****

**Copyright Information of the Article Published Online**

|  |  |
| --- | --- |
| **TITLE** | Orthopedic disorders of the knee in hemophilia: A current concept review |
| **AUTHOR(s)** | E Carlos Rodriguez-Merchan, Leonard A Valentino |
| CITATION | Rodriguez-Merchan EC, Valentino LA. Orthopedic disorders of the knee in hemophilia: A current concept review. *World J Orthop* 2016; 7(6): 370-375 |
| URL | http://www.wjgnet.com/2218-5836/full/v7/i6/370.htm |
| DOI | http://dx.doi.org/10.5312/wjo.v7.i6.370 |
| OPEN ACCESS | This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/ |
| CORE TIP | Hemophilia is an inherited bleeding disorder due to deficiency of factor Ⅷ (hemophilia A) or factor Ⅸ (hemophilia B) resulting in insufficient thrombin generation leading to recurrent intra-articular hemorr­hages (hemarthroses). Prevention of hemarthroses with intravenous infusions of the deficient protein from infancy to adulthood (primary prophylaxis) should be considered to achieve optimal outcomes. If factor replacement therapy (FRT) is insufficient, or if patients are not adherent to the prescribed regimen, recurrent hemarthroses results in chondrocyte apoptosis (cartilage degeneration) and hypertrophy of the synovium (syno­vitis). Many surgical interventions are available for the knee joint. For example, to treat synovitis recalcitrant to FRT, there are two primary orthopedic modalities: Radiosynovectomy and arthroscopic synovectomy. This article reviews the pathogenesis, diagnosis and treat­ment of hemophilic arthropathy of the knee. |
| KEY WORDS | Hemophilia; Knee; Orthopedic problems; Prevention; Surgical treatment |
| COPYRIGHT  | © The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved. |
| NAME OF JOURNAL | World Journal of Orthopedics |
| ISSN | 2218-5836 (online) |
| PUBLISHER | Baishideng Publishing Group Inc, 8226 Regency Drive, Pleasanton, CA 94588, USA |
| WEBSITE | http://www.wjgnet.com |

MINIREVIEWS

Orthopedic disorders of the knee in hemophilia: A current concept review

E Carlos Rodriguez-Merchan, Leonard A Valentino

E Carlos Rodriguez-Merchan,Department of Orthopedic Surgery, La Paz University Hospital-IdiPaz, 28046 Madrid, Spain

Leonard A Valentino,Rush University Medical Center, Chicago, IL 60612, United States

Author contributions: Rodriguez-Merchan EC and Valentino LA wrote the article and reviewed the literature.

Correspondence to:E Carlos Rodriguez-Merchan, MD, PhD, Department of Orthopedic Surgery, La Paz University Hospital-IdiPaz, Paseo de la Castellana 261, 28046 Madrid, Spain. ecrmerchan@gmx.es

Telephone:+34-91-5712871Fax:+34-91-5712871

Received: January 8, 2016 Revised:April 7, 2016 Accepted:April 21, 2016

Published online: June 18, 2016

**Abstract**

The knee is frequently affected by severe orthopedic changes known as hemophilic arthropathy (HA) in patients with deficiency of coagulation factor Ⅷ or Ⅸ and thus this manuscript seeks to present a current perspective of the role of the orthopedic surgeon in the management of these problems. Lifelong factor replacement therapy (FRT) is optimal to prevent HA, however adherence to this regerous treatment is challenging leading to breakthrough bleeding. In patients with chronic hemophilic synovitis, the prelude to HA, radiosynovectomy (RS) is the optimal to ameliorate bleeding. Surgery in people with hemophilia (PWH) is associated with a high risk of bleeding and infection, and must be performed with FRT. A coordinated effort including orthopedic surgeons, hematologists, physical medicine and rehabilitation physicians, physiotherapists and other team members is key to optimal outcomes. Ideally, orthopedic procedures should be performed in specialized hospitals with experienced teams. Until we are able to prevent orthopedic problems of the knee in PWH will have to continue performing orthopedic procedures (arthrocentesis, RS, arthroscopic syno­vectomy, hamstring release, arthroscopic debridement, alignment osteotomy, and total knee arthroplasty). By using the aforementioned procedures, the quality of life of PWH will be improved.

**Key words:** Hemophilia; Knee; Orthopedic problems; Prevention; Surgical treatment

**© The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Rodriguez-Merchan EC, Valentino LA. Orthopedic disorders of the knee in hemophilia: A current concept review. *World J Orthop* 2016; 7(6): 370-375 Available from: URL: http://www.wjgnet.com/2218-5836/full/v7/i6/370.htm DOI: http://dx.doi.org/10.5312/wjo.v7.i6.370

**Core tip:** Hemophilia is an inherited bleeding disorder due to deficiency of factor Ⅷ (hemophilia A) or factor Ⅸ (hemophilia B) resulting in insufficient thrombin generation leading to recurrent intra-articular hemorr­hages (hemarthroses). Prevention of hemarthroses with intravenous infusions of the deficient protein from infancy to adulthood (primary prophylaxis) should be considered to achieve optimal outcomes. If factor replacement therapy (FRT) is insufficient, or if patients are not adherent to the prescribed regimen, recurrent hemarthroses results in chondrocyte apoptosis (cartilage degeneration) and hypertrophy of the synovium (syno­vitis). Many surgical interventions are available for the knee joint. For example, to treat synovitis recalcitrant to FRT, there are two primary orthopedic modalities: Radiosynovectomy and arthroscopic synovectomy. This article reviews the pathogenesis, diagnosis and treat­ment of hemophilic arthropathy of the knee.

**INTRODUCTION**

Hemophilic arthropathy (HA) in one or more joints, mainly ankles, elbows and knees affects about 90% of people with hemophilia (PWH) by 20-30 years of age (Figure 1). Recurrent bleeding into joints (hemarthroses) results in progressive, proliferative and degenerative articular changes. To prevent these complications, regular factor replacement therapy (FRT) with the deficient protein from an early age (primary prophylaxis) is the key to prevent synovitis and HA. However, despite primary prophylaxis, some PWH suffer from clinical bleeding due to an insufficient dosing regimen or non-adherence while others may experience subclinical joint bleeding. Although the pathogenesis of HA is not fully understood[1], it is generally assumed that primary prophylaxis prevents bleeding and HA[2,3].

There are multiple strategies for implementing primary prophylaxis in young children with severe hemophilia including once-weekly injections which has the advantage of avoiding the implantation of a central venous access device in very young children. Unfortunately, this regimen fails to prevent joint bleeding in all but a few children and most develop HA[4].

Prophylaxis must begin early in life because even infrequent or a short durations of blood in contact with cartilage can cause chondrocyte apoptosis that can eventually lead to HA. Once developed, HA can be addressed with basic surgical procedures including radiosynovectomy (RS), chemical synovectomy (CS), arthroscopic synovectomy (AS), arthroscopic joint debri­dement and total knee arthroplasty (TKA)[5,6].

**RESEARCH**

A literature review of knee disorders in patients with hemophilia was performed using MEDLINE (PubMed) and the Cochrane Library. The keywords used were “knee” and “hemophilia”. The time period of the searches was from the beginning of the availability of the search engines until 31 December 2015. A total of 767 articles were found, of which 56 were selected and reviewed because they were deeply focused on the topic. The flow diagram of the study is shown in Figure 2.

**PATHOGENESIS**

Chronic hemophilic synovitis (CHS) and cartilage des­truction are the main findings of HA, both phenomena due to severe or recurrent hemarthroses. The precise pathogenesis of CHS and HA remains poorly understood. *Ex vivo* studies with canine cartilage suggest that a 4-d duration of blood exposure produces loss of cartilage matrix[7]. Experimental studies have also demonstrated that after a major hemarthrosis the joint cavity is filled with a dense inflammatory infiltrate, and the tissues become brown-stained due to hemosiderin deposition following the breakdown of erythrocytes[8,9]. Vascular hyperplasia takes place resulting in tenous and friable vessels prone to bleed creating a viscous cycle of bleeding-vascular hyperplasia-bleeding. The articular surface becomes rugose with pannus formation and the sub­chondral bone becomes dysmorphic. After about one month, cartilage and bone erosions are evident.

It has been reported that the loading of the affected joint may play a role in the mechanism of cartilage dege­neration in hemophilia[10]. Other authors have found that molecular changes induced by iron in the blood could explain the increase in cell proliferation in the synovial membrane (synovitis)[11]. Valentino *et al*[12] found in an experimental murine model that hemorrhage induced by a controlled, blunt trauma injury leads to causes joint inflammation, synovitis and HA.

**DIAGNOSIS**

The diagnosis of CHS is usually made following exami­nation of the knee with typical signs of joint swelling and warmth but with or without painful symptoms and reductions in motion of the knee. Ultrasonography (US) can be used to demonstrate hypertrophy of the synovium and the presence of fluid[13,14]. However, validation of US for the assessment of HA has not been established yet[15-17]. Magnetic resonance imaging is the gold standard for the diagnosis of synovitis.

**ORTHOPEDIC TREATMENT**

***CHS***

**Celecoxib:** Rattray *et al*[18] reported that celecoxib is effective in treating hemophilic synovitis, although the mechanism for this effect remains to be determined and these findings require controlled trials to be confirmed.

**RS:** RS is the optimal choice for treatment of patients with CHS, even in patients with anti-factor antibodies (inhibitors)[19-23]. The current recommendation is to use Yttrium-90 for the knees and Rhenium-186 for elbows and ankles and is supported by more than 40-years of experience with RS by the authors, who believe that the procedure is safe, easy to perform and economical technique for the management of CHS.

**CS:** Many chemical agents have been proposed to scar the synovium of patients with CHS including oral D-penicillamine[24]. A short-term period (3-6 mo) of treatment at a dose of 5-10 mg/kg per day for children and less than 750 mg/d for adults (one hour before breakfast) was recommended. The efficacy of this treatment needs further clinical trial data before it will gain widespread use. Oral D-penicillamine may be especially useful in patients with inhibitors. Another method to perform CS is by means of intra-articular injec­tions of rifampicin[25] or oxytetraycline[26]. Alternative, RS is a favorable alternative to oral D-penicillamine and to rifampicin or oxytetracycline for synovectomy, because its efficacy has been proven over the last 40 years[27].

**AS:** The goal of AS is to reduce the number of hemar­throses in order to maintain the range of motion of the knee joint. However, AS cannot prevent joint dege­neration[28-32].

***Advanced HA***

**Open and arthroscopic debridement:** Both open and arthroscopic debridement with synovectomy has been used in PWH between 20 and 40 years of age, with improvement in pain lasting several years, delaying the need of a TKA[33-35].

**Hamstring release:** Fixed knee flexion contracture is a common complication in PWH and hamstring tenotomy in association with posterior capsulotomy may be used to improve ambulation by reducing the contraction[36,37].

**External fixation for flexion contracture:** More drastic measures have also been used to reduce flexion contractures. For example, Kiely *et al*[38] reported the case of a 13-year-old boy with hemophilia who under­went Ilizarov external fixator with improvement of his knee flexion contracture. In this case, progressive extension reduced the contracture from 50 to 5 degrees.

**Osteotomies around the knee:** Malalignment of the lower limb is common in hemophilia patients and osteotomy around the knee (proximal tibia, distal femur) has resulted in improvements in gait and reduction in painful symptoms[39-42].

**TKA:** Unfortunately, many patients with knee HA continue to deteriorate resulting in life-altering knee pain. For these individuals, TKA is the treatment of choice and has resulted in dramatic improvements in patients with severe HA[43-49]. Therefore, TKA is an excellent option for the treatment of advanced HA of the knee (Figure 3). However the procedure is not without risk as the rate of infection after TKA is 7% on average.

**HEMATOLOGICAL PERIOPERATIVE TREATMENT**

In major orthopedic procedures the preoperative levels of the deficient factor should be maintained at 80%-100%. In the postoperative period factor level must be over 50% in the two weeks and 30% later on, at least until wound healing (removal of staples)[50,51]. Continuous infusion of the deficient factor is better than bolus infusion[52,53] however mechanical malfunction of the venous line and pump must be guarded against. In patients with inhibitors there are two potential hema­tological treatments: Recombinant factor Ⅶ activated or Factor Eight Inhibitor Bypassing Agent[54-57].

**CONCLUSION**

The best treatment for PWH is primary prophylaxis replacing the deficient clotting factor with early institution of regular injections of concentrates of factor Ⅷ or Ⅸ. In this way, not only is bleeding into the joints prevented but also the development of synovitis and articular degeneration (HA). For CHS recalcitrant to aggressive factor replacement, RS must be considered the first option and alternatively, AS. Surgery in PWH has a high risk of bleeding and infection. This kind of surgery must be performed with FRT in a specialized center. This way we will improve the quality of life of PWH minimizing the risk of complications.

**REFERENCES**

1 **Lafeber FP**, Miossec P, Valentino LA. Physiopathology of haemo­philic arthropathy. *Haemophilia* 2008; **14** Suppl 4: 3-9 [PMID: 18494686 DOI: 10.1111/j.1365-2516.2008.01732.x]

2 **Nilsson IM**, Berntorp E, Löfqvist T, Pettersson H. Twenty-five years’ experience of prophylactic treatment in severe haemophilia A and B. *J Intern Med* 1992; **232**: 25-32 [PMID: 1640190 DOI: 10.1111/j.1365-2796.1992.tb00546.x]

3 **Manco-Johnson MJ**, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R, Ingram JD, Manco-Johnson ML, Funk S, Jacobson L, Valentino LA, Hoots WK, Buchanan GR, DiMichele D, Recht M, Brown D, Leissinger C, Bleak S, Cohen A, Mathew P, Matsunaga A, Medeiros D, Nugent D, Thomas GA, Thompson AA, McRedmond K, Soucie JM, Austin H, Evatt BL. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med* 2007; **357**: 535-544 [PMID: 17687129 DOI: 10.1056/NEJMoa067659]

4 **Kraft J**, Blanchette V, Babyn P, Feldman B, Cloutier S, Israels S, Pai M, Rivard GE, Gomer S, McLimont M, Moineddin R, Doria AS. Magnetic resonance imaging and joint outcomes in boys with severe hemophilia A treated with tailored primary prophylaxis in Canada. *J Thromb Haemost* 2012; **10**: 2494-2502 [PMID: 23067060 DOI: 10.1111/jth.12025]

5 **Hilgartner MW**. Current treatment of hemophilic arthropathy. *Curr Opin Pediatr* 2002; **14**: 46-49 [PMID: 11880733 DOI: 10.1097/00008480-200202000-00008]

6 **Rodriguez-Merchan EC**. Aspects of current management: ortho­paedic surgery in haemophilia. *Haemophilia* 2012; **18**: 8-16 [PMID: 21535324 DOI: 10.1111/j.1365-2516.2011.02544.x]

7 **Jansen NW**, Roosendaal G, Bijlsma JW, Degroot J, Lafeber FP. Exposure of human cartilage tissue to low concentrations of blood for a short period of time leads to prolonged cartilage damage: an in vitro study. *Arthritis Rheum* 2007; **56**: 199-207 [PMID: 17195222 DOI: 10.1002/art.22304]

8 **Valentino LA**, Hakobyan N. Histological changes in murine haemophilic synovitis: a quantitative grading system to assess blood-induced synovitis. *Haemophilia* 2006; **12**: 654-662 [PMID: 17083517 DOI: 10.1111/j.1365-2516.2006.01348.x]

9 **Valentino LA**, Hakobyan N, Rodriguez N, Hoots WK. Patho­genesis of haemophilic synovitis: experimental studies on blood-induced joint damage. *Haemophilia* 2007; **13** Suppl 3: 10-13 [PMID: 17822515 DOI: 10.1111/j.1365-2516.2007.01534.x]

10 **Hooiveld MJ**, Roosendaal G, Jacobs KM, Vianen ME, van den Berg HM, Bijlsma JW, Lafeber FP. Initiation of degenerative joint damage by experimental bleeding combined with loading of the joint: a possible mechanism of hemophilic arthropathy. *Arthritis Rheum* 2004; **50**: 2024-2031 [PMID: 15188380 DOI: 10.1002/art.20284]

11 **Hakobyan N**, Kazarian T, Jabbar AA, Jabbar KJ, Valentino LA. Pathobiology of hemophilic synovitis I: overexpression of mdm2 oncogene. *Blood* 2004; **104**: 2060-2064 [PMID: 15172967 DOI: 10.1182/blood-2003-12-4231]

12 **Valentino LA**, Hakobyan N, Kazarian T, Jabbar KJ, Jabbar AA. Experimental haemophilic synovitis: rationale and develop­ment of a murine model of human factor VIII deficiency. *Haemophilia* 2004; **10**: 280-287 [PMID: 15086328 DOI: 10.1111/j.1365-2516.2004.00899.x]

13 **Acharya SS**, Schloss R, Dyke JP, Mintz DN, Christos P, DiMichele DM, Adler RS. Power Doppler sonography in the diagnosis of hemophilic synovitis--a promising tool. *J Thromb Haemost* 2008; **6**: 2055-2061 [PMID: 18823337 DOI: 10.1111/j.1538- 7836.2008.03160.x]

14 **Querol F**, Rodriguez-Merchan EC. The role of ultrasonography in the diagnosis of the musculo-skeletal problems of haemophilia. *Haemophilia* 2012; **18**: e215-e226 [PMID: 22044728 DOI: 10.1111/j.1365-2516.2011.02680.x]

15 **Merchan EC**, De Orbe A, Gago J. Ultrasound in the diagnosis of the early stages of hemophilic arthropathy of the knee. *Acta Orthop Belg* 1992; **58**: 122-125 [PMID: 1632211]

16 **Wallny T**, Brackmann HH, Semper H, Schumpe G, Effenberger W, Hess L, Seuser A. Intra-articular hyaluronic acid in the treatment of haemophilic arthropathy of the knee. Clinical, radiological and sonographical assessment. *Haemophilia* 2000; **6**: 566-570 [PMID: 11012703 DOI: 10.1046/j.1365-2516.2000.00413.x]

17 **Klukowska A**, Czyrny Z, Laguna P, Brzewski M, Serafin-Krol MA, Rokicka-Milewska R. Correlation between clinical, radio­logical and ultrasonographical image of knee joints in children with haemophilia. *Haemophilia* 2001; **7**: 286-292 [PMID: 11380633 DOI: 10.1046/j.1365-2516.2001.00509.x]

18 **Rattray B**, Nugent DJ, Young G. Celecoxib in the treatment of haemophilic synovitis, target joints, and pain in adults and children with haemophilia. *Haemophilia* 2006; **12**: 514-517 [PMID: 16919082 DOI: 10.1111/j.1365-2516.2006.01311.x]

19 **Rodriguez-Merchan EC**, Wiedel JD. General principles and indications of synoviorthesis (medical synovectomy) in haemo­philia. *Haemophilia* 2001; **7** Suppl 2: 6-10 [PMID: 11564137 DOI: 10.1046/j.1365-2516.2001.00102.x]

20 **Rodriguez-Merchan EC**, Luck JV Jr, Silva M, Quintana M. Synoviorthesis in haemophilia. In: The Haemophilic Joints-New Perspectives. Rodriguez-Merchan EC, editor. Blackwell, Oxford, 2003: 73-79 [DOI: 10.1002/9780470986929.ch12]

21 **Mortazavi SM**, Asadollahi S, Farzan M, Shahriaran S, Aghili M, Izadyar S, Lak M. (32)P colloid radiosynovectomy in treat­ment of chronic haemophilic synovitis: Iran experience. *Haemophilia* 2007; **13**: 182-188 [PMID: 17286772 DOI: 10.1111/j.1365-2516.2006.01424.x]

22 **De la Corte-Rodriguez H**, Rodriguez-Merchan EC, Jimenez-Yuste V. Radiosynovectomy in hemophilia: quantification of its effectiveness through the assessment of 10 articular parameters. *J Thromb Haemost* 2011; **9**: 928-935 [PMID: 21352468 DOI: 10.1111/j.1538-7836.2011.04246.x]

23 **de la Corte-Rodriguez H**, Rodriguez-Merchan EC, Jimenez-Yuste V. What patient, joint and isotope characteristics influence the response to radiosynovectomy in patients with haemophilia? *Haemophilia* 2011; **17**: e990-e998 [PMID: 21535325 DOI: 10.1111/j.1365-2516.2011.02546.x]

24 **Corrigan JJ**, Damiano ML, Leissinger C, Wulff K. Treatment of chronic haemophilic synovitis in humans with D-penicillamine. *Haemophilia* 2003; **9**: 64-68 [PMID: 12558781 DOI: 10.1046/j.1365-2516.2003.00676.x]

25 **Radossi P**, Baggio R, Petris U, De Biasi E, Risato R, Davoli PG, Tagariello G. Intra-articular rifamycin in haemophilic arthropathy. *Haemophilia* 2003; **9**: 60-63 [PMID: 12558780 DOI: 10.1046/j.1365-2516.2003.00703.x]

26 **Fernandez-Palazzi F**, Viso R, Bernal R, Capetillo G, Caviglia H. Oxytetracycline clorhydrate as a new material for chemical synoviorthesis in haemophilia. In: The Haemophilic Joints-New Perspectives. Rodriguez-Merchan EC, editor. Blackwell, Oxford, 2003: 80-83 [DOI: 10.1002/9780470986929.ch13]

27 **Rodríguez-Merchán EC**. Orthopedic surgery is possible in hemophilic patients with inhibitors. *Am J Orthop* (Belle Mead NJ) 2012; **41**: 570-574 [PMID: 23431528]

28 **Wiedel JD**. Arthroscopic synovectomy for chronic hemophilic synovitis of the knee. *Arthroscopy* 1985; **1**: 205-209 [PMID: 4096772 DOI: 10.1016/S0749-8063(85)80013-X]

29 **Wiedel JD**. Arthroscopic synovectomy of the knee in hemophilia: 10-to-15 year followup. *Clin Orthop Relat Res* 1996; **328**: 46-53 [PMID: 8653977 DOI: 10.1097/00003086-199607000-00010]

30 **Journeycake JM**, Miller KL, Anderson AM, Buchanan GR, Finnegan M. Arthroscopic synovectomy in children and adolescents with hemophilia. *J Pediatr Hematol Oncol* 2003; **25**: 726-731 [PMID: 12972809 DOI: 10.1097/00043426-200309000-00010]

31 **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**: 414-426 [PMID: 15205625 DOI: 10.1097/01241398-200407000-00013]

32 **Yoon KH**, Bae DK, Kim HS, Song SJ. Arthroscopic synovectomy in haemophilic arthropathy of the knee. *Int Orthop* 2005; **29**: 296-300 [PMID: 16082543 DOI: 10.1007/s00264-005-0666-2]

33 **Soreff J**. Joint debridement in the treatment of advanced hemo­philic knee arthropathy. *Clin Orthop Relat Res* 1984; **191**: 179-184 [PMID: 6499309 DOI: 10.1097/00003086-198412000-00023]

34 **Rodriguez-Merchan EC**, Gomez-Cardero P. Arthroscopic knee debridement can delay total knee replacement in painful moderate haemophilic arthropathy of the knee in adult patients. *Blood Coagul Fibrinolysis* 2015; Epub ahead of print [PMID: 26575489 DOI: 10.1097/MBC.0000000000000443]

35 **Rodriguez Merchan EC**, Magallon M, Galindo E. Joint debri­dement for haemophilic arthropathy of the knee. *Int Orthop* 1994; **18**: 135-138 [PMID: 7927961]

36 **Rodríguez-Merchán EC**, Magallón M, Galindo E, López-Cabarcos C. Hamstring release for fixed knee flexion contracture in hemophilia. *Clin Orthop Relat Res* 1997; **34**: 63-67 [PMID: 9345208]

37 **Pennekamp PH**, Wallny TA, Goldmann G, Kraft CN, Berdel P, Oldenburg J, Wirtz DC. [Flexion contracture in haemophilic knee arthropathy--10-year follow-up after hamstring release and dorsal capsulotomy]. *Z Orthop Unfall* 2007; **145**: 317-321 [PMID: 17607630]

38 **Kiely PD**, McMahon C, Smith OP, Moore DP. The treatment of flexion contracture of the knee using the Ilizarov technique in a child with haemophilia B. *Haemophilia* 2003; **9**: 336-339 [PMID: 12694527 DOI: 10.1046/j.1365-2516.2003.00753.x]

39 **Rodriguez Merchan EC**, Galindo E. Proximal tibial valgus osteotomy for hemophilic arthropathy of the knee. *Orthop Rev* 1992; **21**: 204-208 [PMID: 1538887]

40 **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 [PMID: 10365298 DOI: 10.1046/j.1365-2516.1999.0050s1028.x]

41 **Wallny T**, Saker A, Hofmann P, Brackmann HH, Nicolay C, Kraft CN. Long-term follow-up after osteotomy for haemophilic arthropathy of the knee. *Haemophilia* 2003; **9**: 69-75 [PMID: 12558782 DOI: 10.1046/j.1365-2516.2003.00705.x]

42 **Mortazavi SM**, Heidari P, Esfandiari H, Motamedi M. Trapezoid supracondylar femoral extension osteotomy for knee flexion contractures in patients with haemophilia. *Haemophilia* 2008; **14**: 85-90 [PMID: 18005146]

43 **Sheth DS**, Oldfield D, Ambrose C, Clyburn T. Total knee arthro­plasty in hemophilic arthropathy. *J Arthroplasty* 2004; **19**: 56-60 [PMID: 14716652 DOI: 10.1016/j.arth.2003.08.008]

44 **Rodriguez-Merchan EC**, Luck JV Jr, Silva M, Riera JA, Wiedel JD, Goddard NJ, Heim M, Solimeno PL. Total knee replacement in the haemophilic patient. In: The Haemophilic Joints.-New Perspectives. Rodriguez-Merchan EC, editor. Blackwell Publishing, Oxford, 2003: 116-124 [DOI: 10.1002/9780470986929.ch21]

45 **Norian JM**, Ries MD, Karp S, Hambleton J. Total knee arthro­plasty in hemophilic arthropathy. *J Bone Joint Surg Am* 2002; **84-A**: 1138-1141 [PMID: 12107312]

46 **Ragni MV**, Crossett LS, Herndon JH. Postoperative infection following orthopaedic surgery in human immunodeficiency virus-infected hemophiliacs with CD4 counts & lt; or = 200/mm3. *J Arthroplasty* 1995; **10**: 716-721 [PMID: 8749751 DOI: 10.1016/S0883-5403(05)80065-8]

47 **Rodriguez-Merchan EC**. Total knee arthroplasty in patients with haemophilia who are HIV-positive. *J Bone Joint Surg Br* 2002; **84**: 170-172 [PMID: 11922355 DOI: 10.1302/0301-620X.84B2.13015]

48 **Powell DL**, Whitener CJ, Dye CE, Ballard JO, Shaffer ML, Eyster ME. Knee and hip arthroplasty infection rates in persons with haemophilia: a 27 year single center experience during the HIV epidemic. *Haemophilia* 2005; **11**: 233-239 [PMID: 15876268 DOI: 10.1111/j.1365-2516.2005.01081.x]

49 **Rodríguez-Merchán EC**. Total Knee Arthroplasty in Hemophilic Arthropathy. *Am J Orthop* (Belle Mead NJ) 2015; **44**: E503-E507 [PMID: 26665252]

50 **Jimenez-Yuste V**, Rodriguez-Merchan EC, Alvarez-Roman MT, Martin-Salces M. Hematological concepts and hematological perioperative treatment. In: Joint Surgery in the Adult Patient with Hemophilia. Rodriguez-Merchan EC, editor. Springer International Publishing Switzerland, 2015: 13-19 [DOI: 10.1007/978-3-319-10780-6\_2]

51 **Wong JM**, Mann HA, Goddard NJ. Perioperative clotting factor replacement and infection in total knee arthroplasty. *Haemophilia* 2012; **18**: 607-612 [PMID: 22188657 DOI: 10.1111/j.1365-2516. 2011.02728.x]

52 **Martinowitz U**, Schulman S, Gitel S, Horozowski H, Heim M, Varon D. Adjusted dose continuous infusion of factor VIII in patients with haemophilia A. *Br J Haematol* 1992; **82**: 729-734 [PMID: 1482660 DOI: 10.1111/j.1365-2141.1992.tb06951.x]

53 **Batorova A**, Martinowitz U. Intermittent injections vs. continuous infusion of factor VIII in haemophilia patients undergoing major surgery. *Br J Haematol* 2000; **110**: 715-720 [PMID: 10997985 DOI: 10.1046/j.1365-2141.2000.02226.x]

54 **Jiménez-Yuste V**, Rodriguez-Merchan EC, Alvarez MT, Quintana M, Fernandez I, Hernandez-Navarro F. Controversies and challenges in elective orthopedic surgery in patients with hemophilia and inhibitors. *Semin Hematol* 2008; **45**: S64-S67 [PMID: 18544428 DOI: 10.1053/j.seminhematol.2008.03.009]

55 **Stephensen D**. Rehabilitation of patients with haemophilia after orthopaedic surgery: a case study. *Haemophilia* 2005; **11** Suppl 1: 26-29 [PMID: 16219047 DOI: 10.1111/j.1365-2516.2005.01151.x]

56 **De la Corte-Rodriguez H**, Rodriguez-Merchan EC. The role of physical medicine and rehabilitation in haemophiliac patients. *Blood Coagul Fibrinolysis* 2013; **24**: 1-9 [PMID: 23103725 DOI: 10.1097/MBC.0b013e32835a72f3]

57 **Rodriguez-Merchan EC**, Rocino A, Ewenstein B, Bartha L, Batorova A, Goudemand J, Gringeri A, Joao-Diniz M, Lopaciuk S, Negrier C, Quintana M, Tagariello G, Tjonnfjord GE, Villar VA, Vorlova Z. Consensus perspectives on surgery in haemophilia patients with inhibitors: summary statement. *Haemophilia* 2004; **10** Suppl 2: 50-52 [PMID: 15385047 DOI: 10.1111/j.1365-2516.2004.00933.x]

Figure Legends

****

**Figure 1 Severe bilateral hemophilic arthropathy of the knee in a 37-year-old male.**

****

**Figure 2 Flow chart of our search strategy.**

****

**Figure 3 Severe painful hemophilic arthropathy of the left knee in a 41-year-old male.** A cemented total knee arthroplasty (NexGen, Zimmer, United States) was performed with a satisfactory result: A: Anteroposterior preoperative radiograph; B: Lateral preoperative view; C: Anteroposterior radiograph 5 years later; D: Lateral view at 5 years. The quality of life of this patient improved significantly.

Footnotes

Conflict-of-interest statement: The authors declare no conflicts of interest for this article.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Peer-review started: January 12, 2016

First decision:March 1, 2016

Article in press: April 22, 2016

**P- Reviewer**: Ohishi T, Samulski RJ, Zak L **S- Editor**:Ji FF **L- Editor**: A **E- Editor**:Li D