Ultrasoundographic mound height as predictor of vesicoureteral reflux resolution after endoscopic treatment in children

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A B S T R A C T

Purpose: Endoscopic dextranomer/hyaluronic acid copolymer (Dx/HA) injection is a safe and efficacious treatment option for vesicoureteral reflux (VUR) in children. Endoscopic appearance, hydrodistention and amount of injected Dx/HA have been demonstrated not to be reliable predictors of outcome. Aim of this study was to evaluate Dx/HA mounds on ultrasound scans (US) and find out any eventual correlation with reflux resolution.

Methods: We selected patients treated with endoscopic injection for moderate to high VUR, renal scaring or repeated infections under antibiotic prophylaxis. Success was defined by absence of VUR at control 3 months after surgery; at 3 months we also measured mound height ultrasonographically.

Results: We considered a total of 32 children (15 male, 17 female; 53 ureters) with a median age of 3 years (±24 months). Overall success rate was 77% per ureter. Success rate correlates directly with age and inversely with VUR grade. Mound height is the major predictive parameter for reflux resolution (sensitivity 100%, specificity 65.9%); mean mound heights of success-group vs. persistence-of-reflux group were 9.97 ± 1.61 mm and 7.29 ± 1.74 mm respectively (p < 0.0005).

Conclusion: A mound measuring at least 9.8 mm at post-operative US scan is a predictor of reflux resolution. Age and grade also seems to influence success rate.

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Vesicoureteral reflux (VUR) is a common urological disease affecting approximately 0.4–1.8% of pediatric population who have not presented with urinary tract infection (UTI) and up to 10–40% in patients who presented a UTI [1]. Common consequences of VUR in children are pyelonephritis and renal scarring [2].

Endoscopic injection of dextranomer/hyaluronic acid copolymer (Dx/HA) is a safe and efficacious treatment option for VUR in children, especially because of its minimally invasiveness, high success rate and low complication rate. Advantages of the technique are the reduced hospital stay, reduced perioperative morbidity, quicker return to everyday activity and better quality of life.

Many authors tried to correlate the appearance of the Dx/HA mound with the outcome of the procedure [3]. Some studies demonstrated that the endoscopic appearance of the Dx/HA mound [4] and lack of hydrodistention [5] at the completion of the procedure are not reliable predictors of outcome. All concluded that postoperative voiding cystourethrogram (VCUG) is still required to truly determine reflux resolution. However, VCUG remain an uncomfortable and stressful procedure for both children and parents. Ultrasound scans (US) are routinely performed during post-operative follow-up for VUR patients and represent a less invasive and less expensive monitoring tool.

Aim of this study was to evaluate dextranomer–hyaluronic acid copolymer mounds on ultrasound scans post-operatively and find out any eventual correlation with VCUG results, in order to define it as a predictive sign that could reduce the need for VCUG during follow-up for patients treated with endoscopic Dx/HA injection for VUR.

1. Material and methods

We considered all consecutive patients referred to our urologic outpatient clinic between March 2013 and January 2015 for vesicoureteral reflux. Sex, age, VUR grade and side were collected for each children. We included in the study patients with reflux grade 3 to 5 confirmed by VCUG and patients with grade 2 VUR and persistent upper urinary tract infections.

Exclusion criteria were grade 1 VUR, presence of voiding dysfunction, presence of other complex syndromes, presence of ectopic ureteral
orifice at cystoscopy. Presence of voiding dysfunction or other syndromes were assessed by an accurate clinical history at referral.

Of 52 patients referred, 32 (15 boys, 17 girls; 53 ureters) matched inclusion criteria and parents gave informed consent, after being informed about the nature of the study, in accordance with the Helsinki declaration. The study protocol was approved by the Ethics Committee of the “P. Giaccone” University Hospital in Palermo, Italy.

All eligible patients underwent pre-operative protocol assessment as described below and all VUR were treated with multiple intra-ureteric submucosal injection of Dx/HA. Demographic of patients included in the study is detailed in Table 1.

1.1. Pre-operative evaluation

Standard pre-operative evaluation included history, physical examination, renal and bladder ultrasonography, urinalysis and VCUG.

US bladder and renal evaluation were performed by a single expert sonographer using a 5 MHz convex probe (LOGIQ E9; GE Healthcare, Milwaukee, WI, USA). Optimal images for a complete bladder evaluation were obtained through sagittal and transverse scans; images for renal evaluation were obtained through sagittal, transverse, oblique scans, even through intercostal space or posteriorly if necessary. VCU was performed by an expert radiologist; VUR was graded according to international guidelines. Same sonographer and VCU-radiologist performed both pre-operative evaluation and post-operative assessment double blinded.

Indications for endoscopic treatment included repeated infections on antibiotic prophylaxis, presence of scarring at renal scintigraphy and/or moderate- to high-grade reflux.

All patients were taking prophylactic antibiotic before the procedure and continued the prophylaxis until resolution of VUR was confirmed by VCU control.

1.2. Surgical procedure

All procedures were performed under general anesthesia with the patient in supine position. A single experienced surgeon performed all injections.

Using a 9 Fr cystoscope, the ureteral orifice was hydrodistended to evaluate the intramural course of the ureter and an endoscopic injection with the double hit technique as described by Kirsch [6] was performed. The bladder was kept half full, avoiding overdistension.

Dx/HA was injected trying to obtain a single mound; if mound was not satisfactory, the needle was repositioned and the process repeated. Improper initial placement and subsequent repeat injection occasionally resulted in bilobed or trilobed mounds. The bladder was then emptied and the procedure terminated.

1.3. Post-operative evaluation

All patients underwent a post-operative follow-up consisting of seriate urinary tract US and VCU. Seriate US were performed at day 1 post-operatively and 3 months after surgery by the same sonographer who evaluated the child pre-operatively, blinded to VCU results. Renal and bladder ultrasonography performed at day 1, before discharge from the clinic, aimed to assess presence of any eventual upper tract dilatation; subsequent US at months 3 after surgery, aimed to determine shape and localization of the Dx/HA mound. The mound was visualized as a round-shaped mass with increased echogenicity localized at ureteral orifice in transverse vesical sections at post-operative US (Fig. 1). In case of bilobed or trilobed mounds, “mound height” was considered as the maximal measurable height. A VCUG was performed at 3 months after surgery to confirm reflux resolution by a radiologist blinded to US. Success was considered as a complete resolution of VUR at 3-months VCU control. All images were retrospectively reviewed in consensus by the authors.

1.4. Statistical analysis

Statistical analysis of quantitative and qualitative data, including descriptive statistics, was performed for all items. Continuous data are expressed as mean ± SD, unless otherwise specified. Baseline differences between groups were assessed by the chi-square test or Fisher exact test, as needed for categorical variables, and by the univariate analysis of variance (ANOVA) for parametric variables. Spearman’s rho correlation coefficient was calculated to measure the strength of the relationship between US results with VCG postop findings. Multinomial logistic regression analysis examined the correlation between patient characteristics (independent variables), and success of the procedure (dependent variable) in simple and multiple regression models. To assess the predictive rate of different cutoff values of post operative mound height at US scan with regard to success rate, a receiver operating characteristic (ROC) curve with calculations of area under the curve and 95% CI was constructed, and sensitivity and specificity values were calculated.

Data were analyzed by IBM SPSS Software 22 version (IBM Corp., Armonk, NY, USA). All p-values were two-sided and p < 0.05 was considered statistically significant.

2. Results

We analyzed a total of 32 patients, counting for 53 ureters, underwent Dx/HA injection for grade 2 to 5 VUR confirmed by pre-operative VCU. Of the 32 patients, 15 were males. VUR was unilateral in 11 (32%) and bilateral in 21 (68%) children. Of the 53 ureters, 26 were right-sided and 27 left-sided. Pre-operative VUR grade was 2, 3, 4 and 5 in 11.3% (n = 6), 28.3% (n = 15), 49.1% (n = 26), 11.3% (n = 6) of the ureters respectively. All patients were treated with multiple subureteral injections of Dx/HA. Average age at surgery was 35 (SD ± 24) months, ranging from 12 months to 9 years. Most patients had an intra-operative mound classified as “volcano” at endoscopic appearance, few bilobed and trilobed mounds were recorded. The average volume of Dx/HA injected was 0.85 (SD ± 0.39) mL. Only 2 cases developed transitional slight upper tract dilatation at early post-operative US scan, that spontaneously resolved at following controls. Two patients (1 female/1 male) developed contralateral reflux after the procedure, but both were successfully treated with a subsequent Dx/HA injection. The mean interval between surgery and post-operative US with mound measurement was 3 months (SD ± 1.46).

The overall success rate, defined as no VUR at VCU, was 77.4% by ureter. Success rate by grade was 100%, 86.6%, 80.7%, and 50% for grades 2, 3, 4 and 5 respectively. The success by age was 62.5% for first, 92% for second and 100% older than third years respectively. However in this

Table 1

Pre-operative demographic.

<table>
<thead>
<tr>
<th>Pre-operative demographic</th>
<th>n (%)</th>
</tr>
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<tbody>
<tr>
<td>Patient, sex (M/F)</td>
<td>15 M 17 F</td>
</tr>
<tr>
<td>Age at surgery, mean ± SD (range)</td>
<td>35 ± 24 months (12 months–9 years)</td>
</tr>
<tr>
<td>Unilateral VUR, N(%)</td>
<td>11 (32)</td>
</tr>
<tr>
<td>Bilateral VUR, N(%)</td>
<td>21 (68)</td>
</tr>
<tr>
<td>Ureters</td>
<td>53</td>
</tr>
<tr>
<td>Side VUR, N(%)</td>
<td>26 (49) R; 27 (51) L</td>
</tr>
<tr>
<td>Pre-operative VUR grade, N(%)</td>
<td>6 (11.3) 2</td>
</tr>
<tr>
<td>3</td>
<td>15 (28.3)</td>
</tr>
<tr>
<td>4</td>
<td>26 (49.1)</td>
</tr>
<tr>
<td>5</td>
<td>6 (11.3)</td>
</tr>
</tbody>
</table>

Sex, age at surgery, side and grade of reflux, are recorded for each patient. VUR: vesicoureteral reflux; M: male; F: female; L: left side; R: right side.
case series, as further described below, age and VUR reflux showed no significant difference.

Of the 12 failure of the procedure, half showed a downgrading of the reflux and half a persistent VUR (6/12). Of these 7 were treated by a second injection, 4 were treated by open surgery and 1 spontaneously resolved once completed potty-training.

A strong correlation was found between mound height on post-operative US and VCUG (Spearman’s rho correlation coefficient = −0.571; p < 0.0005). Moreover, success of endoscopic treatment group had a mean mound height of 9.97 ± 1.61 mm while persistence of reflux group had a mean mound height of 7.29 ± 1.74 mm (p < 0.0005, ANOVA test). Other features of these two groups are detailed in Table 2.

Logistic regression analysis in the simple model showed a relationship between mound height and success of endoscopic treatment (OR = 0.391 CI 95%; 0.23–0.67; p = 0.001). Multivariable regression model conducted by evaluation of all different variables, even not significant, maintained a significant correlation between success of endoscopic treatment group with mound height (OR = 0.175 CI 95%; 0.06–0.52; p = 0.001) and evidenced a negative relationship even with VUR grade (OR = 4.1 CI 95%; 1.2–16.0; p = 0.046). The other analyzed factors do not correlate with success/failure of the procedure: no differences were found according to sex (p = 0.745, Fisher exact test), age (p = 0.282, ANOVA test), side of the VUR (p = 0.327, Fisher exact test) or volume of Dx/HA injected (p = 0.348, ANOVA test).

The ROC curve analysis (Fig. 2) showed that the mound height value of 9.8 mm is a predictor of reflux resolution with a sensitivity of 100% and a specificity of 65.9%, with an area under the ROC curve of 0.890 (95% CI 0.774 to 0.959; p = 0.0001).

3. Discussion

Subureteral injection of bulking agents for VUR treatment in children is nowadays accepted as an efficacious, safe and minimally invasive procedure and it usually constitutes the first line treatment option. Overall success rate, recently, has been proved to vary from 69% to 86% irrespectively to grade [7,8]. However, despite this high success rate, factors predisposing to success or failure of the procedure are not fully understood and many authors tried to identify whether any aspect could suggest reflux resolution and thus allow to hypothesize prognosis.

Effect of voiding dysfunction on success rate of Dx/HA injection is still unclear. Capozza et al. [9] noted that almost all patients with treatment failure who had displacement of the Dx/HA mound also had concomitant voiding dysfunction and ascribed displacement to high voiding pressures secondary to voiding dysfunction.

Lavelle et al. [3] did not show a significant difference in the cure rate among patients with and without voiding dysfunction, concluding that voiding dysfunction could not be a contraindication, relative or otherwise, to Dx/HA injection. Because of its unclear role in VUR, we considered voiding dysfunction unresponsive to treatment an exclusion.

Table 2

<table>
<thead>
<tr>
<th>Features</th>
<th>Success (n = 41)</th>
<th>Persistence of reflux (n = 12)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>21/20</td>
<td>5/7</td>
<td>0.745*</td>
</tr>
<tr>
<td>Age at surgery (months), mean ± SD</td>
<td>37 ± 23</td>
<td>28 ± 29</td>
<td>0.282*</td>
</tr>
<tr>
<td>Side VUR (right/left), N°</td>
<td>22/19</td>
<td>4/8</td>
<td>0.327*</td>
</tr>
<tr>
<td>Pre-operative VUR grade 2 (% N°)</td>
<td>5 (12.2)</td>
<td>1 (8.3)</td>
<td>1.0*</td>
</tr>
<tr>
<td>Pre-operative VUR grade 3 (% N°)</td>
<td>12 (29.3)</td>
<td>3 (25)</td>
<td>1.0*</td>
</tr>
<tr>
<td>Pre-operative VUR grade 4 (% N°)</td>
<td>21 (51.2)</td>
<td>5 (41.7)</td>
<td>0.744*</td>
</tr>
<tr>
<td>Pre-operative VUR grade 5 (% N°)</td>
<td>3 (7.3)</td>
<td>3 (25)</td>
<td>0.121*</td>
</tr>
<tr>
<td>Amount of Dx/HA (ml), mean ± SD</td>
<td>0.81 ± 0.37</td>
<td>0.93 ± 0.44</td>
<td>0.348*</td>
</tr>
<tr>
<td>Mound height (mm), mean ± SD</td>
<td>9.97 ± 1.61</td>
<td>7.29 ± 1.74</td>
<td>p &lt; 0.0005*</td>
</tr>
</tbody>
</table>

VUR: vesico-ureteral reflux; M: male; F: female; L: left side; R: right side; Dx/HA: dextranomer/hyaluronic acid copolymer; US: ultrasound scan.

* Chi-square test or Fisher exact test;

Univariate analysis of variance (ANOVA test).
criteria. Moreover, in our case series, younger patients, ranging from 12 to 23 months and thus not fully toilet-trained, showed a higher persistence of reflux to treatment if compared to older children, even if this did not reach statistical significance.

The final endoscopic appearance as a predictor of success, regardless of technique, also do not ensure a favorable result. Puri et al. [10] first described the “volcano” morphology, a cone-shaped mound with a coated ureteral orifice at its apex, but not evaluated statistically success rate. Lavelle et al. [3] described this morphology as successful in 87% of cases, compared with 53% when “other” morphology was present. They described “other” morphology as bilobed or trilobed mounds resulting from attempts to correct a poorly placed initial injection, producing a mound in other than the desired location. However, Hidas et al. [5] created an online survey based on 11 primary vesicoureteral reflux cases e-mailed to 104 pediatric urologists and concluded that the appearance of the Dx/HA mound and lack of hydrodistention at the completion of the procedure are not reliable predictors of outcome. In our opinion the sole volcano appearance cannot be an acceptable predictor of successful outcome because it is not a reliable parameter and it is strongly operator dependent and could vary significantly with endo-vesical pressures.

Amount of dextranomer/hyaluronic acid copolymer injected does not correlate with success rate. Lavelle et al. [3] also reported a case series of 52 patients with a volume injected of 0.94 mL in patients with failure compared to 0.84 mL in successful injections. This apparently anomalous finding is justified by the authors as the result of subsequent attempts to correct an endoscopic morphology other than volcano obtained after first injection.

In recent years some authors also tried to correlate the implant appearance at post-operative US scans with the success of the procedure. Park et al. [11] described three implant appearance at US scans, correlating “large” implants with resolution of VUR at control VCUG, but they did not precisely measure implant volumes. The same result was obtained by McMann et al. [12] who also stated a good correlation between volume retention of the implant and VCUG results. These authors also demonstrated that after the initial volume reduction at 2 weeks from surgery, the Dx/HA mound remained durable with insignificant further volume reduction. In the present study we were able to set a precise cut-off point for mound US appearance. The achievement of a mound measuring at least 10 mm on post-operative scan and localized in the correct position, could suggest a successful procedure, because of the demonstrated strong correlation with VCUG results. Therefore it is important to assess volume and location of mound post-operatively using US, thus allowing to avoid post-operative VCUG in the presence of a mound greater than 10 mm or suggest further controls if this result is not achieved.

The present study has some limitations. First, the retrospective nature of the study could have introduced some sampling bias. A prospective study comparing long-term clinical outcome could validate US appearance of Dx/HA mound as prognostic factor for successful treatment. Second, the limited number of patients with indication to endoscopic injection for VUR could be improved by a larger case series to further confirm our data. Above all, an increased numerosity could lead to significant influence of age and pre-operative VUR grade for reflux resolution: our results only showed a slight direct correlation between success of the procedure and age and an inverse correlation with pre-operative VUR grade. Third, ultrasonography is an operator-dependent modality, particularly measuring small sizes.

4. Conclusion

In conclusion, the present study demonstrates a strong correlation between mound appearance at US and VCUG results: mounds measuring at least 9.8 mm in height were associated with success of the procedure, while smaller implants suggest the need for further assessment. Post-operative US could be used as a first line screening examination in the follow-up of VUR patients treated with Dx/HA injection, thus allowing to select those requiring VCUG to exclude persistence of VUR.

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