



# Efficacy of Bladder Ultrasound in Prediction of Resolution of Vesicoureteral Reflux After Endoscopic Subureteral Hyaluronic Acid/Dextranomer (Deflux) Injection

Hamdy Aboutaleb, Diaa Bakry Eldib, Yasser Farahat, Tamer A. Abouelgreed, and Fouad Zanaty

<b>OBJECTIVE</b>	To evaluate the efficacy of bladder ultrasound (US) in predicting the resolution of vesicoureteral reflux (VUR) after subureteral endoscopic Deflux injection in low-grade vs high-grade VUR patients.
<b>MATERIALS AND METHODS</b>	Between 2014 and 2020, 160 children (220 ureters) were administered subureteral Deflux injection for treatment of primary VUR. The mean age at surgery was 72 months. Low-grade reflux (grades II-III) was observed in 190 ureters and high-grade reflux (grades IV-V) was observed in 30 ureters. Bilateral surgery was performed in 60 patients. All patients had follow-up using bladder US and voiding cystourethrography (VCUG) at 3 months and 12 months. Outcome included identification of Deflux mounds by bladder US and correlation of Deflux mounds identified with radiographic success rates of VUR on VCUG.
<b>RESULTS</b>	Single Deflux injection showed radiographic success rates in 98% of low grade reflux patients and 26.7% of high grade reflux patients at last follow-up. Bladder US was able to detect Deflux mounds in 89% of low grade reflux and 43.3% of high grade reflux patients at last follow up. Our study demonstrated higher sensitivity, Positive predictive value and accuracy in Deflux detection by bladder US in low grade reflux vs high grade reflux patients.
<b>CONCLUSION</b>	Bladder-US was highly sensitive for detection of Deflux implants. Bladder-US could be adjusted in follow-up of patients with low-grade reflux treated by Deflux injection, while VCUG could be preserved for follow-up of high-grade reflux, this will lead to reduction of unnecessary radiation exposure during VCUG for children with low grade reflux. UROLOGY 165: 299–304, 2022. © 2022 Elsevier Inc.

Vesicoureteral reflux (VUR) represents the most common pediatric anomaly of the urinary tract, with increased risk of pyelonephritis and

subsequent renal scarring.<sup>1,2</sup> It affects about 1%-3% of all children.<sup>3,4</sup> It can be managed using the widely known, minimally invasive procedure of endoscopic injection of hyaluronic acid/dextranomer (Deflux). The Deflux injection is considered the first-line surgical intervention for effective VUR correction.<sup>5,6</sup> Voiding cystourethrography (VCUG) is the diagnostic examination of choice for pediatric patients with suspected VUR or follow-up of patients after surgical intervention. However, it is associated with the risk of radiation exposure in pediatric patients. The fluoroscopy time and the number of radiographs taken during the procedure vary between institutions depending on the operator's preference and experience.<sup>7,8</sup> Renal/bladder ultrasound (KUB-US) is noninvasive and widespread imaging modality that has been widely used to determine the size and precise location of the subureteral injection as well as for the evaluation of hydronephrosis after the injection. Its advantages include its

Abbreviations: US, Ultrasound; VCUG, Voiding cystourethrography; VUR, Vesicoureteral reflux; KUB-US, Kidney-Ureter-Bladder Ultrasound; PPV, Positive predictive value; NPV, Negative predictive value; CI, Confidence interval; LR+, Positive likelihood ratio; LR-, Negative likelihood ratio

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From the Urology Department, Menoufia University, Shibin El Kom, Egypt ; the Radiodiagnosis Department, Faculty of Medicine, Benha University, Benha, Egypt; the Urology Department, Tanta University, Tanta, Egypt; the Urology Department, Al-Azhar University, Cairo, Egypt ; and the Urology Department, Gulf Medical University, Ajman, UAE

Address correspondence to: Hamdy Aboutaleb, M.D., Ph.D., Urology Department, Menoufia University Hospitals, Menoufia, P.O 52533, Shebin El-Kom, Egypt. E-mails: hamdyaboutaleb@yahoo.com; diaaeldieb74@yahoo.com; yasserfarahat@yahoo.com; dr\_tamer\_ali@yahoo.com; drfouad80@gmail.com

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wide availability and absence of ionizing radiation exposure.<sup>9,10</sup> Thus, the present study aims to determine the efficacy of bladder US in the detection of subureteral implants after endoscopic (Deflux) injection. It also investigates whether US can be used as a substitute for VCUG so that radiation exposure can be minimized in pediatric patients.

## MATERIALS AND METHODS

### Study Design and Patient Population

This prospective study was conducted between 2014 and 2020. We initially recruited 211 consecutive patients, after exclusion, a final cohort of 160 children (220 ureters) who were administered subureteral Deflux injection for VUR were enrolled). The research ethics board at our hospital approved the study protocol. The parents of each selected pediatric patient signed an informed consent form before inclusion in the study. Exclusion criteria included patients with cloacal anomaly, neurogenic bladder, posterior urethral valve, ureteric abnormalities such as duplication, ureterocele, and diverticulum (33 patients), previous open anti-refluxing surgery (3 patients), or those patients who had not complied with scheduled follow-ups (15 patients) (see Flowchart in Supplementary Fig. 1). According to the International Reflux Study committee classification,<sup>11</sup> our patients with VUR were defined as grades I to V. Based on the patient classifications used in previous studies who considered grades I-III as low grade VUR and grades IV and V as high grade VUR.<sup>12,13</sup> Patients in present study had been classified into two groups: low-grade VUR (grades II-III) and high-grade VUR (grades IV and V). There were no patients with grade I VUR indicated for Deflux injection in our study.

Observational therapy with prophylactic antibiotics (trimethoprim plus or minus sulfamethoxazole or nitrofurantoin) was used initially in all patients. In general, patients were followed for 4 to 6 years. Surgical intervention was only considered for patients in whom conservative medical management failed. Indications for Deflux injection were persistent reflux for more than 4 years, breakthrough urinary tract infections (UTIs), and upper urinary tract deterioration (deterioration in degree of hydronephrosis, vesicoureteral reflux grade or renal function).

### Surgical Technique

Briefly, Deflux injection was administered under general anesthesia using a pediatric straight working channel cystoscope. The Deflux metal needle was used to inject subureteral Deflux at 6 o'clock position inferomedially as a double HIT technique (Hydrodistension Implantation Technique), and the needle was held for 30 seconds before withdrawal (Fig. 1). About 0.5 to 1.3 mL Deflux was injected to obtain a well-formed mound of the injected material and a slit-like appearance of the ureteral orifice. The procedure was performed as described in published studies.<sup>14-16</sup> All Deflux injections were performed by highly experienced urologists (Four surgeons with over 15 years of experience in pediatric urological procedures. All surgeons used the same technique of Deflux injection) (Fig. 1).

### Imaging Technique

All patients had postoperative follow-ups. Our protocol included kidney-Ureter-bladder ultrasound (KUB)-US, and VCUG at 3 months (mean  $3 \pm 0.5$ ) and 12 months (mean  $12 \pm 1.3$ ) after

surgery. Resolution of VUR was defined as the disappearance of VUR on VCUG images. If reflux persisted, the VCUG was repeated after 1 year. All US examinations were performed using the same US machine (Philips EPIQ 7 (Philips Medical Systems, Bothell, WA) with multifrequency transducers (7.5 MHz linear or 3.5 MHz convex transducers, depending on the patient's age). The patients underwent US examinations with full bladders. The bladder base and ureterovesical junctions were sonographically evaluated at least in two anatomic planes. Any solid oval-shaped structure at or around the ureterovesical junction with an echogenicity equal to or slightly greater than that of bladder wall, was accepted as the Deflux mound (Fig. 2). The examination was performed as described in published study by Özcan et al.<sup>9</sup> Highly experienced radiologists (with over 10 years of US experience and has performed >1000 US examinations per year) independently performed all US examination. Before the study started, several clinical sessions of lecture-based and hands-on instructions that explained the detection of Deflux implants at the base of the urinary bladder. The same team of radiologists also performed KUB-US. The radiologists were blinded to the VCUG results but informed about the interest in detection of Deflux implants at the base of the urinary bladder (Fig. 2).

### Statistical Analysis

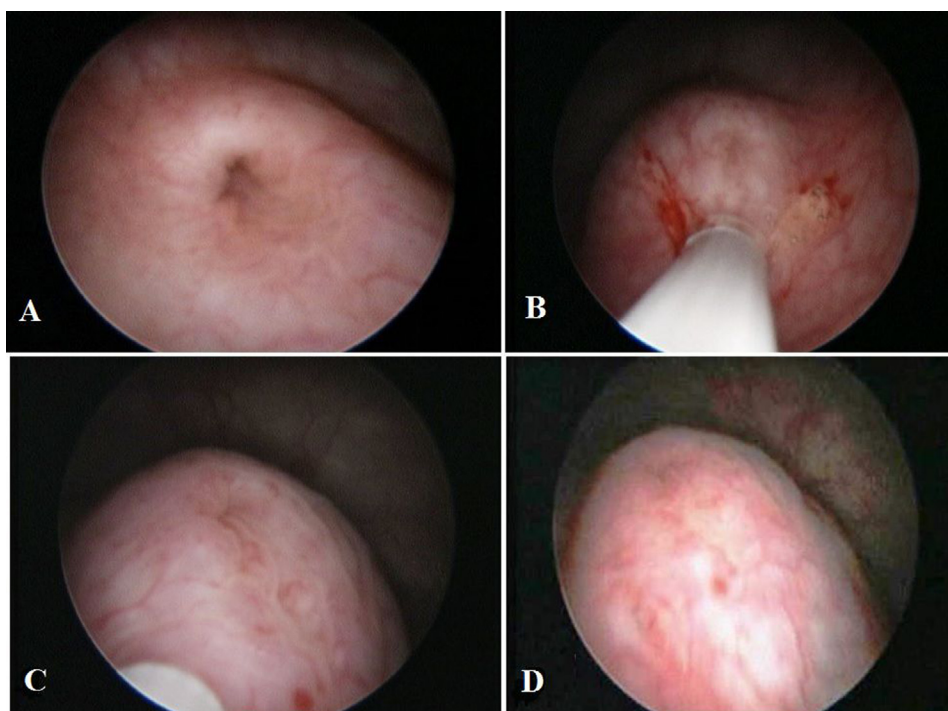
All descriptive data are shown as means and standard deviation, median or numbers (%). Performance characteristics were calculated as follows: sensitivity, specificity, positive predictive value (PPV), PPV (95% CI), negative predictive value (NPV), NPV (95% CI), accuracy, positive likelihood ratio (LR+) and negative likelihood ratio (LR-).

## RESULTS

Overall, subureteral injection of Deflux was administered in 160 patients who had primary VUR (220 ureters). Male to female ratio was 1:3 (40 males (25%) and 120 females (75%)). The mean age of patients was  $5.4 \pm 3$  years (Range: 6 months-10 years) and the mean age at surgery was  $72 \pm 5$  months (Range: 24-180 months). Bilateral surgery was performed in 60 patients (37.5%), while unilateral surgery was performed in 100 patients (62.5%).

With respect to grades of VUR, Patients had been classified into two groups: Low grade VUR group (Grades II and III) including 190 ureters (86.4%) and high grade VUR group (Grades IV and V) including 30 ureters (13.6%).

Outcome analysis included: Primary outcome aimed to identification of Deflux mounds by bladder US and secondary outcome included correlation of Deflux mounds identified with radiographic success rates by presence or absence of VUR on VCUG. In low grade VUR patients (190 ureters), bladder US detected Deflux mounds in 185 ureters (97.4%) at first follow up and 167/190 ureters (88.9%) at last follow up. Of them, 177/190 (93.2%) showed radiographic resolution of VUR at first follow-up and 167/190 (88%) at last follow up. While in high grade VUR patients (30 ureters), bladder US detected Deflux mounds in 21 ureters (70%) at first follow up and 17 ureters (56.7%) at last follow up. Of them, 5/30 (16.7%) showed radiographic resolution of VUR at first follow-up and 3/30 (10%) at last follow up. In all 220 ureters, in both low-grade and high-grade VUR groups, Deflux injection showed radiographic resolution of VUR in 187/220 ureters (85%) at first follow-up and 194/220 ureters (88.2%) at last follow-up (Table 1).



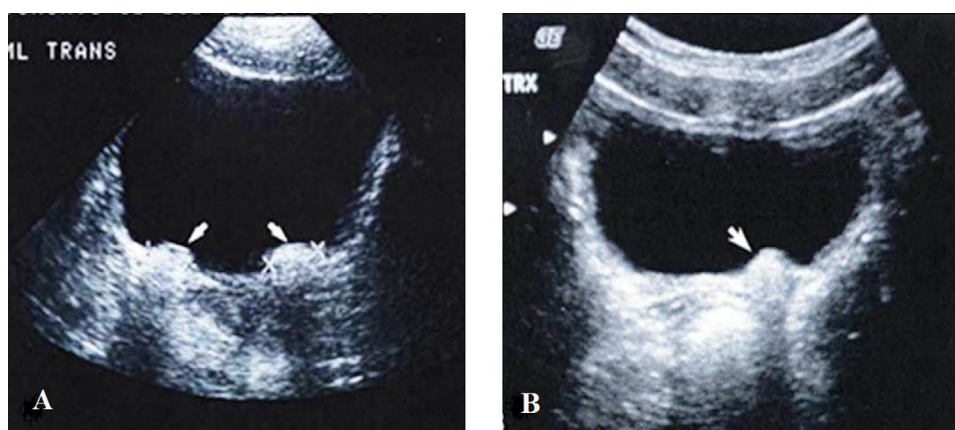
**Figure 1.** Pediatric cystoscopy with Subureteral Deflux injection at 6 o'clock position with double HIT technique and a well-formed mound was obtained. (Color version available online.)

Bladder US in predicting radiographic resolution of VUR in low grade VUR group had high sensitivity, PPV and accuracy at first and last follow-up. While in high grade VUR group, it showed low sensitivity, PPV and accuracy at first and last follow-up. The present study documented low specificity and NPV of bladder US in predicting radiographic resolution of VUR in low and high grades VUR groups at the first and last follow up (Table 2).

In low grade VUR, Negative likelihood ratio (LR-) at first follow up was 0.08 and 0.2 at last follow up reflecting conclusive decrease in the likelihood of VUR after Deflux injection. While, in high grade VUR (LR-) was not conclusive (LR- was 0.94 at first follow up and 1.72 at last follow up) (Table 2).

Persistent VUR was observed in 33 ureters (15%) at first follow-up that decreased to 26 ureters (11.8%) at last follow-up.

Radiographic persistence of VUR after the first injection was observed in 22 patients (26 ureters) and required a second injection 1 year later. Out of 26 ureters (22 patients), 22 ureters in 18 patients had high grade VUR (4 patients bilateral and 14 patients unilateral) and 4 ureters in 4 patients had low grade VUR and denovo hydronephrosis in 8 ureters that were resolved spontaneously. None of the patients had contralateral reflux. Five patients had UTIs after Deflux injections post radiologic VUR correction. These Patients are kept on toilet training and prophylactic antibiotics with follow up with VCUG after 1 year. None of these patients had VUR. In our study, Preoperatively, 25 patients (15.6%) with voiding dysfunction was managed with behavioral modification during conservative treatment before surgery. Postoperative of Deflux injection, 15 patients had radiographic correction of reflux and 10 patients had radiographic



**Figure 2.** Bladder Ultrasound showing Deflux mound at the base of the urinary bladder. A: Bilateral sides, B: Unilateral left side.

**Table 1.** Correlation between Deflux mounds detection and radiographic resolution of VUR in low grade versus high grade VUR patients

		Low Grade VUR (Grades II-III) (190 Ureters)			High Grade VUR (Grades IV-V) (30 Ureters)		
		Visible Mount	Absent Mount	Total	Visible Mount	Absent Mount	Total
First follow-up	Radiographic resolution of VUR (187/220 ureters, 85%)	177 (93.2%)	3 (1.6%)	<b>180/190 (94.8%)</b>	5 (16.7%)	2 (6.7%)	<b>7/30 (23.4%)</b>
	Persistent VUR (33/220 ureters, 15%)	8 (4.2%)	2 (1%)	<b>10/190 (5.2%)</b>	16 (53.3%)	7 (23.3%)	<b>23/30 (76.6%)</b>
Total 220 ureters (100%)		<b>185 (97.4%)</b>	<b>5 (2.6%)</b>	<b>190 (100%)</b>	<b>21 (70%)</b>	<b>9 (30%)</b>	<b>30 (100%)</b>
Last follow-up	Radiographic resolution of VUR (194/220 ureters, 88.2%)	167 (88%)	19 (10%)	<b>186/190 (98%)</b>	3 (10%)	5 (16.7%)	<b>8/30 (26.7)</b>
	Persistent VUR (26/220 ureters, 11.8%)	2 (1%)	2 (1%)	<b>4/190 (2%)</b>	14 (46.7%)	8 (26.6%)	<b>22/30 (73.3)</b>
Total 220 ureters (100%)		<b>169 (89%)</b>	<b>21 (11%)</b>	<b>190 (100%)</b>	<b>17 (56.7%)</b>	<b>13 (43.3%)</b>	<b>30 (100%)</b>

VUR, vesicoureteral reflux.

**Table 2.** Sensitivity, specificity, PPV, PPV (95% CI), NPV, PPV (95% CI), accuracy, positive likelihood ratio and negative likelihood ratio of bladder US in diagnosing radiographic success rate of VUR in low grade versus high grade VUR

		Low Grade VUR	High Grade VUR
First follow-up	Sensitivity (%)	98.33	71.43
	Specificity (%)	20	30.43
	PPV % (95% CI)	95.68 (94.2-96.8)	23.81 (15.4-35)
	NPV % (95% CI)	40 (11.13-78)	77.78 (48.21-92.9)
	Accuracy (%)	94.21	40
	Positive Likelihood Ratio (LR+)	1.23	1.03
	Negative Likelihood Ratio (LR-)	0.08	0.94
Last follow-up	Sensitivity (%)	89.78	37.5
	Specificity (%)	50	36.36
	PPV % (95% CI)	98.82 (97-99.5)	17.65 (7.6-35.6)
	NPV % (95% CI)	9.52 (3.5-99.5)	61.54 (42.5-77.6)
	Accuracy (%)	88.95	36.67
	Positive Likelihood Ratio (LR+)	1.8	0.59
	Negative Likelihood Ratio (LR-)	0.2	1.72

CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

persistence of VUR (mean age  $5.6 \pm 1.4$  years, 18 females). With continued behavioral modification voiding pattern returned to normal and reflux resolved in 6 patients (60%).

## DISCUSSION

Although VCUG and radionuclide cystography are presently the examinations of choice for the evaluation of VUR, radiation exposure from both these techniques is still a cause of worry. Also, there is other disadvantages of radioisotope cystography include bladder catheterization, poor anatomical details of the urethra, and vesicoureteral junction. So, every effort should be made toward minimization of radiation exposure during evaluation of VUR in infants and children. In this regard, US is the most advantageous alternative because it is a safe, simple, and widely accessible modality with no radiation exposure to rule out residual hydronephrosis and examine the Deflux injection site.<sup>9,17</sup>

In our study, US detected Deflux mounds at the base of the urinary bladder in 194/220 ureters (88.2%) at last follow-up, of them 186/190 ureters (98%) with low grade reflux and 26/30 ureters (26.7%) with high grade reflux.

Park et al<sup>18</sup> studied 56 ureters (36 children) and found Deflux mounds on bladder US in 38 ureters (68%). The sensitivity was 73%, specificity was 44%, PPV was 76%, and NPV was 39%. In comparison, our study showed higher sensitivity, specificity and PPV; this may be explained by the separation of low vs high grade reflux patients and comparatively higher number of patients included in our study.

Lee et al<sup>19</sup> examined 149 patients (220 ureters), of them, 122 patients (82%) were injected with Deflux and 27 patients (18%) were injected with polydimethylsiloxane (Macroplastique). Bladder US detected injection implants in 152 ureters (69%). VUR showed radiographic correction in 128 ureters (84%). The success rate in visualized injection implants group was 84.2%, while that in



absent injection implants group was 48.5%. Bladder US had 79.5% sensitivity, 59% specificity, 84% PPV, 51.5% NPV, and 74% accuracy as a diagnostic tool for successful correction of VUR. Injection implants were detected by US in only 69% ureters compared to 88% ureters in our study in last follow-up. This may be explained by the use of Macroplastique and Deflux injections in their study, while all patients in our study were administered Deflux injections only. Also, US is an operator-dependent modality, and the results may differ depending on the operator or the machine used in the examination.

In our study, the number of Deflux implants identified by bladder US decreased from 93.2% at first follow-up to 88% at last follow-up in low grade VUR group and from 16.7% to 10% in high grade VUR group. This finding is in line with Özcan et al<sup>9</sup> study, who described reduced rates of US detection of implants during follow-up from 80% in the first postoperative month to 45% at a mean follow-up of 2.2 years. He suggested that reduction in implant volume could be due to the replacement of dextranomer particles by collagen.

Our study showed low specificity and NPV for the identification of Deflux implants on bladder US in both low and high grade VUR groups as compared to prediction of VUR resolution. So, the non-visualized Deflux implants could not be diagnostic option of persistent VUR. This finding has also been described in previous reports.

Park et al<sup>18</sup> stated that low specificity and NPV of non-visualized implants on bladder US for persistent VUR could be explained by ureteral orifice anti-reflux mechanism caused by tissue expansion resulting from endogenous collagen between microspheres. Lee et al<sup>19</sup> and Yucel et al<sup>20</sup> attributed this to treatment-associated factors such as surgeon skills, injection technique, injection mound location, injectable volume, US machines used, and operator-dependent factors.

Our study demonstrated higher sensitivity, PPV and accuracy in Deflux detection by bladder US in low grade VUR vs high grade VUR patients. Our study concluded that postoperative bladder US could be adjusted as a screening examination in the follow up of low grade VUR patients while high grade VUR will require subsequent VCUG to exclude persistent VUR. Our protocol was thus modified in the last few years to use US only on the follow-up of low-grade reflux cases.

Our study has several strengths. To our knowledge, this is the first study that compared the Deflux injection efficacy in low grade vs high grade VUR and compared bladder US sensitivity in detection of Deflux mounds correlated to radiographic resolution of VUR in VCUG. Also, our study included large number of patients compared to previous studies with high success rate. It is a prospective study, which avoids the selection bias of retrospective study. Also, the same team of urologists and radiologists perform the procedures. Patients with other anomalies that may affect prognosis had been excluded. Limitations of the present study included lack of standardized definitions of sonographic appearance of Deflux

mounds. Also, validation of the sonographic appearance and volume of the implants as a prognostic factor for treatment success in VUR cases may be necessary.

## CONCLUSION

Hyaluronic acid/dextranomer (Deflux) offers a simple minimally invasive endoscopic procedure with high success rates for primary low grade VUR. Bladder-US was highly sensitive for detection of Deflux implants and can predict resolution of reflux in low grade VUR with high positive predictive value and accuracy. Postoperative bladder-US could be adjusted as a screening tool in the follow-up of patients with primary low-grade VUR treated by Deflux injection, while VCUG could be preserved for follow-up of high-grade VUR patients, this will lead to reduction of unnecessary radiation exposure during VCUG for children with low grade reflux.

## AUTHORS' CONTRIBUTIONS

HA. and YF. have made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data. HA., TA., DBE., YF. and FZ. has been involved in drafting the manuscript or revising it critically for important intellectual content and has given the final approval for the version to be published. All authors read and approved the final manuscript.

## INFORMED CONSENT FOR PARTICIPATION AND PUBLISH

Informed written consent was obtained from all patients before the study for participation and publish.

## ETHICAL APPROVAL

All procedures performed in this study were in accordance with the ethical standards of the Institution and/or National Research Committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The protocol and written informed consent were approved by the local ethical committee of Thumbay Hospital (affiliated to Gulf Medical University, Ajman, UAE; REC number: 1216).

## GUARANTOR

None

## AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.urology.2022.01.015>.

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