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MINIREVIEWS

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

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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

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.

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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.

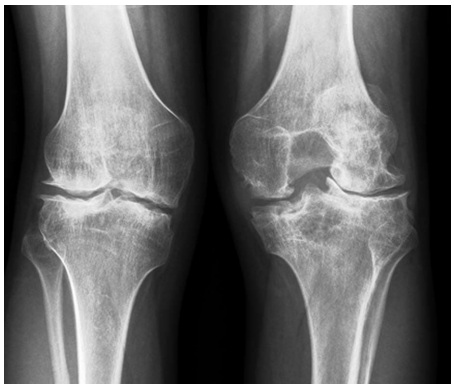

Figure 1 Severe bilateral hemophilic arthropathy of the knee in a 37-year-old male.

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].

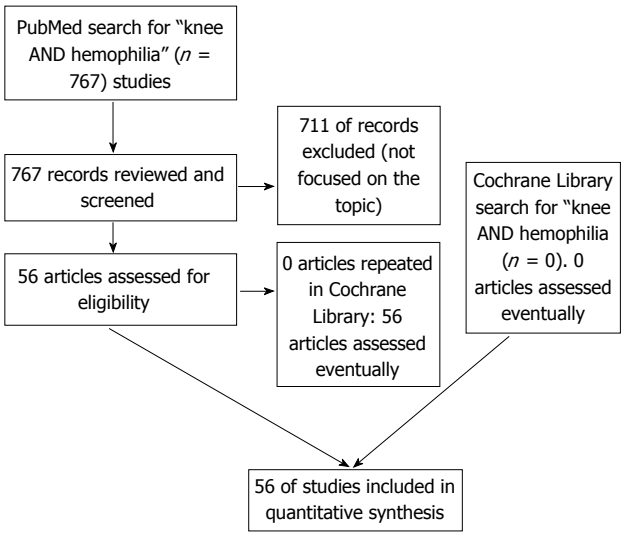

Figure 2 Flow chart of our search strategy.

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

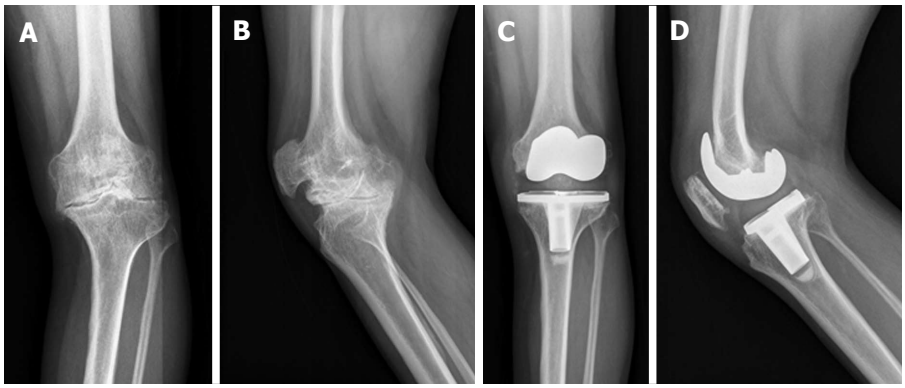

Figure 3 Severe painful hemophilic arthropathy of the left knee in a 41-year-old male. A cemented total knee arthroplasty (NexGen, Zimmer, United States) was performed with a satisfactory result: A: Anteroposterior preoperative radiograph; B: Lateral preoperative view; C: Anteroposterior radiograph 5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

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.

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