Point-of-care Ultrasonography in Orthopedic Management of Hemophilia: Multiple Uses of an Effective Tool

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Abstract Even in our current era of hemophilia prophylaxis, articular complications can arise and there is a growing need for strategies in the prevention, diagnosis, and treatment of hemophilic arthropathy, a significant contributor to disability in patients with hemophilia. One useful tool, point-of-care ultrasonography (POC-US), offers diverse diagnostic and therapeutic possibilities. This article reviews the literature on the uses of POC-US in hemophilia, including early diagnosis of joint damage, differential diagnosis of articular pain, follow-up of joint injury, and guidance for both arthrocentesis and intra-articular injection. Studies show that for patients with hemophilia, POC-US enhances diagnostic accuracy and targeted treatments. Further research is required into the most efficient use of POC-US and the training needed to develop clinicians' skills. The attributes of POC-US should be understood more fully to enable its widespread application.

Keywords hemophilia · ultrasonography · point-of-care · arthropathy

Introduction

Hemophilia A and B are X-linked recessive genetic disorders that cause a deficiency of clotting factors VIII and IX, respectively [6]. A typical clinical manifestation of hemophilia is intra-articular bleeding (hemarthrosis), chiefly into the ankles, knees, and elbows [32, 41].

Repeated joint bleeding eventually results in hemophilic arthropathy, which is typically visible on imaging studies and leads to impaired joint function [14]. Clinical confirmation of hemarthrosis and changes to the synovium and osteochondral structures is critical to the process of selecting from the options available to treat patients with hemophilia [1, 20].

Given the absence of biomarkers or other laboratory findings that might help diagnose musculoskeletal abnormalities in hemophilic patients [35], imaging techniques are used to provide objective information on joint status [1] and improve treatment effectiveness and timeliness. Subjective assessments by either patient or physician cannot ascertain the existence of hemarthrosis in over half of the cases [8], suggesting a need for supplementing physical examination with imaging tests [44].

Magnetic resonance imaging (MRI) and ultrasonography (US) have been shown to be particularly effective in detecting early soft and osteochondral tissue changes in patients with hemophilia, before such changes become apparent on physical exam or plain radiographs [10, 16, 36]. In addition, the findings of both imaging techniques seem to be well correlated with each other [13, 43].

US is a safe and effective imaging technique used in medicine for over half a century to diagnose multiple conditions and assist in the treatment of certain injuries [30], including musculoskeletal disorders related to hemophilia.

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Although the first US images were obtained in the 1950s, US was not used to evaluate hemophilic joints until the 1980s, when multiple scientific articles were published on its use [12]. In 1992, the first comparative study demonstrated its usefulness in detecting hemarthrosis, synovitis, and chondral damage in patients with hemophilic arthropathy [29]. Since then, particularly in the last few years, musculoskeletal US (MSK-US) has become widespread in hemophilia, especially in providing instantaneous, highly reliable information on joint status [20], including the presence of hemarthrosis, synovial hypertrophy (synovitis), chondral injury, and subchondral bone damage [11, 13, 20, 21, 28, 37]. Moreover, US provides data usually well correlated with clinical outcomes, with close correspondence between US findings and patients' functional status [22]. Most important, MSK-US is readily available, economical, noninvasive, and suited to detecting the earliest stages of arthropathy [11, 30, 31, 44].

Point-of-care ultrasonography (POC-US) is increasingly used in limited-resource environments. The World Health Organization (WHO) has stated that plain radiographs and sonograms, either separately or combined, will meet two-thirds of the diagnostic imaging needs of developing countries [30]. The purpose of this article is to review the most recent literature on the uses of POC-US in hemophilia.

Methods

A Cochrane Library and PubMed (MEDLINE) search related to the role of ultrasonography in hemophilia was conducted. The only language searched was English. Scientific meeting abstracts and other sources of evidence were not considered. The main criteria for selection were articles that were focused on the role of US in hemophilia. Figure 1 shows our search strategies. The searches were dated from the establishment of the search engines (PubMed and Cochrane Library) until December 26, 2017.

Results

We have classified our search results into five groups, which cover the uses of POC-US in a coagulopathy unit from diagnostic assessments to US-guided procedures.

Routine Joint Assessment

Joint bleeding constitutes the most common type of hemorrhage in patients with hemophilia. Although widespread use of prophylaxis has helped prevent arthropathy, a significant percentage of patients experience inflammatory and/or degenerative articular changes. US can identify bleeding at asymptomatic joints and assist in determining hemarthrosis severity [28]. Several studies have shown that US is useful in the detection of subclinical articular findings [2, 10, 16, 36, 45]. As a result, regular sonographic joint status monitoring has been recommended in patients with hemophilia, so as to identify early articular changes and prevent the development or progression of hemophilic

arthropathy [11]. POC-US involves a series of specific sonographic exams intended to evaluate certain articular alterations typical of hemophilia [30]. It facilitates routine joint assessment and contributes to a rational use of healthcare resources, helping determine whether other imaging techniques may be required [44].

So far, Hemophilia Early Arthropathy Detection with Ultra Sound (HEAD-US) is the only system developed for use by nonradiologists [27]. Routine assessment using HEAD-US makes it possible to detect the presence of hemarthrosis, synovitis, and chondral and subchondral damage in the elbow, knee, and ankle [27]. An example can be seen in Fig. 2. One of its chief advantages is that it is more sensitive than subjective physical examination (as measured by Hemophilia Joint Health Score [HJHS]) [2, 16, 45]. Therefore, routine exams of patients with hemophilia should include an ultrasound assessment. In fact, some groups have recommended the use of HEAD-US as a POC-US assessment every one or two years to monitor patients' evolution [15].

Differential Diagnosis of Articular Pain

Rapid and accurate diagnosis is needed in order to treat hemophilic patients with joint damage. Usually, therapeutic strategies for patients with hemophilia and joint pain are based on the use of coagulation factors; however, such treatment should be administered only in the event of a bleeding episode. This optimizes treatment costs and allows faster recovery of the lesion [8]. US has shown more sensitivity than MRI for detecting the presence of hemarthrosis [33]. For that reason, POC-US is an effective aid in performing a differential diagnosis of joints with specific signs or symptoms [30, 45]. An example can be seen in Fig. 3. Use of POC-US in the assessment of hemarthrosis has revealed discrepancies between sonographic findings and the clinical suspicions of physicians and their patients [8].

Ceponis et al. used POC-US to distinguish intra-articular hemorrhage, inflammation, and joint degeneration from other syndromes causing regional pain [8]. They found an erroneous clinical diagnosis made prior to the use of US in over half of cases. US made it possible to determine that hemarthrosis was not present in many of the clinically identified cases. Conversely, cases identified as cartilage degeneration were, in fact, joint hemorrhages. In short, hemarthrosis was present in only around one-third of joints with acute pain. This resulted in a change of therapeutic strategy in over 70% of episodes, shortening the time to symptom relief by 60% [8].

Various US examinations have been described to assess joint pain. Some are more complex than others and a few include the use of color Doppler and grayscale imaging [13, 19, 21, 27, 28, 31, 38, 46]. The HEAD-US protocol is very useful for making the differential diagnosis between hemarthrosis, synovitis, and osteochondral damage [27]. Considering that the high-resolution (7–15 MHz) linear probes used to evaluate hemophilic joints [12] allow exploration of other periarticular structures such as tendons, ligaments, or muscles, some authors have advocated the use of POC-US for more comprehensive joint evaluation [20].

Fig. 1. Flow chart of our search strategy regarding the use of ultrasonography in hemophilia.

Kidder et al. carried out 65 MSK-US exams in 34 hemophilic patients with acute and chronic joint pain [20]. Among other things, they found that two-thirds of the joints (66.5%) exhibited inflammatory soft tissue changes including synovitis, tendinitis, enthesitis, bursitis, and fat-pad inflammation requiring treatment. Tendon sprains and partial tears were observed in around 10% of joints [20]. Intra-articular effusion was detected in 55.5% of joints with acute pain and in 46.8% of those with chronic pain [20]. In

patients with hemophilia, bleeding does not always cause acute pain, but persistent bleeding may cause chronic pain, and POC-US allows identification of hemarthrosis as well as exclusion of other potentially treatable causes. These findings could be used to optimize coagulation factor replacement therapy [20].

Lesion Follow-up

In patients with hemophilia, POC-US is also a valid and sensitive tool for continuous monitoring of joints [11, 28, 31, 37, 43] and of treatment response [4, 28]. Some expert groups have recommended sonographic follow-up of acute joint lesions using the HEAD-US system, repeating the exam every one or two weeks until resolution [15]. In cases of hemarthrosis, an isolated clinical examination is not sensitive enough to detect small residual amounts of blood in the joint, which may lead physicians to discontinue treatment prematurely and allow the patient an early return to certain activities [37]. For that reason, it is of the essence to combine clinical examination with more sensitive diagnostic techniques, including POC-US [44], which has shown itself useful in monitoring joint lesions [4, 28].

Particularly in acute hemarthrosis, POC-US provides accurate information on the presence, location, and amount of blood in the joint. It can be used to monitor the evolution of hemarthrosis and to follow up on the status of the joint recesses where blood was initially detected and checking their echogenicity. An example can be seen in Fig. 4. These serial periodic evaluations make it possible to determine disease progression or regression [12], confirm its full resolution, and determine the duration of treatment [1, 4, 20, 37].

Ultrasound-guided Arthrocentesis

Appropriate treatment of hemarthrosis is essential to preserving joint function in persons with hemophilia [18]. In the early stages of bleeding, arthrocentesis can be an effective treatment option [25, 41]. It is crucial to

Fig. 2. Subclinical findings in a routine US evaluation of an asymptomatic elbow. **a** Incipient chondral damage at the distal humeral epiphysis on a short axis plane (arrowheads). **b** Subacute hemarthrosis and synovitis at the posterior elbow recess on a long axis plane (arrowheads).

Fig. 3. Different adult patients with hemophilia, all of them with recent onset ankle pain. US allowed determination of the different causes of pain in every case (HEAD-US scanning protocol). **a** Synovitis in the anterior recess of the tibiotalar joint on a long axis plane (arrowheads). **b** Osteochondral damage at the talar dome on a short axis plane (arrowheads). **c** Acute hemarthrosis at the anterior recess of the subtalar joint on a short axis plane (arrowheads). **d** Subacute hemarthrosis at the posterior recess of the tibiotalar joint on a long axis plane (arrowheads). Each case required a different therapeutic approach.

confirm sonographically that intra-articular blood is in the liquid phase by echogenicity and compressible material [13, 23]. Not all hemarthroses require aspiration, although draining the blood confirms diagnosis, relieves symptoms, improves function, and possibly prevents the arthropathic changes that typically result from hemarthrosis. The procedure must always be conducted aseptically under factor cover [39, 40]. The use of POC-US to guide simple procedures such as arthrocentesis enhances their safety, as it allows real-time visualization of anatomy, improving procedure success rates and reducing complications [34]. An example can be seen in Fig. 5. The use of color Doppler imaging also allows visualization of the vascular structures, which need to be protected during the procedure [5].

Ultrasound-guided Musculoskeletal Infiltrations

Hemophilic patients may require therapeutic injections to relieve their articular symptoms and reduce the incidence of repeated hemarthrosis. Several options have been proposed, depending on the therapeutic goal. Local intra-articular injections have recently re-emerged in hemophilia and should be considered a treatment option. Therapeutic agents introduced by intra-articular injections include radioactive isotopes (radiosynovectomy), as well as the administration of corticoids, local anesthetics, and hyaluronic acid, among other products [7, 26, 42]. As with other invasive techniques, injections must always be performed under factor cover and aseptic conditions.

Fig. 4. Hemarthrosis in the tibiotalar joint (long axis) of a nine-year-old male (arrowheads); the POC-US helped make a diagnosis and start treatment early. It also made it possible to monitor the progression of bleeding over time and to rule out re-bleeding (same planes in days 1, 3, 5, 8, 14, and 21).

Fig. 5. Acute hemarthrosis in the knee of a hemophilic patient. **a** POC-US shows the presence of intra-articular fluid in the knee, on a long axis plane of the suprapatellar recess (arrowheads). **b** The US serves as a guide to introduce the needle (arrow) into the intra-articular space; the probe is placed in a short axis plane of the suprapatellar recess. **c** Note the direction of the needle (hollow arrow), as it is positioned in the suprapatellar recess at the level of the effusion (short axis image). Subsequently, the blood is aspirated. **d** The same image (short axis) after removal shows the needle still positioned in the suprapatellar recess (hollow arrow) once the blood has been extracted.

Understanding the joint anatomy and achieving an accurate placement of the needle within the articular space are critical for the success of injections [9]. An example can be seen in Fig. 6. Regarding the efficacy and safety of intra-articular injections, the American College of Rheumatology Musculoskeletal Ultrasound Task Force supports US-guided procedures, given that their accuracy is superior to that of blind injections, especially when administered by inexperienced physicians [3]. A comparative analysis of US-guided vs. blind injections has shown the superiority of the former in terms of precision, efficacy, and avoidance of drug deposition in non-target tissues, such as the synovium, fatty tissue, cartilage, tendons, and ligaments [3].

In hemophilia, POC-US has been found useful in guiding intra-articular corticosteroid injections in joints affected by hemophilic arthropathy. Such injections have been shown to be safe and effective for the relief of chronic articular pain in patients with hemophilic arthropathy [26].

Discussion

POC-US should become a valuable and reliable tool in hemophilia clinical practice [1] when nonradiologist physicians are trained in the technique [24]. POC-US should be considered a strategy of comprehensive care capable of

Fig. 6. Intra-articular injection of a knee in a hemophilic patient. US guidance helps correctly position the needle. **a** Long axis plane of the suprapatellar recess showing the tip of the needle between the suprapatellar and the prefemoral fat pads (hollow arrow). **b** Drug administration immediately afterward (same long axis); note the tip of the needle in the same position (hollow arrow) and the fluid filling the surrounding area in the suprapatellar recess (dotted line).

detecting articular changes in patients with hemophilia, allowing a more effective management of resources and faster and more efficient therapeutic interventions [11, 20, 26, 27, 37].

Limitations in the Use of POC-US

US has limitations related to operator skill and its inability to assess marrow edema. That is why a well-defined methodology is crucial. Recruitment of a seasoned operator, particularly one who specializes in radiology of patients with coagulation disorders, is ideal [12, 17].

POC-US is not comparable to an examination conducted by a radiology specialist [1, 11, 27]. Nevertheless, standardized protocols allow a systematic evaluation of the joint damaged by hemophilia. Over the last two decades, multiple joint-examination US protocols have been developed [13, 19, 21, 27, 28, 31, 38, 46]. These protocols can broadly be classified into full peripheral joint US (FPJ-US) protocols, which are more exhaustive and are carried out by experts in radiology, and POC-US, which have been developed for specific purposes. It is still to be determined whether the differences between these protocols could be clinically relevant [17]. Because POC-US is an operator-dependent technology and has become more widespread, the need will arise to certify clinicians to operate these devices, to better define the technology's clinical scope, and to limit inappropriate use [30, 44].

Conclusions

There is a growing need to optimize therapeutic strategies in hemophilia. At present, ultrasound-based diagnosis (rather than subjective assessment) is crucial to make a rational use of coagulation factors and other therapies. In hemophilia, POC-US makes it possible to enhance diagnostic accuracy, provide targeted treatment, and monitor patient response, precisely and safely. Further research is required into when and how POC-US can be used most efficiently and the kind of training needed to develop clinicians' skills and to promote its use. Encouraging units treating hemophilic patients to use ultrasound as a standard technique is a recommended step to improve the care provided.

Compliance with Ethical Standards

Conflict of Interest: Hortensia De la Corte-Rodriguez, MD, PhD; E. Carlos Rodriguez-Merchan, MD, PhD; and Víctor Jimenez-Yuste, MD, PhD, declare that they have no conflicts of interest.

Human/Animal Rights: N/A

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Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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