

Point-of-care ultrasonography (POCUS) in hemophilia A: a commentary on current status and its potential role for improving prophylaxis management in severe hemophilia A

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Abstract: In patients with severe hemophilia A, recurrent bleeding into joints results in increased morbidity and reduced quality of life. Prophylaxis using replacement factor products, especially when initiated early, has established benefits in terms of reducing joint bleeds and preserving joint function. Poor adherence to prophylactic regimens is a common cause for breakthrough bleeds and resultant arthropathy. Improving prophylaxis management, especially in the transitional age group, is a challenge. Here, we discuss the current status of ultrasonography (US) in hemophilia A, challenges in its wider implementation, and the potential for use of point-of-care US (POCUS) as an adjunct in the routine management of patients with hemophilia following prophylaxis regimens. Using POCUS, in which US is performed by trained hematologists and nonphysician operators (rather than comprehensive US performed by imaging specialists), specific clinical questions can be addressed in a time-efficient, user-friendly manner to promote adherence to prophylaxis and guide or modify treatment approaches. This review also discusses barriers to acceptance of POCUS as a part of routine management of patients with hemophilia, including questions related to its diagnostic accuracy, dependence on trained operators, agreement on appropriate scoring systems, and potential usefulness in patient management.

Keywords: adherence, arthropathy, hemophilia, magnetic resonance imaging, prophylaxis, ultrasonography

Severe hemophilia A is a bleeding disorder characterized by an inherited deficiency of plasma clotting factor VIII (levels <1%), which leads to persons with hemophilia (PWH) experiencing spontaneous bleeding events. At some point in their lifetime, most PWH experience joint bleeding or hemarthroses, primarily in the knees, ankles, and elbows. Over time, this repeated extravasation of blood into the joints leads to joint disease specifically referred to as hemophilic arthropathy [Acharya *et al.* 2011]. This is characterized by recurrent joint bleeding, inflammation, synovial hypertrophy, and cartilage destruction, leading to morbidity and reduced quality of life [Melchiorre *et al.* 2011].

Manco-Johnson and colleagues demonstrated that routine replacement with recombinant factor VIII, referred to as prophylaxis, reduces the incidence of joint hemorrhages and life-threatening hemorrhages and lowers the risk of joint damage among young boys with severe factor VIII deficiency [Manco-Johnson *et al.* 2007]. Therefore, early detection of joint bleeds in PWH is critical in the effort to preserve joint function. By detecting joint bleeds early in life using imaging technology, a patient may become more motivated and willing to initiate or continue prophylaxis. However, the maximum patient benefits of prophylaxis can be realized only if patients adhere to the prescribed regimen. Patients with hemophilia transitioning

Ther Adv Hematol

2017, Vol. 8(4) 153–156

DOI: 10.1177/
2040620717690316

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through their teen years (13 through 18 years of age) who are self-infusing, face challenges with prophylaxis and need emphasis on adherence and compliance to their prescribed prophylaxis at annual comprehensive visits to their hemophilia treatment center (HTC) [Young, 2012]. Visual evidence of good or poor compliance documented by ultrasonography (US) presented and discussed during HTC visits may serve to improve compliance. Published estimates of adherence to prophylaxis described by patients, caregivers, and prescribers vary widely from a very optimistic 80% to a low of 41% [Armstrong *et al.* 2015]. A recent study using a commercial database estimated that 66% of patients with severe hemophilia A or B were adherent <70% of the time [Armstrong *et al.* 2015].

Potential barriers to the use of point-of-care ultrasonography (POCUS) include its diagnostic accuracy in hemophilia, the dependence of operator training, agreement on scoring systems, and agreement on the value of POCUS in routine patient management. What are the published data to counter these potential barriers?

Magnetic resonance imaging (MRI) is currently the gold standard for detecting joint damage in PWH. Although MRI scans have been shown to have increased sensitivity in identifying hemophilic arthropathy compared with other types of radiography, the technique is very expensive and may require sedation in certain patient populations [Acharya *et al.* 2008]. However, US is a less expensive alternative to MRI scans, does not require sedation in pediatric patients, is a quick and reproducible study, and can obtain high-quality images dynamically to screen multiple joints at the same sitting [Acharya *et al.* 2008]. There is now general agreement that US performed by experienced operators correlates well with MRI in evaluating hemophilia joints, both with and without arthropathy [Acharya *et al.* 2008; Di Minno *et al.* 2013; Doria *et al.* 2015].

Ultrasound is highly operator-dependent and training is required to reduce inter-individual assessment variability, especially when not conducted by trained ultrasonographers [Doria *et al.* 2015]. Published papers comparing US with MRI [Acharya *et al.* 2008; Di Minno *et al.* 2013; Doria *et al.* 2015] report US conducted by trained radiologists. However, additional published studies in hemophilia in which US was performed by rheumatologists [Ceponis *et al.*

2013], other trained physicians [Aznar *et al.* 2011], and physiotherapists [Aznar *et al.* 2015] have also shown utility and accuracy when compared with trained personnel. It therefore appears that with sufficient training, POCUS can be accurately performed by nonphysicians, enhancing its usefulness in the clinical setting. The published uses of POCUS in hemophilia include evaluating a patient for a bleed *versus* nonbleed in adult patients presenting with a painful joint [Ceponis *et al.* 2013], and determining the duration of on-demand treatment for a bleed in adult patients [Aznar *et al.* 2015].

Despite the general agreement that prophylaxis is effective in severe hemophilia, it seems that adherence might benefit from a new approach. Could ultrasonic joint imaging, preferably at point-of-care with rapid feedback, be useful in promoting adherence to prophylaxis both in the case of a painful joint and joints judged 'normal' by the patient and caregiver? This commentary proposes a new use for US as an adjunct in supporting adherence to prescribed prophylaxis regimens. With respect to its use as an adjunct to managing PWH, POCUS should be defined as US conducted by a trained nonphysician operator with results interpreted rapidly and communicated to the patient by the physician at the same visit as part of the annual comprehensive visit treatment plan. The approach would be focused on answering specific clinical questions in a time-efficient, user-friendly manner. This type of US would therefore differ from a comprehensive US performed by imaging specialists [Martinoli *et al.* 2016]. The goal would be to devise a unique approach to comprehensive hemophilia care to promote patients' compliance to prophylaxis or to modify the approach based on the US findings to preserve joint function.

For our stated proposal of using POCUS to support adherence, it is important to note two publications on the use of US in the management of hemophilia patients. In the first, a retrospective analysis in pediatric and adult patients, where the operator for the US was not specified, 304 joints judged normal by the Orthopedic Joint Score (Gilbert) revealed 38% of joints with US abnormalities [Muca-Perja *et al.* 2012]. In the second publication pertinent to the proposed use of POCUS to support adherence, Di Minno and colleagues studied PWH > 18 years of age and a comparator nonhemophilia group with US and MRI. The hemophilia group had clinically

asymptomatic joints never involved with bleeding events (healthy joints) and an Orthopedic Joint Score of 0. US detected joint effusion in 55% of hemophilic arthropathic joints *versus* 5% of non-hemophilic joints ($p < 0.001$). The findings from US were confirmed *via* MRI scans. The findings of effusion, synovial hypertrophy, and cartilage erosions were higher in the PWH group with significant p values for trend. US and MRI data significantly correlated for effusion ($r = 0.819$; $p = 0.002$), synovial hypertrophy ($r = 0.633$; $p = 0.036$), and cartilage erosion ($r = 0.734$; $p = 0.010$) [Di Minno *et al.* 2013].

Scoring systems for US to guide the approach to the evaluation of joints in PWH have been proposed [Martinoli *et al.* 2016; Melchiorre *et al.* 2011]. In keeping with the suggestion that POCUS is different from a comprehensive US examination performed by trained radiologists and should deliver answers to specific clinical questions [Martinoli *et al.* 2016], is a scoring system feasible in this setting? A POCUS scoring system should be easy to learn and apply by non-physicians and user-friendly. Melchiorre and colleagues have proposed a 9-point semiquantitative score that grades several findings that could be the target for a POCUS exam: joint effusion, synovial hypertrophy, with power Doppler to determine synovial vascularity, hemosiderin deposition, and structural bone and cartilage abnormalities [Melchiorre *et al.* 2011]. Groups studied were healthy individuals, PWH (pediatric patients and adults), and those with rheumatoid arthritis, and it appears (not specified) that the exams were performed by a nonradiologist physician. The time required was not mentioned. X-rays were performed and evaluated by the Pettersson score. Significant correlations were found for US *versus* the X-ray scores for several findings, including bone remodeling [Spearman's rho correlation coefficient (SRCC), 0.429; $p < 0.01$] and osteophytes (SRCC, 0.308; $p < 0.05$).

The HEAD-US scoring system (additive score for synovial hypertrophy with emphasis on quantitative scoring of cartilage and bone changes) was developed with several goals important for a POCUS application: to be used by non-imaging specialists, fast to perform, and capable of screening six joints (elbows, knees and ankles) at a time [Martinoli *et al.* 2016]. The Hemophilia Joint Health Score (HJHS) was the comparator in a study of children with primarily severe disease. A strong correlation ($r = 0.70$, $p < 0.01$) was

reported between HEAD-US and HJHS [Martinoli *et al.* 2016]. A short learning curve and the fact that HEAD-US examination needs <2 min per joint make it an excellent adjunct to physical examination for hemophilic arthropathy to detect early joint changes in which joint function is still preserved [Martinoli *et al.* 2016]. Despite these scoring systems and ability of POCUS to detect joint changes, a question that needs to be addressed includes ability of POCUS to detect changes attributed on MRI to subclinical joint bleeds reported in the absence of reported joint bleeding in the Joint Outcomes Study [Manco-Johnson *et al.* 2007].

In an effort to encourage prophylaxis-reluctant adults and teens to engage in a more routine regimen and adhere to that regimen, early detection of joint damage from recurrent bleeds by way of US can be used as a motivational tool to emphasize the importance of prophylaxis treatment and compliance by making use of the evidence of joint bleeds or lack thereof [Young, 2012].

Although there is no clinical trial evidence to support POCUS as a method to improve prophylaxis compliance, there is some published evidence that documents benefit to patients beyond seeing and discussing the findings on US. Ceponis and colleagues reviewed the usefulness of US examination of the hand in 51 adult patients with established rheumatoid arthritis [Ceponis *et al.* 2014]. Although termed point-of-care by the authors, the US examination was performed by experienced ultrasonographers who used a highly detailed approach that is different from the point-of-care concept described in this review. However, patient satisfaction documented in an exit questionnaire showed that 88.4% stated that the US examination increased their confidence in the clinical recommendations [Ceponis *et al.* 2014]. In a small exploratory study also in patients, age not specified, with rheumatoid arthritis [Thakkar *et al.* 2011], there was a greater perceived understanding with US ($p < 0.007$) and a positive trend toward increased compliance with their management plans ($p < 0.066$).

This commentary has documented the diagnostic accuracy of US as compared with MRI, the fact that nonphysicians can be trained to perform US accurately, and that US findings may contribute to the clinical care of PWH, often changing the approach to a given patient. Scoring systems have been developed and with further validation may

be applicable to a POCUS setting with adequate training. Perhaps a next step might be to conduct a trial of POCUS in PWH in several centers using the HEAD-US system, preceded by training of nonphysician treatment team members in both US and the HEAD-US system. This trial should be conducted in patients from late teens to young adults, because the results in younger patients may differ.

Funding

Editorial assistance was provided by Complete Healthcare Communications, LLC (Chadds Ford, PA) and was fully funded by Bayer.

Conflict of interest statement

S. Acharya has received honoraria as a speaker in meetings organized by Novo Nordisk and Bayer and has served on advisory boards unrelated to this work. B. Rule and O. McMillan are full-time employees of Bayer. T. Humphries was a full-time employee of Bayer at the time the commentary was written.

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