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A new and simplified comprehensive ultrasound protocol of haemophilic joints: the Universal Simplified Ultrasound (US-US) protocol

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AIM: To present a new protocol to optimise ultrasound (US) assessment of haemophilic arthropathy.

MATERIALS AND METHODS: Ultrasound of haemophilic arthropathy joints was performed using three different ultrasound protocols, namely, the Toronto-Vellore Comprehensive Ultrasound (TVC-US) protocol, the Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US), and the newly developed Universal Simplified Ultrasound (US-US) protocol. Synovial hypertrophy, haemosiderin deposition, effusion, erosion, and cartilage loss were evaluated in 20 joints. The reliability and diagnostic efficiency of these protocols was compared using magnetic resonance imaging (MRI).

RESULTS: The correlation between the TVC-US and US-US protocols for synovial hypertrophy was excellent: kappa significance (KS) was 1, but was substantial (KS=0.65) with the HEAD-US protocol. For effusion, both the TVC-US and the HEAD-US protocols had substantial correlation with the US-US protocol (KS=0.7 and 0.6 respectively). The correlation for erosion and cartilage loss was excellent between the TVC-US and the US-US with MRI (KS=1), but poor (KS=0) with the HEAD-US protocol. The US-US protocol also had good interobserver agreement (KS=1).

CONCLUSION: The accuracy of the US-US protocol is comparable to the TVC-US protocol and MRI and is superior to the HEAD-US protocol in the assessment of haemophilic arthropathy.

Introduction

Various radiological techniques have been used to assess the status of the haemophilic joint, including plain radiographs, ultrasound (US), and magnetic resonance imaging (MRI). Each technique has its unique advantages and disadvantages.[1,2] Although MRI is considered the reference standard for assessment of early haemophilic arthropathy,

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it is both expensive and time-consuming.[3–6] US is a sensitive tool for assessing soft-tissue changes such as effusion, synovial hypertrophy, and haemosiderin deposition; however, it shows variable diagnostic accuracy for assessment of osteochondral abnormalities.[7,8]

Keshava *et al.* previously reported a comprehensive protocol for US assessment of the haemophilic joint, namely the Toronto-Vellore Comprehensive Ultrasound (TVC-US) protocol.[9] This protocol is reliable and valid when compared to MRI, but is time-consuming and cumbersome in practice. Point of care ultrasound (POC-US) protocols, such as the HEAD-US protocol,[10] are quicker and simpler, but use predefined views, and are thus likely to miss out potentially affected areas. To address its limitations, the TVC-US protocol was modified. In particular, axial images were eliminated, as these are prone to errors and pitfalls.[7] The US-US protocol includes a scan of the entire joint and images documented at predetermined views (Fig 1). The nomenclature of the views can be applied to any joint, making the protocol universally applicable, and hence it is referred to as the Universal Simplified Ultrasound (US-US) protocol. The aim of this study was to evaluate how the US-US protocol correlates with MRI and with the comprehensive TVC-US and HEAD-US protocols.

Materials and methods

This study included haemophilic patients aged 7–20 years who presented to the Haemophilia Clinic of Christian Medical College, Vellore, and had haemophilic arthropathy. The study was approved by the Institutional Review Board. Informed written consent or assent was taken from the patients or guardians. The knee and ankle joints were assessed in the study. Patients with recent haemarthrosis (less than 2 weeks), claustrophobia, severe joint pain, or contractures were excluded from the study. As ultrasonography was primarily targeted at detecting early changes in the joint, patients were initially screened clinically using the Haemophilia Joint Health Score (HJHS) scale and included more joints with minimal dysfunction. All patients underwent an MRI initially followed by an US within 24 hours of the MRI.

US protocol

US was performed using a Philips Epic 5G machine with a L18-5 MHz transducer. Joints were scanned by the principal investigator using the TVC-US, HEAD-US, and the US-US protocols and the images were documented as per these protocols. To study the reliability of the US-US protocol, the joints were screened within 48 hours by another radiologist who was blinded to the first radiologist's findings. Both the radiologists were blinded to the MRI findings.

The TVC-US protocol documents 27 grey-scale images and 11 Doppler images.[9] It assesses synovial hypertrophy, effusion, haemosiderin, erosion, cartilage loss, and subchondral cysts. The HEAD-US protocol includes five predetermined views for knee joints and four views for ankle joints. It scores synovial hypertrophy and osteochondral damage. The HEAD-US protocol assesses osteochondral changes in one window (K3 for knee and A1a and A1b for ankle). It does not score effusion, haemosiderin deposition, or subchondral cysts; however, for the sake of comparison, in this study these changes were documented in the views assessed by the HEAD-US protocol.

In the new US-US protocol, the entire index joint was scanned, starting from the anterior aspect in the suprapatellar region in sagittal plane and extending to the parapatellar recesses. The specified images were documented while performing the scan. Subsequently, the patient was asked to lie down prone and was scanned in the sagittal and axial planes (Fig 1). Additional images were documented if abnormalities were found elsewhere. Doppler US was performed for all joints. The degree of soft-tissue changes was graded as per the TVC-US protocol.

MRI protocol

A 1.5 T MRI machine (Siemens 1.5T Avanto TIM) was used to image the joints, as per the International Prophylaxis Study Group (IPSG) MRI scale protocol.[5] The sequences obtained were T2-weighted (W) fat-suppressed gradient coronal, T2W fat-suppressed gradient sagittal, T2W axial and T1W sagittal. The following parameters were used: field of view (FOV) read=160 mm, FOV phase=100%, 1.5 mm section thickness, no intersection gap, 50 ms repetition time (TR), 11 ms echo time (TE), using an elliptical filter. All MRI images were reviewed by musculoskeletal (MSK) specialist radiologists familiar with IPSG scoring. Images were analysed for soft tissue and osteochondral abnormalities and were compared with the US findings.

Statistical analysis

Correlation between the findings observed by different imaging protocols and the interobserver reliability of the findings of the US-US protocol were assessed using the kappa coefficient. Kappa was interpreted according to guidelines by Landis and Koch: >0.8, almost perfect; 0.61–0.8, substantial; 0.41–0.6, moderate; 0.21–0.40, fair; 0.00–0.20, slight; and 0.00, poor agreement.[11] Statistical analysis was performed using IBM SPSS version 24.

Results

Twenty joints were assessed: 11 knee joints and nine ankle joints. Based on the HJHS, five joints (four knee and one ankle) were classified as minimal changes (score 0–2), 12 joints (four knee and eight ankle) as mild (score 3–5), two joints (only knees) as moderate (score 6–9), and one knee joint as severe (score >9). The median age of the study population was 11 years (range 7–20 years). Fig 2 shows the type of soft-tissue and osteochondral changes that were detected by different imaging protocols. Although the TVC-US protocol and the US-US protocol detected a large percentage of the arthropathy changes that were also detected on the MRI, the HEAD-US protocol was not as sensitive.

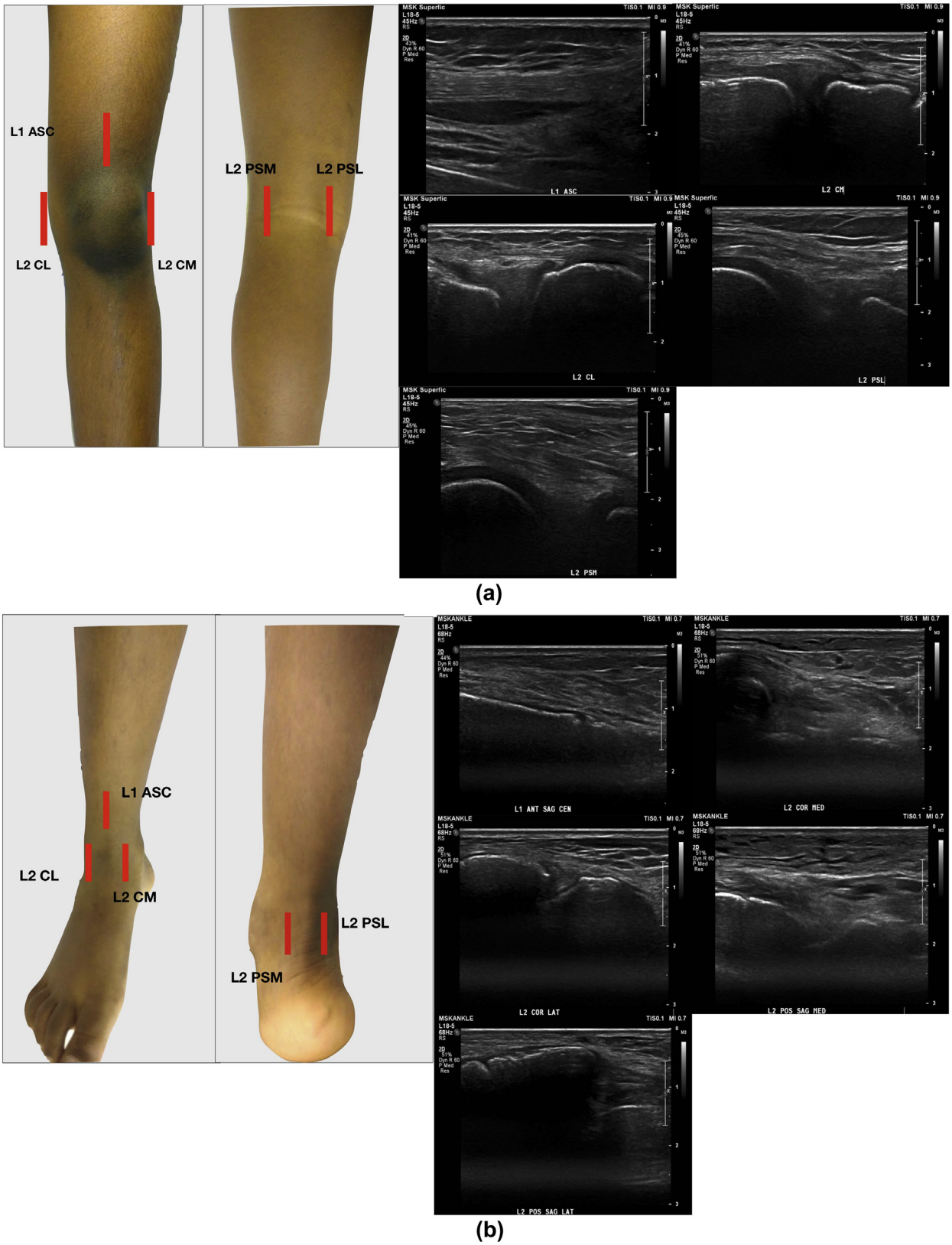

Figure 1 (a) Frontal and posterior views of the right knee and (b) of the right ankle with rectangular boxes (red coloured) representing the footplate of the ultrasound probe in standard views of the US-US protocol with the representative ultrasound images. L1 is above the level of the joint and L2 is at the level of the joint.

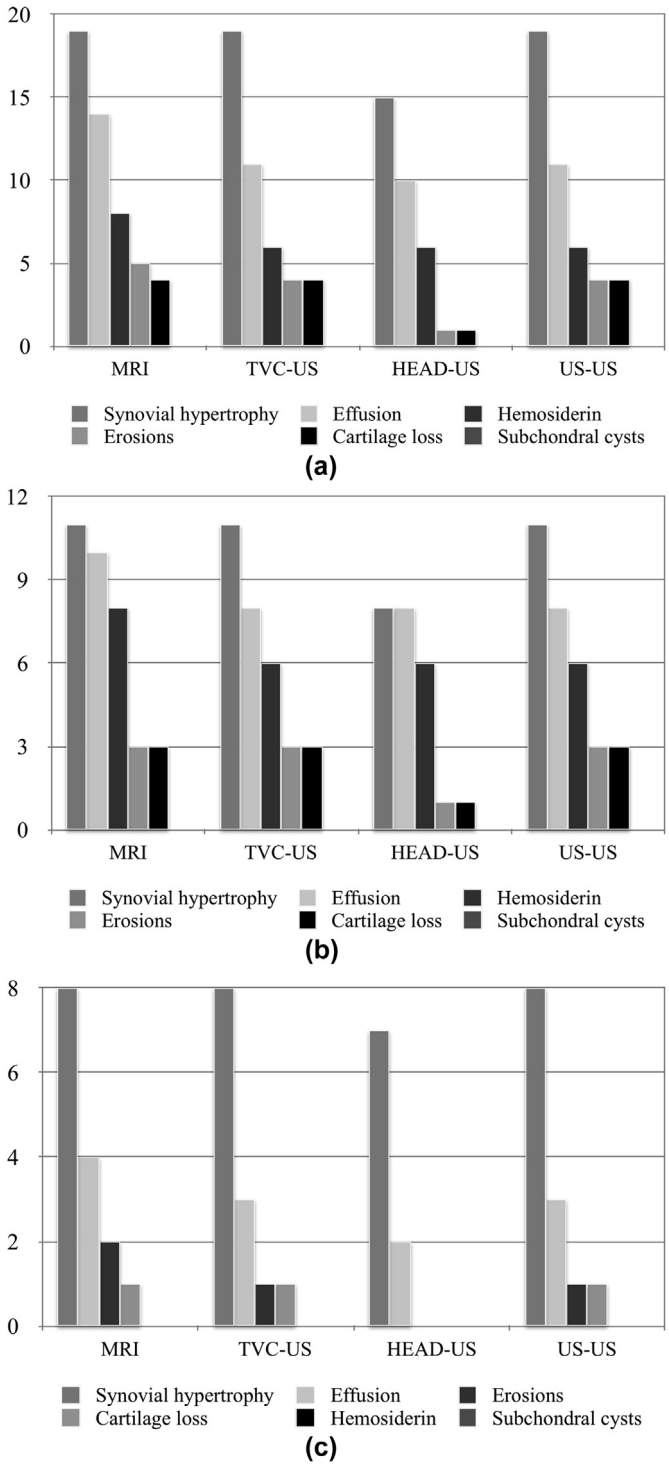

Figure 2 (a) Summary of the soft-tissue and osteochondral changes picked up by the various protocols for 20 joints in ultrasound and MRI. Summary of the soft tissue and osteochondral changes for (b) knee and (c) ankle joints.

Soft-tissue changes

Soft-tissue changes were present in 19 of 20 joints on MRI. One patient, aged 11 years, with right ankle joint of HJHS score of 5, had no soft-tissue or osteochondral changes in the MRI or US. Soft-tissue changes were detected by the TVC-US and the US-US protocols in all 19 joints. The soft-tissue changes were detected in the five pre-defined views of the US-US protocol; no additional views needed to be documented. The HEAD-US protocol did not pick up any soft-tissue changes in four patients.

Synovial hypertrophy

Synovial hypertrophy was present in the MRI of all 11 knee joints and in eight of the nine ankle joints. The kappa coefficient for comparison of the TVC-US protocol, the US-US protocol and MRI for synovial hypertrophy was 1, indicating perfect agreement. The kappa coefficient for comparison of the HEAD-US protocol and MRI for synovial hypertrophy in the knee joint was 0.593, indicating moderate agreement, and in the ankle joint was 0.647, which indicates substantial agreement. For all 20 joints, kappa coefficient was 0.658.

The HEAD-US protocol missed synovial hypertrophy in three of the 11 knee joints: two with mild hypertrophy (seen in the L2 coronal lateral views of the US-US protocol) and one with moderate hypertrophy (seen in the L2 coronal lateral, L2 posterior sagittal medial and posterior sagittal lateral views of the US-US protocol). These views (L2 coronal lateral and L2 posterior sagittal) are not routinely included in the HEAD-US protocol of the knee. In one of the eight ankle joints, the HEAD-US protocol missed synovial hypertrophy that was seen in the L2 posterior sagittal lateral view of the US-US protocol; this view of the ankle is not routinely screened by the HEAD-US protocol.

None of the joints with hypertrophied synovium showed hypervascularity on Doppler.

Effusion

Effusion was noted in the MRI of 10 of the 11 knee joints. All three protocols detected the effusion in eight knee joints (four with mild, two with moderate, and two with severe effusion). The kappa coefficient for comparison of all three protocols was 0.625 (substantial agreement). Effusion was missed in two knee joints, which had minimal effusion in the L1 region (above the joint line) as seen on the MRI. In the ankle, effusion was detected by the MRI in four of the nine joints. It was detected by the TVC-US and the US-US protocols in three joints. The US-US protocol missed mild effusion in one ankle joint (in the L2 coronal lateral view). The kappa coefficient for comparison of the TVC-US protocol, the US-US protocol, and the MRI for effusion was 0.769 (substantial agreement).

The HEAD-US protocol missed effusion in two ankle joints with mild effusion (as detected on MRI): one in the L2 coronal lateral and the other in the L2 posterior sagittal lateral view. The kappa coefficient of agreement with MRI was 0.526 (moderate agreement).

Haemosiderin

Haemosiderin was detected in eight knee joints on the MRI. The TVC-US, the US-US, and the HEAD-US protocols identified haemosiderin in six joints with a kappa

coefficient of 0.500 (moderate agreement). None of the ankle joints had haemosiderin detected on the MRI and US.

Osteochondral changes

There were three knee joints and one ankle joint that had osteochondral changes detected on the MRI. All three knee joints had subchondral erosions and partial thickness cartilage loss. None of the joints with early arthropathy (HJHS <3) had osteochondral changes on the US or the MRI. Two of the 12 joints with mild arthropathy (HJHS 3–5; one ankle, one knee) had osteochondral changes, while one of the two knee joints with a moderate score (HJHS 6–9) had osteochondral changes. One knee joint with an HJHS score of 14 (severe arthropathy) had both erosion and cartilage loss.

Erosion

There were three knee joints with erosion present on the MRI. In one joint, the erosion was present in the L2 posterior sagittal lateral and the second joint had erosion in L2 posterior sagittal medial and L2 posterior sagittal lateral view. All these erosions were detected by the TVC-US protocol and the US-US protocol, but were missed on the HEAD-US protocol (Fig 3). The third knee joint had erosions in L2 coronal medial and L2 coronal lateral, which were identified using both the TVC-US and the US-US protocols. The HEAD-US protocol picked up the erosion in K4 (L2 coronal medial), but missed the erosion in L2 coronal lateral view. One ankle joint had erosions in the central window and anterolateral aspect on the MRI. The central erosion was missed by all the US protocols. An additional view that is normally not documented on the US-US protocol — the L2 anterior sagittal lateral view — documented anterolateral erosions in the ankle. The HEAD-US protocol did not pick up the erosions as the L2 anterior sagittal lateral view is not part of the HEAD-US protocol.

Cartilage loss

The kappa coefficient for comparison of the TVC-US and the US-US protocols with MRI for cartilage loss was 1.00 (perfect agreement). Cartilage loss (partial thickness) was found in three knee joints: in the L2 coronal medial window in one joint and the L2 posterior sagittal lateral view in the

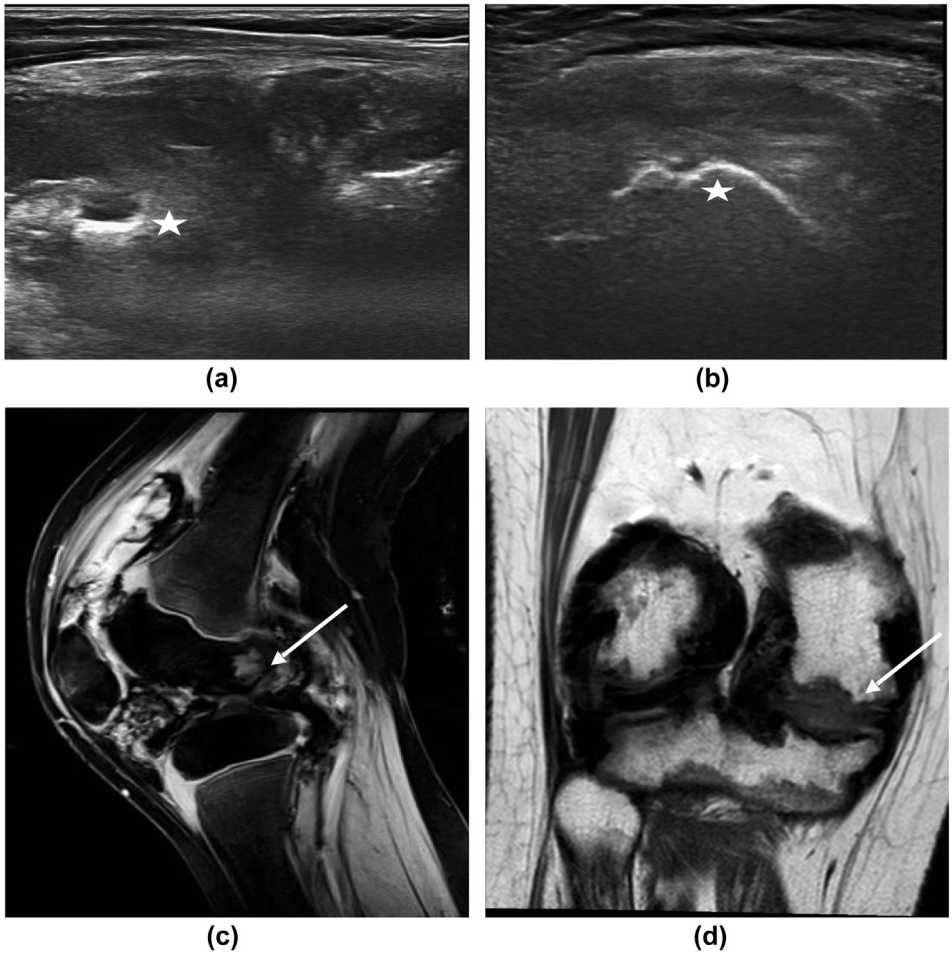

Figure 3 An 8-year-old boy with known haemophilic arthropathy of the left knee with a severe HJHS score of 14, underwent musculoskeletal US (US-US protocol), which revealed erosions (white asterisk) in the posterior sagittal medial (a) and posterior sagittal lateral (b) views and were further confirmed with MRI in the gradient sagittal (c) and T2 coronal (d) images (white arrows).

other two joints. The K3 window of the HEAD-US protocol did not detect any of these changes.

In the ankle, cartilage loss (partial thickness) was found in the L2 anterior sagittal lateral view and in the L2 posterior sagittal lateral views and this was detected by the TVC-US protocol and the US-US protocol. The HEAD-US protocol missed cartilage loss in these locations, as these views are not part of the standard HEAD-US protocol.

Subchondral cysts

None of the joints had subchondral cysts detected on MRI.

Reliability of the US-US protocol

All joints were screened with the US-US protocol by two independent radiologists within 48 hours of each other. The kappa coefficient for interobserver agreement for the soft-tissue and osteochondral changes was 1 (perfect agreement).

Duration

The median time taken to complete the TVC-US protocol was 20 minutes (range: 18–30 minutes), while for both the US-US and the HEAD-US protocols, it was 3 minutes (range: 3–5 minutes). In the present study series, the scans were performed in the order of the TVC-US, HEAD-US and US-US protocols. This perhaps would have resulted in a shorter duration for the latter, as the operator and patient gained familiarity with scanning.

Discussion

With an increasing use of regular replacement therapy (prophylaxis) of clotting factor concentrates to patients with haemophilia, there is a need to monitor joint outcomes with tools that are sensitive and comprehensive enough to detect early changes. Although MRI is the reference standard for such assessments, it is not practical for many reasons including access to technology, data acquisition time, and the need for sedation in very young children.[12,13]

US has emerged as an alternative imaging tool.[14,15] Although the protocol developed by the TVC-US is both comprehensive and sensitive and correlates well with MRI, it is time-consuming. Other POC-US protocols, such as the HEAD-US and the JADE protocols,[16] have also been developed to quantify arthropathy. As the POC-US protocols use specific predefined views, they are simpler and quicker; however, they are likely to miss out other potentially affected areas. The US-US protocol was designed to simplify the comprehensive TVC-US protocol by reducing documentation and maintaining the opportunity to screen the entire joint. The documentation of images was limited to five views, instead of the 38 views in the TVC-US protocol, thereby making it faster and easy to perform. When correlated with MRI, it was found that the TVC-US and US-US protocols detected synovial hypertrophy in all the joints. Synovial hypertrophy was more pronounced at the joint level (L2) and in the posterior aspect of the joint, rather than above (L1) and below (L3) the joint line. As the HEAD-US protocol predominantly scans above the joint level and does not scan the posterior aspect of the joint, it missed synovial hypertrophy in 20% of the joints. The TVC-US and US-US protocols did not miss any synovial hypertrophy as these protocols screen the entire joint and hence, there was an excellent correlation (100%) between them.

On US, haemosiderin appears as hypoechoic areas within the hypertrophied “isoechoic to hyperechoic” synovium (Fig 4). All the US protocols missed the mild deposition of haemosiderin that was detected on MRI in two knee joints. As Soliman *et al.* observed,[8,17] it is often difficult to

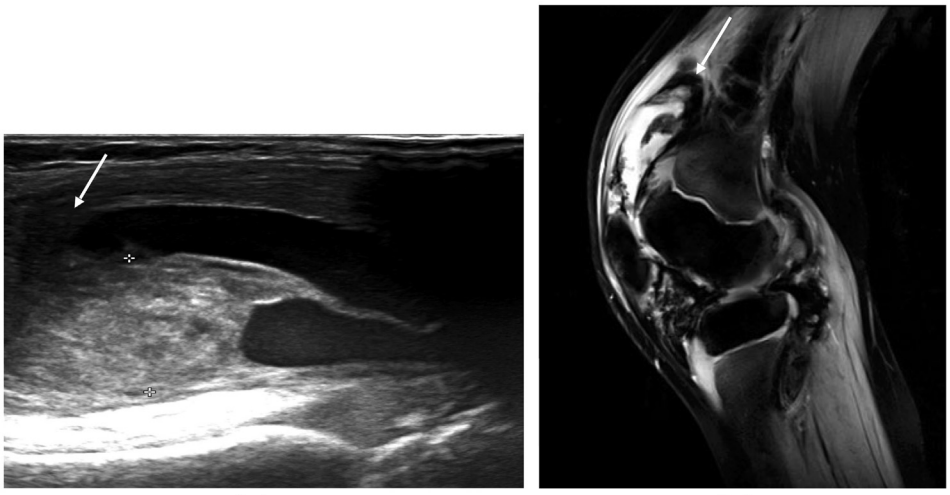

Figure 4 An 8-year-old boy with known haemophilic arthropathy with a severe HJHS score of 14, underwent musculoskeletal US (US-US protocol) of the left knee, which revealed grossly hypertrophied synovium (+) with marked hypoechoic areas (white arrow) within the anterior sagittal central view (a) and this corresponds to the hypointense area in the gradient sequences of MRI (b) confirming the gross haemosiderin deposition.

differentiate mild haemosiderin deposition from mild synovial hypertrophy and minimal joint fluid on the US, and hence haemosiderin can be missed on the US when present in small amounts.

In order to simplify imaging and documentation, the HEAD-US protocol screens only one window (K3 in the knee and A1a and A1b in the ankle) for osteochondral changes. In this study, four joints had osteochondral changes on the MRI, which were detected by the TVC-US and the US-US protocols, but were not detected by the HEAD-US protocol, as there were no changes in the K3 of the knee and A1a and A1b window of the ankle. The presumption that a single window is sufficient and representative of the entire joint is incorrect, and may lead to erroneous conclusions when following up or comparing data.

Unlike MRI, which images the entire joint, US cannot be used comment on osteochondral changes in the centre of the joint, as it is able to screen only the periphery. It cannot be assumed that changes in the periphery will reflect changes in the centre of the joint. One ankle joint had a central lesion that was missed on US, but this joint also had another lesion in the periphery, that was detected by the US-US and the TVC-US protocols.

In an earlier study by Dorea *et al.*, the TVC-US was found to be highly sensitive (>92%) for assessing synovial hypertrophy and haemosiderin in both the ankles and the knees; however, the overall specificity for the soft-tissue domain was found to be suboptimal (specificity was 50% for diagnosing synovial hypertrophy in the ankle and 67% for haemosiderin deposition in the knee) [10]. In patients with early arthropathy (Pettersson score of 0), the sensitivity of the US for detection of effusion was poor <50%.[18] In the current study, the US missed effusion in 25% of the joints.

Most osteochondral changes seen on the MRI were detected by the US-US and the TVC-US protocols. Dorea *et al.* also found that a comprehensive ultrasonographic examination had high sensitivity for osteochondral changes, but was relatively non-specific (ankles=46%, knees=50%) [10]. Keeping these observations in mind, they suggested that the interpretation of ultrasound findings in haemophilic arthropathy should be done with caution [16]. None of the joints in the present study had subchondral cysts in the MRI. Hence, the reliability of US in identifying subchondral cysts has not been confirmed.

The TVC-US was developed keeping the MRI as the reference standard. It was developed by radiologists familiar with both imaging methods. In order to get a comprehensive assessment of the joint on US, it was necessary to document as many views as possible to represent all the changes seen on the MRI adequately. Documentation of images with proper labelling makes it a protracted process. The simplified POC-US protocols, such as the HEAD-US protocol, were developed such that they can be used after focused training and can provide information quickly at the bedside or in a clinic. Although they have been shown to be useful in identifying abnormalities and in the follow-up of patients, they can miss several findings in the joint, as shown in the present study. Thus, the POC-US protocols have limited application in serial assessment of joint arthropathy, as they do not scan the entire joint and hence, do not pick up all changes in the joint. The small sample size in the present study is a limitation, which can be addressed in future studies.

In conclusion, in this prospective study, a new protocol, the US-US protocol, was established. This has formed a useful bridge between the comprehensive, but time-consuming TVC-US protocol and the limited point of care HEAD-US protocol. The study has shown that the US-US protocol is as rapid as the shorter POC-US protocols and nearly matches MRI in its comprehensive coverage. The US-US protocol is as sensitive as the MRI in identifying most soft-tissue and osteochondral findings and is superior to the POC HEAD-US protocol. This could, therefore, be used as a tool for regular evaluation of joints of patients with haemophilia.

Conflict of interest

The authors declare no conflict of interest.

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