Orthopedic surgery in hemophilic patients with musculoskeletal disorders: A systematic review

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Abstract. Hemophilia is a hereditary coagulopathy caused by factor VIII (hemophilia type A) or by coagulation factor IX (hemophilia type B) dysfunction, characterized by an increased bleeding predisposition, which is either spontaneous or secondary to minimal trauma. Currently, hemophilia may also be considered an 'orthopedic' condition, due to the fact that it affects the musculoskeletal system of most hemophilic patients. In recent years, constant prophylaxis using coagulation factors has led to a significant improvement in the hemophilic patient's quality of life, by reducing both life-threatening hemorrhagic phenomena, as well as the occurrence of chronic complications. Nevertheless, progressive joint bleeding remains unavoidable in this category of patients, and the onset of chronic arthropathy with secondary motor deficiency remains the main complication with an invalidating character. In such cases, orthopedic management is imperative; osteoarticular complications being managed most often with the help of conservative or surgical techniques. The purpose of this review is to provide an overview of modern orthopedic practices which are useful in the management of hemophilic patients suffering from osteoarticular disorders.

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1. Introduction

Hemophilia is the most common coagulopathy, caused by factor VIII deficiency or by coagulation factor IX, characterized by an increased bleeding tendency, but also by chronic complications of the musculoskeletal system, with an invalidating character (1). The severity of the hemorrhagic phenomena is usually related to the residual level of the coagulation factor; therefore, in severe forms of hemophilia, bleeding can occur spontaneously, in the absence of any traumatic factor (2-5).

In recent decades, the onset of continuous coagulation factor prophylaxis in the hemophilic patient has reduced both the occurrence of life-threatening acute bleeding phenomena and chronic complications related to the locomotor system (6). However, the failure of administering this type of prophylaxis in every country due to its high costs, the reduced compliance of some patients with this type of treatment, the physical overload in the absence of prophylactic administration of the coagulation factor, are situations that frequently lead to bleeding at the musculoskeletal level, which is usually recurrent in the same joint, known as 'target joint' (7). Hemophilic patients diagnosed with a severe or moderate form of hemophilia, or those with inhibitors present (antibodies developed against clotting factor replacement), often suffer from severe joint problems (7).

Arthropathy usually develops in childhood, between the ages 1 and 5 and subsequent occurrences are relapses. The trigger factor is often a traumatic one, of different intensity, but bleeding can sometimes occur spontaneously. The topography of the affected joints, in order of decreasing frequency, is as follows: Knee (36%), ankle (30%), elbow (23%), hand (6%), shoulder (3%) and hip (2%) (8).

In most cases, hemarthroses are monoarticular; sometimes they are biarticular, but in this case symmetry is not mandatory. Every joint hemorrhagic episode causes local disturbances, which predispose to recurrences: The anatomical structures are weakened, the muscles become atrophied and fibrosed affecting joint mechanics, the synovial becomes hypertrophied and hypervascularized, and more easily hemorrhagic (a vicious circle). This marks the beginning of 'hemophilic arthropathy', which gradually evolves throughout the patient's life and generates severe ankylosis (4,9).

The initial stages of arthropathy are associated with pain which increases in the morning and at night, decreasing during the day. In advanced stages, an intense pain is felt at the level of the joints, along with a significant decrease in the degree of movement (ROM), malalignment, instability, impaired muscle tone and severe functional impairment (10).

During X-ray examination, early osteoarticular changes cannot be detected, ultrasound evaluation (in children and young patients) or MRI (young and adult patients) being required (11).

The following anomalies can be determined on the standard X-ray: Local osteoporosis, the presence of subchondral cysts, narrowing of the joint space, loss of the physiological axis and the presence of osteophytes (12-14). The ultrasound evaluation can assess the presence and activity of the synovitis, the type of intra-articular fluid (blood, synovial fluid) and even the continuity and width of the chondral layer (15).

Prophylaxis with coagulation factor, changes in lifestyle, physical and medical therapy can be useful methods to prevent the onset of arthropathy (16).

In the early stages of arthropathy, conservative treatment is usually enough (17). When this type of treatment is no longer effective or severe arthropathy is developed, orthopedic surgery becomes necessary.

2. Search strategy

The literature search was carried out on PubMed, ScienceDirect, and Google Scholar and covered the last 20 years. Literature selection was made based on the key words: Arthropathy, arthroplasty, hemophilia, orthopedic techniques. Only full-text, English-language articles were selected for this study. Duplicate publication, irrelevant topics and book chapters were excluded. A total of 234 articles were reviewed. From these, 45 articles which offered information about modern orthopedic practices that are useful in the management of hemophilic patients suffering from osteoarticular disorders, were selected.

3. Conservative therapy

Conservative therapy targets the use of orthotics, joint aspiration, intra-articular administration of anti-inflammatory drugs, radiosynoviorthesis, gradual corrective straightening of ankylosis in flexion, and treatment of closed fractures (12,18).

The role of orthotics in the treatment of hemophilic osteoarthropathies. An orthosis is an externally applied device that helps to prevent or correct limb deformities, stabilizes, facilitates or prevents joint movement. In hemophilic patients, orthoses are used to prevent bleeding at the level of the joints, being indispensable for the treatment of problems related to the process of progressive joint destruction. Orthoses are also an important part in postoperative recovery (18-20).

The characteristics of these devices vary depending on the joints to which they are applied. There are two categories: Static and functional. When it comes to the upper limbs, the most affected joints are the elbow and the shoulder, which require immobilization. From the lower limbs, the most affected joints are the knee, the ankle and the hip which in the acute phase must be immobilized and the patient must be advised not to walk. After stopping the bleeding and restoring muscle and movement balance, the patient can gradually return to normal activity. The main role of orthoses, in this case, is to immobilize and unload the respective segment, offering stability and aid while walking (21).

Orthoses improve the quality of life of the hemophilic patient with musculoskeletal lesions and are useful in preventing injuries resulting from demanding or daily activities.

Orthotic insoles and the plantar cup pads attenuate and change posture and can consequently prevent a series of injuries. Walkers and walking frames are used to protect injured joints and to restore normal walking.

Aspiration puncture. Significant joint bleeding (>20 ml in the knee joint) requires puncture or aspiration of blood. After decompression, the joint must be protected with a compressive dressing; furthermore, it is necessary to apply an anti-inflammatory ointment and an ice bag. The joint is then left to rest for 1 or 2 days, after which medical gymnastics must be resumed (17).

Intra-articular corticotherapy. Intra-articular corticotherapy is a controversial method that can be applied in the case of advanced chronic synovitis (grade III and IV) and comprises an intra-articular injection of dexamethasone every 3 weeks (3 sessions), repeating the treatment after a 6-month break (maximum 3 treatments) (22).

Hyaluronic acid injections. Hyaluronic acid is a constituent of cartilaginous tissue at the level of the joint. The intra-articular administration of hyaluronic acid is used in case of large joint damage. This method is superior to cortisone shots, lacking the latter's side effects (such as osteoporosis, diabetes, high blood pressure, Cushing's syndrome); it can be recommended before resorting to surgical treatment (10,14).

Nonsurgical synovectomy (synoviorthesis). Synoviorthesis consists of the intra-articular shot of a substance that produces synovial fibrosis (radioactive yttrium, rifampicin, and doxycycline). It is recommended in chronic I grade (transient synovitis, without sequelae and with >3 hemarthroses in 6 months) and II grade synovitis (permanent synovitis with joint enlargement, synovial thickening and movement limitation) with recurrent bleeding episodes (3 hemarthroses in 6 months) and with diminution of joint movements (23).

It is, however, not recommended in acute bleeding or in the ankylosing phase. The purpose of this intervention is to reduce synovitis, to minimize the number of hemarthrosis at the level of the respective joint and to recover range of motion

in the joint. In the long term, nonsurgical synovectomy does not prevent joint destruction (24).

Gradual corrective straightening of ankylosis. This method aims to reduce the range of motion in the large joints (knees, elbows, hips). It is performed under anesthesia, with the firm application of forces that aim towards the gradual straightening of flexion contractures, with corrective plaster immobilization of the anatomical region (9).

Treatment of closed fractures. The incidence of fractures in hemophilic patients is a controversial topic: On the one hand, they develop osteoporosis, on the other hand, their reduced mobilization protects them from this risk. In all situations, corrective substitution is required, aiming at a concentration of 30-40% FVIII/IX over an extended period, until the fracture becomes stabilized: in this regard, FVIII/IX concentrates are used, to which antifibrinolytic drugs can be associated (25).

Orthopedic treatment must consider the quality of the bone structure: If the structure is normal, the treatment is regular; however, if it is pathological, intramedullary consolidation with rod becomes necessary (5).

4. Surgical treatment

Even if modern substitute preparations are available, orthopedic surgical treatment of the hemophilic patient is a highly specialized surgery, requiring competence and experience in the field. In order to obtain optimal results, surgical interventions must be performed under the guidance of multidisciplinary teams, including a hematologist, orthopedist, kinetotherapist and specialized nurses (5,9,17,18).

In the assessment of the hemophilic patient who is due to undergo surgical intervention, the following issues must be taken into account: i) Severity and type of hemophilia to estimate the substitute treatment; the required concentrate factor also depends on the extent of the intervention and recovery; ii) Determining the presence of circulating inhibitors where it is crucial to avoid potentially lethal complications, even low-titre inhibitors can increase spectacularly after administering large doses of factor, immediately pre- and post-operatively; iii) Exploring the viral status as the serological tests must be repeated to detect hepatitis B, hepatitis C and HIV infection pre-operatively, if they have not been performed over the last 3 months (active hepatitis is a contraindication for this intervention); iv) Complete pre-operative clinical imagistic assessment to perform multiple corrective interventions, for the same consumption of coagulation factors to solve several orthopedic issues.

Orthopedic surgery is recommended in: Chronic synovitis which cannot be conservatively controlled, with synovectomy recommended; joint and bone deformities; muscle contracture with osteotomy and arthroscopic arthrolysis recommended; degenerative joint disease with prosthesis or arthrodesis recommended; hemophilic pseudotumors with exeresis recommendation; open fractures; invalidating pain, accompanying all situations mentioned above (17).

Synovectomy. Synovectomy, as an isolated intervention, is performed initially on the knee. The classic indications for synovectomy are recurrent or chronic hemarthroses in joint arthropathy, which fail to respond to conservative treatment for 6 months. Conservative treatment usually lasts 4-6 months. Therefore, when intervention is required, there is usually a significant erosion of the articular cartilage (23). Synovectomy is rarely curative, but it is effective in treating recurrent hemarthrosis and possibly arthropathy progression, reducing hemarthrosis frequency and variably improving joint mobility (5,17).

The intervention is arthroscopic, presenting minimal post-operative risks. It is a second-line invasive procedure in the early stages of arthropathy, which can be recommended after failed synoviorthesis.

Arthrotomy and resectionary osteotomy. Arthrotomy and resectionary osteotomy involve remodelling the ends of the joint, with the exeresis of hypertrophied bone segments, which prevent the normal movement of the joint as well as its instability. It is generally recommended for the elbow joint (17).

Arthrodesis. This is a method of stabilizing the joint, which is usually recommended for the ankle joint. It is only rarely performed on knees and elbows, where an open surgical synovectomy is preferred (26).

Endoprosthetic arthroplasty. Severe arthroplasty of the hip is much less common than that of the knee, elbow or ankle. The X-ray image can have the appearance of a juvenile arthritis or coxarthrosis. The increased pressure in the intra-articular space can determine the aseptic necrosis of the femoral head. Total hip arthroplasty has been highly effective in patients with major damage to the coxofemoral joint, significantly improving range of motion in the joint (27).

Knee arthropathy is the most common cause of pain and disability in hemophilic patients. Indications for arthroplasty are: pain and invalidity that do not respond to conservative treatment and advanced radiological changes. The results consist of pain reduction, improvement of range of motion in the joint and correction of deformation (5,8).

Total endoprostheses, in their cemented version, are recommended in major joint destructions, entailing a significant functional deficiency. The indication of total endoprosthesis is yet to be assessed from the viewpoint of distant prognosis. Their main risks are infection and aseptic widening of bone structures, influencing the stability of endoprosthesis (28,29). The major indication of endoprosthesis is mostly focused on the joint of the hip and the knee, carefully performed at young ages. The surgical technique and the material used to make the prostheses are currently perfected, so the indications of use have extended in terms of the age and joints targeted (including ankle joints) (28-30).

As previously mentioned, a major problem of hemophilic patients with indication of arthroplasty is represented by the increased risk of bleeding and infection (5,8,28,30,31).

A recent meta-analysis of hemophilic patients who underwent total knee arthroplasty has revealed a complication rate of 31.5% (32). In another study, performed on the same category of patients with indication of total endoprosthesis of the knee, Ernstbrunner *et al* highlighted a rate of infection of 12% and a rate of revision of the prosthesis of 30% (33).

When it comes to total hip arthroplasty, 49 cases of patients with hip endoprosthesis, of which 43 hemophilic, were examined in a recent report. The patients were monitored, on average, for 11 years. In hemophilic patients, the rate of infection was 6%, while the rate of aseptic loosening of the prosthesis was 10% (34). In endoprosthesis of the elbow, the rate of complications in hemophilic patients secondary to this intervention was 62%. The study included 13 patients who underwent total elbow arthroplasty, 9 of whom were hemophilic patients. The average period of monitoring the patients was 8 years, and the average age of the patients subjected to study was 55 years (35).

Treatment of open fractures. Treatment of an open fracture is a therapeutic measure that involves an important substitution with coagulation factor, given the open wound, debridements and frequent dressing changes. The treatment in itself follows the general orthopedic principles, facing the risk of septic complications, compartment syndromes or the need for multiple interventions (36,37).

Orthopedic surgery should always be the last resort for treating hemophilic arthropathy. In cases of synovitis, radiosynovectomy is recommended as the first line of treatment (38,39). Additionally, arthroscopic synovectomy can be used. In case of painful arthropathies and severe joint degeneration with severe motor deficiency, total arthroplasty is necessary (38).

In developed countries, the possibility of administering primary prophylaxis may lead to a more reduced use of orthopedic surgical procedures, while in developing countries, orthopedic complications of the hemophilic patient may persist due to the lack of funds necessary to ensure this type of treatment, and surgical interventions will always be necessary (40-44).

According to the studies carried out, orthopedic surgical procedures in the hemophilic patient are usually safe; however, complications occur with a higher frequency in hemophilic patients with inhibitors. In total knee arthroplasty, intra-articular administration of tranexamic acid and local infiltration with analgesics are recommended. Nonetheless, the average rate of periprosthetic infection after total knee arthroplasty is 7% (45).

5. Conclusions and prospects

To conclude, modern orthopedic surgery has ameliorated musculoskeletal problems of hemophilic patients. The most commonly affected joints are the knees, ankles and elbows. The most frequent orthopedic procedures used in hemophilic patients are radiosynovectomy, arthroscopic synovectomy, arthroscopic joint debridement, ankle arthrodesis and total joint arthroplasty. Each surgical procedure requires hematological support, in accordance with the indications of the hematologist. In hemophilic patients, except those with inhibitors, routine pharmacological thromboprophylaxis is not recommended. The main complications of hemophilic patients with total endoprosthesis remain bleeding and infections.

Improved results can only be obtained in comprehensive hemophilia treatment centres where multidisciplinary teams are prepared to manage such a complex type of patient.

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Authors' contributions

OVB, PDS and CU analyzed and interpreted the patient data regarding the hematological and orthopedic disease. NF and EC searched the literature and wrote the first draft of the manuscript. MV, AP and IBB collected and interpreted data and participated in discussion regarding the content. MC designed the study and supervised the whole process of this study. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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