tibia relative to the femur. In ACL and/or PCL deficient knee, abnormal tibiofemoral translation may result in cartilage injury.¹⁶ In this patient, this effect might further exacerbate cartilage injury due to haemophilic arthropathy.

As mentioned above, synovectomy reduce the frequency of bleeding by removing the hyperplastic and hypervascular synovial tissue. Open synovectomy as the treatment of

haemophilic arthropathy was first reported by Storti et al. in 1969.⁷ Although open synovectomy was effective in reducing the frequency of joint bleeding, its main complication is reduced postoperative range of motion of the joint. As stated by Montane et al. that the haemophilic joint that has been performed open synovectomy “do not bleed (very often), do not hurt (very much), and do not move (very well)”.¹⁷ To overcome this problem, synovectomy with arthroscopic technique was developed. The advantages of arthroscopic synovectomy compared to open technique are less invasive, faster recovery time, less postoperative bleeding, shorter hospitalization, less complication, and better postoperative range of motion of the joint.⁷

In this case, synovectomy was performed by arthroscopy. Postoperatively, there was a decrease in pain and bleeding frequency and increase in functional outcome. A study conducted by Dunn et al. showed 97% reduction of bleeding frequency in patients with haemophilic arthropathy performed arthroscopic synovectomy.¹⁰ Other study showed that despite a dramatic reduction in the frequency of bleeding, synovectomy do not stop the progression of joint destruction.^{7,18} In patients who underwent a second operation because of recurrent symptoms, intraoperative findings showed that those symptoms was more likely caused by cartilage destruction, there was no evidence indicating the presence of synovitis at the second operation.^{10,19}

After the operation, the patient was hospitalized to receive coagulation factor replacement therapy and intensive physiotherapy. The purpose of physiotherapy is to maintain or restore range of motion, strengthen muscles, prevent or treat joint contracture, relieve pain, increase tolerance to activity, improve balance, coordination, and proprioceptive. Physiotherapy in patients with haemophilia often accompanied by coagulation factor replacement therapy to prevent bleeding.⁷

In follow-up care, the patient had a mild decrease in range of motion (preoperative 10°-135°, 6 weeks postoperative 10°-125°). This was consistent with those reported by Wiedel that arthroscopic synovectomy in haemophilic arthropathy usually result in reduction of ROM

5-15° extension and 5-15° flexion.¹⁹ Six months postoperatively the knee condition was stable, VAS was 1-2, ROM was 0-125°, and IKDC score was 66. Postoperative X-ray of the left knee showed stage IV haemophilic arthropathy based on Arnold-Hillgartner scale and Pettersson score 9, which was the same as the preoperative X-ray. This is consistent with the literature stated that arthroscopic synovectomy may slow but can not stop the progressivity of haemophilic arthropathy.^{11,18-19}

When joint damage has reached an advanced stage, characterized by marked narrowing of cartilage space, significant decrease in ROM, and severe pain, the patient will not have significant clinical improvement after synovectomy, arthroplasty should be done.⁷ Until now, the absolute indication for arthroplasty in haemophilic arthropathy has not been determined. Arthroplasty is usually performed at advanced stage of joint disorder characterized by marked cartilage damage, severe pain, deformity, and loss of joint motion that cause severe functional impairment.²⁰

CONCLUSION

Arthroscopic synovectomy performed in this case show good results, indicated by a marked decrease in pain and frequency of haemarthrosis and an increase in IKDC score. ACL and PCL deficiency found in this case have not been reported in other literature. The underlying mechanism requires further study. Arthroscopic synovectomy may slow but cannot avoid the progressivity of haemophilic arthropathy.

REFERENCES

- Rodriguez NI, Hoots WK. Advance in haemophilia: experimental aspect and therapy. *Pediatr Clin N Am*. 2008;55:357-76.
- Rodriguez-Merchan EC, Goddard NJ, Lee CA. *Musculoskeletal aspect of haemophilia*. Oxford: Blackwell Science Ltd.; 2000.
- Rodriguez-Merchan EC. Articular bleeding (haemarthrosis) in haemophilia (an orthopaedist's point of view). *Treatment of haemophilia*. 2000.
- Hoots WK. Pathogenesis of haemophilic arthropathy. *Semin Haematol*. 2006;10:S18-S22.
- Silva M, Luck JV, Llinas A. *Chronic haemophilic synovitis. Treatment of Haemophilia*. 2004.
- Kilcoyne R, Nuss R. Radiological evaluation of haemophilic arthropathy. *Semin Thromb Haemost*. 2003;29:43-8.
- Raffini L, Manno C. Modern management of haemophilic arthropathy. *Brit J Haematol*. 2007;136:777-87.
- Lafeber F, Miossec P, Valentino L. Physiopathology of haemophilic arthropathy. *Haemophilia*. 2008;14(suppl.4):3-9.
- Valentino L. Blood-induced joint disease: the pathophysiology of haemophilic arthropathy. *J Thromb Haemost*. 2009;8:1895-902.
- Dunn AL, Busch MT, Wyly B, Sullivan KM, Abshire TC. Arthroscopic synovectomy for haemophilic joint disease in a pediatric population. *J Pediatr Orthop*. 2004;24:414-26.
- Yoon KH, Bae DK, Kim HS, Song SJ. Arthroscopic synovectomy in haemophilic arthropathy of the knee. *SICOT*. 2005;29:296-300.
- Jelbert A, Vaidya S, Fotiadis N. Imaging and staging of haemophilic arthropathy. *Clin Radiol*. 2009;64:1119-28.
- Maclachlan J, Gough-Palmer A, Hargunani R, Farrant J, Holloway B. Haemophilia imaging: a review. *Skeletal Radiol*. 2009;38:949-57.
- Fischer K, van der Bom JG, Molho P, et al. Prophylactic versus on-demand treatment strategies for severe haemophilia: a comparison of costs and long-term outcome. *Haemophilia*. 2002;8(6):745-52.
- Ishizue KK, Lyon RM, Amiel D, Woo SL-Y. Acute haemarthrosis: a histological, biochaemical, and biomechanical correlation of early effect on the anterior cruciate ligament in a rabbit model. *J Orthop Res*. 1990;8(4):548-54.
- Akhtar S, Mofidi A, Wilson C, Williams R. Time dependent chondral changes in the anterior cruciate deficient knee. *J Bone Joint Surg Br*. 2009;91-B:419-20.
- Montane I, McCollough NC, Lian EC-Y. Synovectomy of the knee for haemophilic arthropathy. *J Bone Joint Surg*. 1986;68-A:210-6.
- Verma N, Valentino L, Chawla A. Arthroscopic synovectomy in haemophilia: indication, technique and result. *Haemophilia*. 2007;13(Suppl.3):38-44.
- Wiedel JD. Arthroscopic synovectomy of the knee in haemophilia. *Clin Orthop Relat Res*. 1996;328:46-53.
- Wiedel J, Stabler S, Geraghty S, Funk S. Joint replacement surgery in haemophilia. *Treatment Haemophil*. 2010;50:1-10.