Bladder Ultrasound in the Evaluation of the Efficacy of Dextranomer/Hyaluronic Acid Injection for Treatment of Vesicoureteral Reflux

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ABSTRACT: *Purpose.* To determine whether sonographic examination of subureteral implants after endoscopic dextranomer/hyaluronic acid (DHA) injection would help to evaluate the efficacy of this method in the treatment of vesicoureteral reflux.

Materials and Methods. Thirty-six patients (49 ureters) who underwent endoscopic subureteral DHA injection were evaluated using voiding cystourethrography (VCUG) and bladder sonography for a mean duration of 2.1 years (range, 3 months to 6.5 years) after treatment. Patient records—including the results of VCUG, renal sonography, Dimercapto succinic acid (DMSA) scintigraphy, and periodic urinary analysis—were also reviewed to determine the outcome of treatment.

Results. Reflux was corrected in 43/49 (88%) ureters (complete cure in 38, downgrading of reflux in 5). No change was noted in 6 (12%) ureters on VCUG. The reflux was found to be corrected in 19/22 (86%) ureters, with the implants clearly identifiable on sonography. However, reflux was documented in only 3/27 (11%) ureters, around which no implant was seen on sonography.

Conclusion. The identification of the implant in the subureteral region by bladder sonography correlated with resolution of reflux in the early postinjection period. On the other hand, the majority of the implants disappeared on sonography in the long term despite correction of reflux. Therefore, we believe that the use of bladder sonography is not useful in the evaluation of patients in long-term follow-up. © 2007 Wiley Periodicals, Inc. *J Clin Ultrasound* **35**:357–362, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jcu.20359

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Subureteral injection of implant materials is an important therapeutic alternative to correct vesicoureteral reflux (VUR) in children. The principle of submucosal injection is identical to that of an open ureteroneocystostomy that aims to create solid support behind the refluxing intravesical ureter.[1] Dextranomer/hyaluronic acid (DHA) copolymer is a novel substance that has favorable properties for endoscopic treatment of VUR.[2] It has been approved in the United States recently and has proved to be effective and well tolerated during long-term follow-up in children, even in those with dilating reflux.[3–6]

Being a noninvasive and widespread imaging modality, renal/bladder sonography has been widely used to determine the size and precise location of the subureteral mass as well as for the evaluation of hydroureteronephrosis after the injection.[3,5,7–10] Although some investigators have suggested that the size and volume of the implant as assessed with imaging studies may be an important factor in predicting the outcome of the procedure, this assumption could not be supported entirely.[3,7,8] Recently, Herz et al[9] reported that sonography was accurate in identifying the presence of subureteral implant and correlating implant stability on renal sonography with correction of reflux after polydimethylsiloxane injection. In the current study, we describe the sonographic assessment of a subureteral implant

TABLE 1
Indications for Subureteral Injection of DHA Copolymer in Low-Grade Vesicoureteral Reflux

Grade of Vesicoureteral Reflux	Mean No. of Months between Diagnosis and Treatment (Range)	Indication for Subureteral Injection
Grade I (n = 7)	37.1 (2*–84)	Renal scarring + contralateral agenesis (n = 1)* Renal scarring + recurrent UTI (n = 3) Recurrent UTI (n = 3)
Grade II (n = 9)	33.4 (8–96)	Recurrent UTI (n = 5) Renal scarring + recurrent UTI (n = 2) Contralateral high-grade reflux + recurrent UTI (n = 2)

Abbreviation: UTI, urinary tract infection.
* Patient with solitary kidney who underwent subureteral injection 2 months after diagnosis of vesicoureteral reflux.

after endoscopic DHA injection. The purpose of the study was to determine whether the sonographic appearance of a subureteral implant may help to evaluate the efficacy of this DHA injection in the treatment of VUR.

PATIENTS AND METHODS

During a period of 6.5 years (1996–2003), 36 patients (49 ureters) who underwent endoscopic subureteral DHA (Deflux; Q-MED AB, Uppsala, Sweden) injection were included in the study population. There were 21 girls and 15 boys with a mean age of 6.7 years (range, 3 months to 14 years). According to the classification system adopted by the International Reflux Study Committee,[11] the following reflux grades were found before the intervention: grade I in 7, grade II in 9, grade III in 24, grade IV in 6, and grade V in 3 ureters. Reflux was unilateral and bilateral in 24 and 12 children, respectively. Bladder dysfunction accompanied VUR in 19 patients (24 ureters), all of whom were treated with anticholinergic therapy before the DHA injection. Associated anatomic abnormalities were noted in 3 patients (bladder exstrophy in 1, posterior urethral valve in 2; 4 ureters). Two patients had previous failed ureteral reimplantation for the treatment of VUR.

The indications for endoscopic DHA injection were high-grade VUR, low-grade VUR with renal scarring on nuclear imaging, or recurrent urinary tract infection despite antibiotic prophylaxis (Table 1). All patients underwent subureteral injection of a mean volume of 0.9 ± 0.4 ml DHA under general anesthesia. Endoscopic subureteral injection was performed according to the technique described by O'Donnell and Puri.[12] Prophylactic antibiotics were continued until resolution of reflux was documented. No procedure-related complications were observed in any patient. A repeat injection was required in 1 ureter.

All children who underwent endoscopic subureteral DHA injection were evaluated via voiding cystourethrography (VCUG) and bladder sonography a mean of 2.1 years (range, 3 months to 6.5 years) after treatment to determine the presence of subureteral implant and the final status of VUR. Radiologic VCUG study was performed using a regular technique with a single filling. Patient records including renal sonography, DMSA scintigraphy, and periodic urinary analysis were also reviewed to determine the final therapeutic outcome. Sonography was performed using one of the scanners, an HDI 5000 (Philips, Bothell, WA) equipped with broadband transducers (5–8- and 2–5-MHz convex transducers, depending on the child's age) or Siemens Elegra (Siemens Ultrasound, Mountain View, CA) equipped with multifrequency transducers (7.5-MHz linear or 3.5-MHz convex transducers, depending on the child's age). All sonographic examinations were performed by the same sonologist (S.S.Ö.) blinded to the VCUG results. The children underwent sonographic examinations with distended bladders. The bladder and ureterovesical junction were sonographically evaluated in at least 2 anatomic planes. Any solid nodular or oval-shaped space occupying structure outside the ureteral lumen, but at or around the ureterovesical junction with an echogenicity equal to or slightly greater than that of bladder wall, was accepted as the implant.

The resolution of reflux was documented with a negative VCUG. Downgrading of reflux indicated a minimum 2-grade decrease according to the International Reflux Study classification in asymptomatic patients with stable renal function. Thus, complete resolution or downgrading

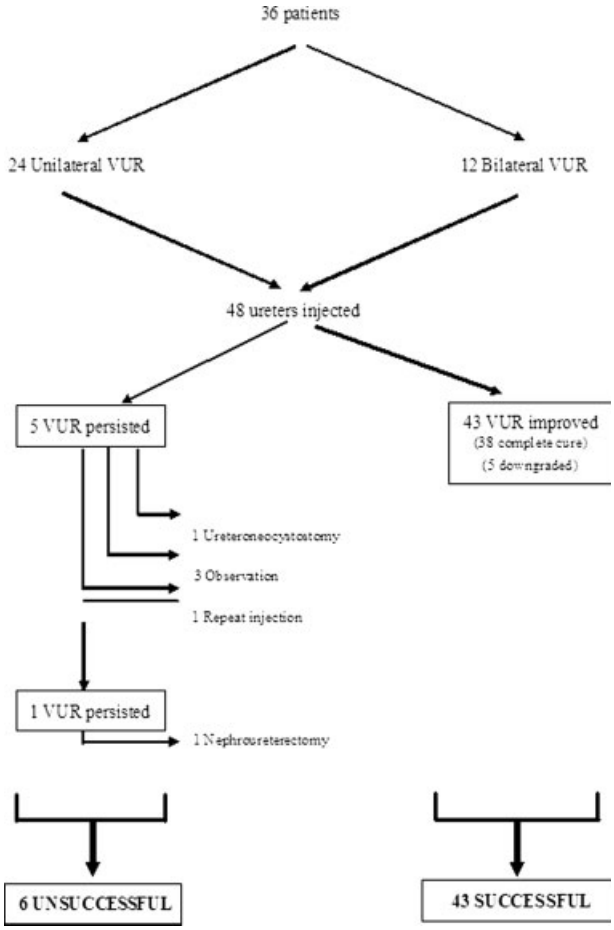

FIGURE 1. Flowchart of clinical progress after DHA injection.

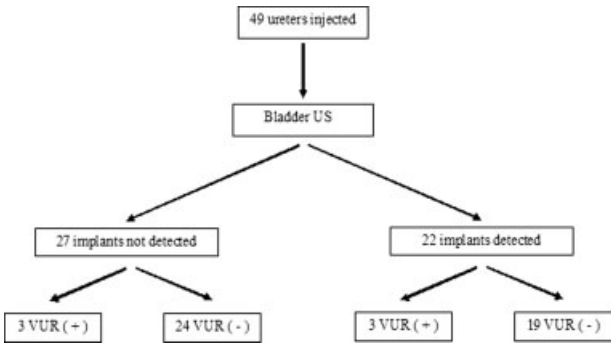

FIGURE 2. Presence of DHA implant identified on sonography.

of VUR with no clinical or radiologic deterioration was considered a successful result. Using these data, the correlation of the success of treatment with sonographic demonstration of the implant was investigated.

RESULTS

After a mean follow-up of 2.1 years (range, 3 months to 6.5 years), reflux was found to be corrected in 43/49 (88%) ureters (complete cure in 38, downgrading in 5). No change was noted in 6 (12%) ureters (Figure 1). DHA injection had a success rate of 100% and 81.1% in patients with nondilating (grade $\leq$2) and dilating (grade $\geq$3) reflux, respectively.

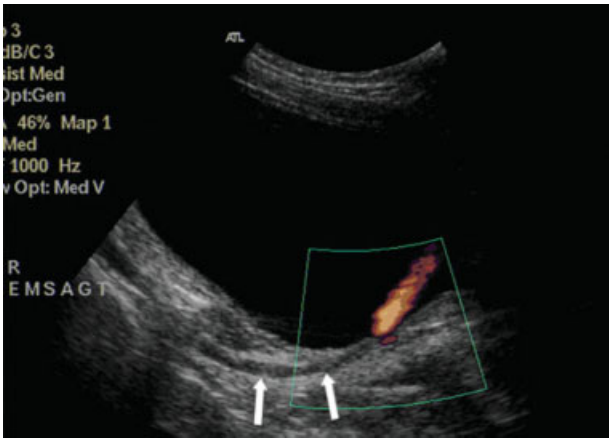

FIGURE 3. Right parasagittal power Doppler sonogram along the right distal ureter (arrows) shows the urinary discharge. No subureteral implant was detected at the expected position beneath the ureter at postoperative month 36.

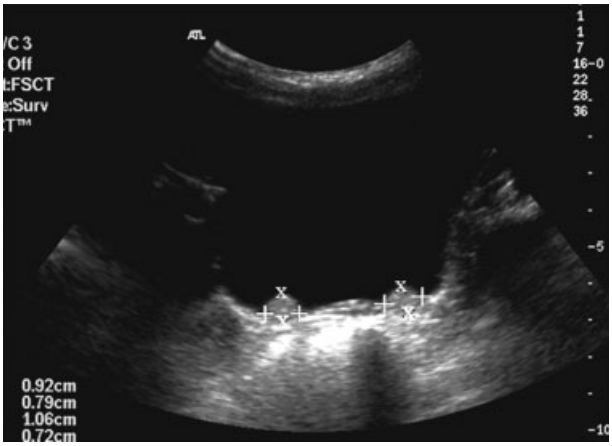

FIGURE 4. Transverse sonogram of the bladder shows bilateral implants (calipers) 1 month after injection.

There were 27 (55 %) ureters in which the implant could not be visualized on sonography (Figures 2 and 3). However, only 3 of these 27 ureters had persistent reflux as determined with VCUG.

A DHA implant was identifiable in 22/49 (45%) ureters on bladder sonography (Figures 4 and 5). In 19 of these 22 ureters, there was no reflux. On the other hand, there were 3 ureters with persistent reflux, despite the identification of the implant by sonography (Figure 2).

The sonographic examinations performed in different periods during follow-up demonstrated

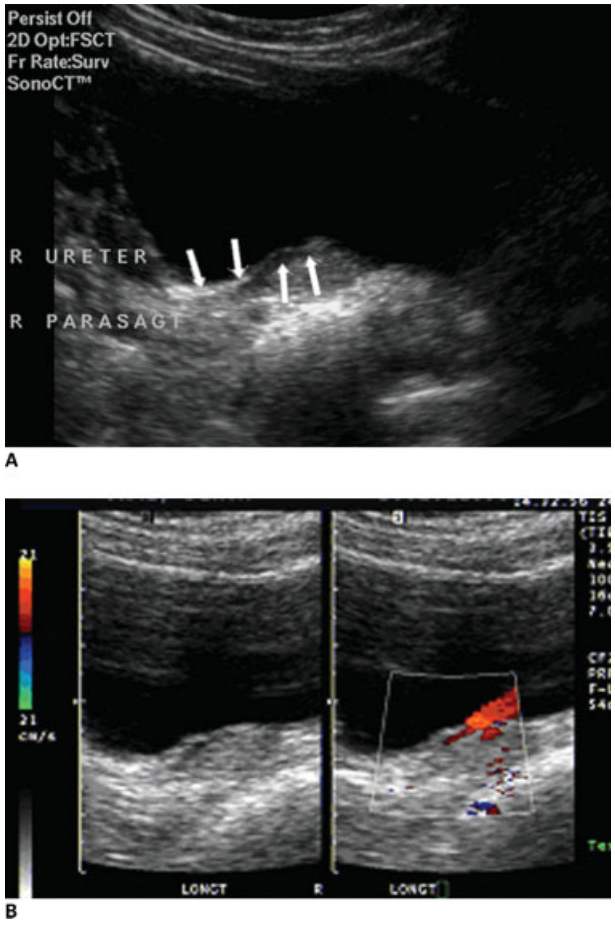

FIGURE 5. (A) Parasagittal sonogram along the long axis of the right ureter (arrows) shows the precise location of the DHA implant beneath the ureterovesical junction; the distal portion of the ureter is lifted up and is tapered by the DHA implant beneath. **(B)** Color Doppler sonogram through the same plane shows the ureteral urine discharge into the bladder.

TABLE 2
Sonographic Identification of the Implants at Different Periods Following Injection

Time Elapsed between Injection and Sonographic Examination	No. of Implants Identified
0–1 month	12/15 (80%)
1–3 months	15/18 (83%)
3–12 months	19/29 (66%)
Overall mean 2.2 years	22/49 (45%)

decreasing rates of sonographic identification of the implants (Table 2). The initial rate of 80% at the first postoperative month decreased to 45% at mean of 2.2 years.

DISCUSSION

Subureteral endoscopic injection of DHA is a promising alternative for the treatment of VUR

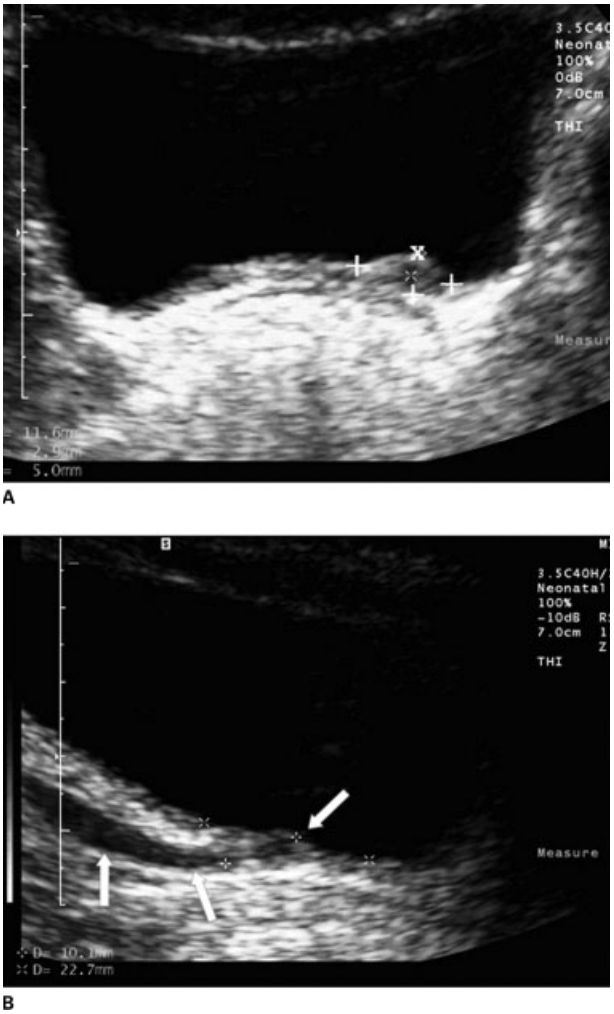

FIGURE 6. (A) Transverse sonogram shows the DHA implant (calipers) on the left side of the bladder floor in a patient with persistent reflux after injection. **(B)** Parasagittal sonogram along the axis of the ureter in the same patient shows the ureterovesical junction (arrows) but does not show any implant.

in children. It is a biodegradable substance with a larger particle size, thus eliminating the risk of migration. Moreover, it has been suggested that this material induces fibroblastic growth, which leads to endogenous tissue augmentation.[2,13] Despite encouraging results with a subureteral injection technique, there are concerns about the long-term efficacy of this method, and clinical follow-up with imaging studies has been recommended. Although VCUG or radionuclide cystography are currently the choices for the assessment of reflux, radiation is still a concern. This concern limits the use of these techniques, particularly in children who should undergo subsequent follow-up examinations. Therefore, most clinical follow-up protocols include a more selective use of VCUG when the initial assessment is negative. Thus, sonography is the most

available option, because it is a simple and ideal method to rule out obstruction and to evaluate the injection site.

After a mean follow-up of 2.1 years, a DHA implant could not be visualized in 27/49 ureters (55%) in this series. The increasing rate of disappearance of the implants on sonographic examinations performed over different periods during follow-up may be attributed to temporal reduction in the volume of DHA implants. However, this observation may be considered discordant with those of Puri et al,[5] who found no change over time in patients with corrected reflux. It is noteworthy that, only a minority of patients in that series (11/113 [9.7%]), had a 1-year follow-up. In fact, this reduction in the volume of DHA was shown earlier both clinically and experimentally. Stenberg et al[13] demonstrated a 23% reduction in the volume of DHA implant due to the hydrolysis of dextranomer microspheres over a period of 1 year in rats. Kirsch et al,[3] using a volumetric analysis with sonography, found a 20% volume reduction within the first 3 months after DHA injection in children. This reduction probably extends beyond the first 3 months, resulting even in total disappearance of the implant on sonography in the long term.

It is noteworthy that despite the absence of sonographic evidence of the DHA implant in 27 ureters, there was no reflux in 24 of them, suggesting that the disappearance of the implant itself does not necessary indicate the presence of reflux. This finding has also been reported in previous studies using different injection materials. Herz et al[9] reported that the absence of subureteral polydimethylsiloxane implant on sonography was neither sensitive nor specific for persistence of reflux. They stated that the erosion of the overlying mucosa, experience of the sonographer, or insufficient amount of the implant to allow for sonographic detection, may result in inaccurate assessment of subureteral implant by sonography.[9] Blake and O'Connell[7] stated that soft tissue distortion or swelling caused by teflon particles might be responsible for modifying the ureteral orifice sufficiently to prevent reflux despite the absence of granuloma formation. Based on their experimental studies, Stenberg and colleagues[2,13] stated that hydrolysis of dextranomer microspheres causes a volume reduction following injection but the production of endogenous collagen between the microshperes results in tissue augmentation. We believe that this tissue augmentation contributes to the antireflux mechanism at the ureterovesical junction in the long term, and this may be a good explanation for the inconsistency between the absence of the implant and the presence of reflux.

DHA implant was identified in 22/49 (45%) ureters after a mean follow-up of 2.1 years, and 19 (86%) of these had correction of reflux. The presence of the implant strongly correlates with resolution of reflux. There were 3 refluxing ureters despite an implant identified by sonography. In those ureters, the implant was found to be displaced on sonography (Figure 6). This finding was also reported by Herz at al,[9] who found the implant to be medial or lateral to the long axis of the ureter on repeat injections in patients with persistent reflux after polydimethylsiloxane injections. Moreover, as noted by Kirsch et al,[3] local migration should also be considered after DHA injection in children.

To our knowledge, this is the first study to investigate the relation between the status of DHA implant on bladder sonography and the success of treatment in the long term. We believe that the majority of implants are not seen on sonography because of the temporal reduction in implant volume that is most likely due to the replacement of dextranomer particles by collagen. Thus, these tissue reactions may be modifying the ureteral orifice sufficiently to prevent reflux in the long term.

In conclusion, the absence of the implant on sonography is not useful as an indicator of persistent reflux, especially in long-term follow-up. On the contrary, its presence in the subureteral region strongly suggests that reflux has been corrected after injection treatment with DHA. Thus, bladder sonography may only be used in the early postinjection period as a screening test to select patients who will further require a VCUG to exclude reflux if the implant cannot be demonstrated. On the other hand, our data do not support the reliability of sonography in long-term follow-up.

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