Contrast enhanced Voiding Urosonography (ce-VUS) as a radiation-free technique in the diagnosis of vesicoureteric reflux: Our early experience

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ABSTRACT

Objective: Contrast-enhanced ultrasound has become increasingly utilised as an alternative imaging modality for the diagnosis of vesicoureteric reflux (VUR) in paediatric patients. The study objective is to evaluate the efficacy of contrast enhanced Voiding Urosonography (ce-VUS) compared with fluoroscopic micturating cystourethrography (MCU) in the detection of VUR.

Methods: This prospective study was carried out between July 2011 and January 2013 on paediatric patients who underwent MCU. All consented patients would undergo ce-VUS prior to MCU. We documented the epidemiology details, the number of Kidney-Ureter (K-U) unit studied, baseline renal and bladder sonogram, as well as presence of VUR on ce-VUR. The technique for ce-VUS was standardized using normal saline to fill the bladder prior to administration of SonoVue® (2.5 ml) to assess the kidney-ureter (K-U) unit. Dedicated contrast detection software was used to discern the presence of microbubbles in the pelvicaliceal system (PCS). The findings were then compared with MCU.

Results: 27 paediatric patients were involved in the study [17 males (63%) and 10 females (37%)] involving 55 K-U units (one patient had a complete duplex system). MCU detected VUR in 10 K-U units while ce-VUS detected VUR in 8 out of the 10 K-U units. There were 2 false negative cases (both Grade 1) with ce-VUS. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of ce-VUS were 80%, 98%, 95%, 89% and 96%, respectively.

Conclusion: ce-VUS is a sensitive and specific radiation-free alternative for the detection of VUR in the paediatric population.

INTRODUCTION

Vesicoureteric reflux (VUR) is a condition, which occurs in 1-2% of the general population and may affect between 30-40% of children with recurrent urinary tract infections (UTIs).[1,2] Since the condition can lead to other morbidities such as hypertension and chronic kidney disease, early diagnosis is paramount in preventing such sequelae.[3,4]

The principal diagnostic imaging techniques for detection of VUR in children are micturating cystourethrography (MCU) and/or radionuclide cystography (RC).[2,4-6] Since both imaging techniques utilise radiation, a radiation-free alternative is greatly desirable and thus, ultrasound of the bladder, using echo-enhancing materials, has gradually been developed since the 1990's.[4,5,7,8]

The use of air bubbles administered intravesically to detect the presence of VUR was based on the principle of increased echogenicity of the air bubble, itself. However, even though the technique was as sensitive as MCU or RC, air bubbles were subjected to artefact as well as instability.[9,10] The emergence of commercially available echocontrast materials (such as sonicated albumin, galactose based SH U 508, Levovist®, Echovist®,and SonoVue®) appeared to improve the sensitivity and specificity of echocontrast sonography (ce-VUS) in detecting VUR.[5,7,11-13]

Using SonoVue® as contrast material, we aimed to determine the efficacy of ce-VUS in diagnosing VUR, with MCU as the gold standard. We also sought to determine methods that would improve the sensitivity and specificity of ce-VUS in detecting VUR.

MATERIALS AND METHODS

Subject selection

This prospective study was approved by our Institutional Review Board. We obtained both verbal and written consent from either the child's parents or guardian prior to enrolling any subject in this study. Between July 2011 and January 2013, a total of 27 children (17 males and 10 females), who required MCU at our centre, were enrolled in the study. Their age ranged from 1 month to 16 years (mean age: 25 months). Whenever both ce-VUS and MCU could not be performed on the same day, the case was excluded.

The most common clinical indication for the study was the persistence of antenatal hydronephrosis (n=12) on postnatal ultrasound. This was followed by recurrent UTIs (n=8), follow-up assessment of VUR prior to discontinuation of medical therapy or following surgical management (n=4), and neurogenic bladder (n=3). One patient had a complete

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Fig. 1: ce-VUS in a 2-year-old boy with right duplex kidney. a Pre-contrast scan of the right kidney shows dilated lower moiety renal pelvis (black arrow) and normal upper moiety renal pelvis (black arrowhead). b Post-intravesical administration of SonoVue reveals the lower moiety pelvis is filled with contrast whereas the upper moiety pelvis is dilated with no contrast within. c Upon applying the contrast software, the contrast within the dilated lower moiety becomes more conspicuous, accentuated by the black subtraction of the kidney. MCU revealed a Grade III VUR of the right lower moiety.

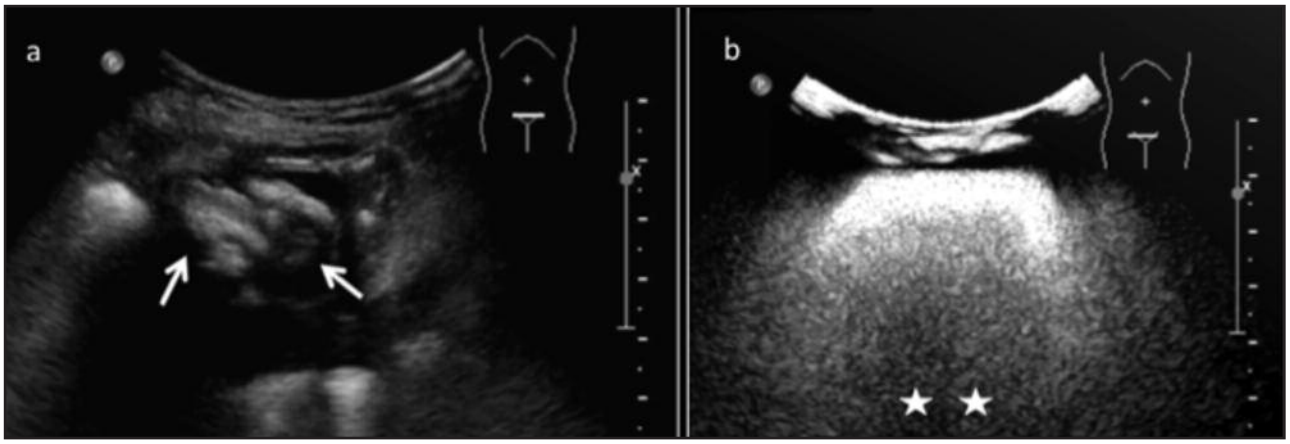

Fig. 2: ce-VUS in a 6 months old boy with recurrent urinary tract infection. a During the initial phase of intravesical contrast administration the contrast appears to be insoluble in saline and this produces posterior shadowing (white arrows) later, b the contrast mix more diffusely with the saline but still produces posterior shadowing at the retrovesical region (white stars).

duplex kidney but none had a solitary kidney. Therefore, a total of 55 kidney-ureter (K-U) units were evaluated for reflux.

Methodology

ce-VUS technique

ce-VUS was performed with the Phillips IU-22 (Eindhoven, The Netherlands), equipped with C5-2MHz convex transducer. Specific contrast detection software with mechanical index of 0.7 was used.

The child was placed in either prone or supine position during the procedure. Baseline ultrasound was performed in the prone position in order to assess renal size, parenchymal echogenicity, pelvicaliceal and/or ureteric dilatation, and in particular, to exclude the presence of dilated ureters at the retrovesical space. Using a 20 ml syringe, saline was then slowly instilled into the bladder via a urethral catheter, while the child was in the supine position, until the bladder volume reached the estimated age-related maximum. This was estimated using the following equation:

Bladder capacity volume (ml) = [age (years) + 2] x 30ml [14].

Using its solvent, SonoVue® was diluted into a 5ml solution. A total of 2.5ml of the SonoVue® solution was administered into the saline-filled urinary bladder. The echogenic contrast was traced along both ureters, as well as the pelvicaliceal system, by using the contrast software. The distal ureter, the proximal ureter, and the renal pelvis were observed intermittently (similar to intermittent screening during MCU). The renal pelvis was imaged in two planes (longitudinal and transverse) to ensure that any observed echogenic foci were not secondary to artefact. The contrast button was intermittently applied to further accentuate the presence of contrast in the K-U unit. Images were only documented during the bladder-filling phase, as evaluation of the micturition phase was not performed.

Documentation of the sonographic findings was done prior to MCU to avoid bias. The VUR graded was based on previous literature: [2] Grade I, echoes in the ureter above ureteral orifice; Grade II, echoes extending up to the renal pelvis without pelvis and ureter dilatation; Grade III, echoes extending up to the renal pelvis and calyces (non-dilated) with mild dilatation of the ureter; Grade IV, echoes in dilated ureter, renal pelvis and calyces; and Grade V, echoes in markedly dilated ureter, renal pelvis and calyces. The bladder was then emptied via the catheter and child proceeded to the fluoroscopy room for the MCU examination.

Micturating cystourethrography
MCU was performed using the digital fluoroscopy Toshiba KXO-80G system, Tokyo, Japan. It was performed by radiology trainees, who were blinded to the ce-VUS result. Based on our institution's standard operating procedure (SOP), it was performed using room temperature saline mixed with contrast agent (Ultravist® 300mg/ml) to obtain a 30% concentration and introduced into the bladder by gravity drip. VUR seen on MCU was graded according to the International Reflux Study Committee Classification.[15] Images were recorded and stored as hardcopy films or saved in our PACS system (Medweb®) via a DICOM DBOX6000 image viewer system.

Parents were instructed to call the investigator if the child developed any of the known adverse effect of contrast administration such as haematuria or skin rashes within 48 hours of the examination.

Data Analysis
The diagnosis of VUR by ce-VUS was compared with the diagnosis achieved with MCU and the sensitivity, specificity, accuracy, positive predictive value and negative predictive values of ce-VUS was calculated.

RESULTS

Out of 55 K-U units studied, ce-VUS detected eight of the 10 K-U units that demonstrated VUR on MCU (Fig. 1). There were two false negative cases (both cases were Grade I VUR). Table I shows the concordance between ce-VUS and MCU findings. The sensitivity and specificity of ce-VUS in the detection of VUR was 80% and 98%, respectively. The overall accuracy was 95%. ce-VUS had a positive predictive value of 89%, and a negative predictive value of 96%.

We further analysed the concordance between ce-VUS and MCU with respect to reflux grading. For this reason we only analysed the reflux cases that were found to be true positives using ce-VUS. ce-VUS and MCU findings were in agreement with VUR grades in six of eight cases (75%). ce-VUS indicated a lower grade than MCU in two cases (Table II).

There were no adverse effects related to the ultrasound contrast observed during the examination or reported by the parents during the 48 hours after the examination.

DISCUSSION

The majority of our cohort came from the group that was diagnosed with antenatal hydronephrosis. Our standard protocol for these cases is that to perform post-natal ultrasound at first week of life and again at the age of one month, before deciding on the need to proceed to MCU. Persistence of moderate and gross hydronephrosis was then investigated with MCU since the incidence of VUR in antenatal hydronephrosis is between 9-15%.[16,17] For suspicion of obstructive uropathy such as pelviureteric junction obstruction, we performed a radionuclide (RC) study followed by MCU only in equivocal cases.

The intermittent nature of VUR leads to difficulty in determining the best imaging modality to diagnose the condition.[18] Current diagnostic techniques, such as MCU or RC, involve radiation exposure, which precludes continuous imaging acquisition. MCU is considered the technique of choice in children who have suspected VUR,[2] especially when excluding the diagnosis of posterior urethral valves in boys whilst RC is normally used in follow-up cases and in women of childbearing age.[1,19]

Previous studies established ultrasound as an alternative method for the diagnosis of VUR but it has less sensitivity and specificity as compared with MCU or RC.[20,21] Addition of colour Doppler to ultrasonography was found to be comparable to RC in detecting VUR.[22] Then, followed the various contrast-enhanced techniques since the year 1990's.

Sonicated albumin was among the first ultrasound contrast material studied.[11] Later, first generation contrast-enhanced materials such as Echovist® and Levovist® were introduced but were used primarily in echocardiography prior to their utilisation for intravesical assessment in children.[5,7,11-13] Together with the use of Doppler ultrasonography, these first generation contrast materials allowed for longer sonographic assessment times and improved depiction of fluid propagation from the bladder into pelvicaliceal system.[23]

The later development of tissue and contrast-specific harmonic imaging further increased the sensitivity and specificity of ce-VUS.[6-8,18,24-26] Contrast-specific harmonic imaging also improved the sonographer's confidence in excluding VUR. This fact was reflected in our study, as the number of our true negative cases was high.

Darge *et al.* devised a comprehensive reflux grading for ce-VUS. Their reflux grading system is similar to the MCU grading system with an additional parameter involving reflux into a primary dilated or non-dilated ureter and/or pelvicaliceal system.[7,12] A few other studies have concluded that grading of ce-VUS is comparable to MCU grading.[2,11,24,27] We did not include the additional parameter of 'degree of ureteric dilatation' in our study but, instead, used a grading system based on the MCU reflux grading system. In our study, two Grade V reflux cases diagnosed by MCU were under-diagnosed as Grade III on ce-VUS.

Although ce-VUS has been shown to pick up a higher grade of VUR compared with MCU, this finding was not supported by our study.[12,18,24] This may be explained by the fact that we did not consider primary dilatation of the ureter in our assessment. We found that consistent visualisation of contrast within dilated ureter(s) was difficult as the visualization was subjected to technical pitfalls such as obliteration of the ureters due to air-filled bowel.

Our study had several additional limitations. Our false negative cases were both Grade I VUR. In retrospect, we found that both cases showed intense posterior shadowing at the retrovesical space, obscuring the region where the distal ureters were located. This finding could have contributed to these two false negative interpretations, as most Grade I VUR cases occur at the distal ureters. In addition, we experienced posterior shadowing at the base of the bladder during our procedure due to the strong echogenicity of the contrast material. Posterior shadow in the bladder base has been

known to obliterate visualization of contrast within a dilated distal ureter. [5,18] The contrast appeared insoluble in saline upon its initial introduction into the bladder and this produced a strong acoustic shadow (Fig. 2). When it was transient, the contrast did not obscure the retrovesical region. However, when it was persistent (and it could take 5-10 minutes before the contrast completely mixed with the saline within the bladder) it may have obscured the retrovesical region and ultimately the contrast within a dilated distal ureter. This suggests that a Grade I VUR can be missed whenever there is no obvious reflux into the upper caliceal system. Unfortunately, we did not consistently record this observation while performing ce-VUS.

This particular pitfall of ce-VUS, i.e., posterior shadowing at the bladder base, can be minimized by a recent modification of the technique proposed by Duran et al. Premixing the contrast with a bottle of saline prior to intravesical administration allowed visualization of the posterior bladder in 99% of their cases.[28] The passive introduction of contrast into the bladder appeared to cause slow mixing of contrast and saline preventing the persistent strong echogenicity that can cause significant posterior shadowing.

Assessment of the urethra is incorporated in the MCU protocol since one of the causes of VUR is a posterior urethral valve. This component of the MCU protocol can also be performed with ce-VUS and thus, VUR can also be assessed during voiding.[18,28] However, we did not perform this assessment in our study as we wanted to concentrate in the assessment of the pelvicaliceal system only for this study. Also we did not want to re-catheterize the child again for MCU.

CONCLUSION

ce-VUS is a sensitive and specific technique for diagnosing VUR that eliminates the need for radiation exposure in children. Its longer dynamic imaging acquisition also suits the intermittent nature of VUR. Several technical modifications of ce-VUS have been developed to increase the sensitivity and specificity of this technique in diagnosing VUR and minimising imaging pitfalls. VUR grading in ce-VUS is comparable with reflux grading on MCU.

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