

Are there predictive factors for the outcome of endoscopic treatment of grade III–V vesicoureteral reflux with dextranomer/hyaluronic acid in children?

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Abstract Dextranomer/hyaluronic acid (Dx/HA) copolymer has been used widely for the treatment of vesicoureteral reflux (VUR) in children since 2001. However, the factors that influence the outcome of injection therapy with Dx/HA have remained unclear. In this study, we retrospectively evaluated the outcomes in 101 consecutive children to determine the cure and to identify the factors that can impact treatment outcomes of Dx/HA injection. Endoscopic treatment with Dx/HA was performed in 133 ureters, in 101 patients with grade III–V VUR. Of the patients, 68 (67.3%) were girls and the mean age was 6.5 years. Before and after the treatment, the presence and grades of VUR were determined by voiding cystourethrograms. The patients' age, gender, laterality, preoperative reflux grade, ureteral duplication, morphology of ureteral orifice, renal hypoplasia and experience with surgery were assessed as predictive factors related to the success rates of Dx/HA injection therapy. The cure rates were 54.8% after the first injection, 66.9% after the second and 73.6% after the third injection. Patients with a high grade (grade IV or V), duplicated system, golf hole-shaped orifice and renal hypoplasia had significantly lower cure rates ($P < 0.05$). Experience with the technique also correlated with the positive outcome of the procedure. New contralateral vesicoureteral reflux developed in five (7.2%) patients with unilateral VUR, and all of them resolved spontaneously during the first year of followup. No treatment-related

significant complication was encountered. Although, endoscopic treatment of VUR with Dx/HA provides a high rate of success in children with medium or high grade VUR, treatment failure may be seen in some patients. However, we showed that endoscopic treatment with Dx/HA was effective in selected patients with grade V VUR, and we emphasize the need for further large-scale studies to confirm our findings.

Keywords Vesicoureteral reflux · Injections · Predictive factors · Dextrans · Hyaluronic acid

Introduction

Vesicoureteral reflux (VUR) is one of the most common urinary tract anomalies affecting about 10% of children [1]. Generally it is identified during investigation of the etiology of urinary tract infection. Mild cases of VUR are likely to resolve spontaneously, but in more severe cases, a combination of VUR, recurrent pyelonephritis and renal scarring may ultimately lead to renal failure.

The optimal treatment of VUR remains controversial. The primary treatment options are antibiotic prophylaxis, open ureteral reimplantation and endoscopic submucosal biomaterial injection. The long-term requirement of prophylactic antibiotic therapy and some of the complications of surgical techniques led to the development of endoscopic treatment of VUR in the early 1980s [2]. In 1981, Matouschek described the technique of subureteral injection of a bulking agent for the correction of reflux [2]. This technique was popularized clinically by O'Donnell and Puri, who used polytetrafluoroethylene paste [3]. Since 1980, many foreign materials such as polytetrafluoroethylene, polydimethylsiloxane and bovine collagen have been

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used for treatment. The search for an ideal biomaterial for injection has been continuing [4, 5].

Following the approval of dextranomer/hyaluronic acid (Dx/HA) copolymer by the Food and Drug Administration in 2001, endoscopic management of VUR has become increasingly popular, and this treatment has become the first choice for the treatment of VUR, reserving open surgery for those with grade V reflux or those in whom endoscopic correction had failed [6]. However, treatment failure with Dx/HA injection therapy is still seen and the predictive factors related to cure rate are not yet clear. Therefore, the purpose of this study was to report our results of the Dx/HA injection therapy in patients with VUR and to determine whether risk factors related to treatment outcome could be identified.

Materials and methods

From September 2001 to January 2004, a total of 121 patients with 149 refluxing ureters underwent endoscopic Dx/HA injection in our clinic. Only those patients younger than 17 years with proven grade III–V VUR on voiding cystourethrogram (VCUG) preoperatively and having follow-up data from postoperative 12th month were included in the study. The patients with secondary VUR due to neuropathic voiding dysfunction, ureteroceles, megaureters, anterior or posterior urethral valves, ectopic ureter and failed ureteral reinjection were excluded. A total of 101 patients with 133 refluxing ureters, fulfilling those criteria, were included in our analysis. Of the patients, 68 (67.3%) were girls and 33 (32.6%) were boys. The mean age was 6.5 years (5 months to 17 years).

Routine urinalyses and urine cultures were carried out. Renal ultrasonography and ^{99m}Tc DMSA renal scan were performed preoperatively. VUR was graded according to the classification system of the International Reflux Grading System (I–V) by VCUG. Dx/HA was chosen by the parents after the risks, benefits and uncertainties regarding continued antibiotic prophylaxis, open reimplantation and Dx/HA treatment were discussed. The age, laterality, preoperative VUR grade, ureteral duplication, ureteral orifice type, and surgeons' experience were examined as possible risk factors.

Under general anesthesia, routine cystoscopy was performed. Then, the bladder was filled to half to three-fourths volume to permit visualization of the ureter and to avoid tension within the submucosal layer of the ureter, secondary to overdistention. A Storz cystoscopic injection needle consisting of a 10 mm long, 21 gauge, 3Fr needle was placed within the submucosa of the submural ureter at the 6 o'clock position, approximately 1–2 mm distal to the ureteral orifice and was advanced proximally into the

submural area to increase the length of ureteral coaptation. Then, Dx/HA was injected until the orifice was elevated and coapted, and a volcano bulge narrowed the ureteral orifice. In patients with golf-hole ureteral orifices, the injection was performed mostly inside the refluxing ureteral orifice. All children were discharged on the day of procedure or the next day. In the postoperative period, antibiotic prophylaxis was continued until VUR resolution was demonstrated by VCUG.

Follow up consisted of periodic urine analysis, renal and bladder ultrasonography 1 month after the treatment to evaluate for the presence of hydronephrosis and VCUG 3 months after the treatment. Patients were considered cured if postoperative VCUG revealed no further evidence of reflux; improved if there was a decreased, although still present, reflux in one or both ureters; and failed if there was no change bilaterally or reflux grade had worsened in either ureter on postoperative imaging. In patients whom the first endoscopic treatment was not successful, a second or, if necessary, a third injection was offered. After a normal VCUG was obtained, postoperative repeat VCUG was not performed except in patients with febrile urinary tract infection (UTI) or recurrent nonfebrile UTIs. The data were evaluated using chi-square test and Wilcoxon rank sum tests, and those with *P* values less than 0.05 were considered as statistically significant.

Results

The mean followup was 19.9 (14–47) months, and the evaluation is still ongoing. The mean injected volume of Dx/HA was 0.9 (0.5–4) cc for each orifice/injection. There was no case of increasing hydronephrosis at the first month of follow-up USG.

After 3 months of initial therapy, VCUG revealed that 74/133 (54.8%) refluxing ureters were cured. The cure rate for patients undergoing a second or third injection was diminished and the overall cure rate was 73.6% (98/133) after the third injection therapy. None of the cured patients had recurrent UTIs or pyelonephritis during the follow-up period. When the patients with improved VUR were taken into account, the overall success rates were improved and these rates were 78.9% (105/133) after the first injection, 81.9% (109/133) after the second and 84.9% (113/133) after the third injection. Table 1 shows treatment results of injection therapy with Dx/HA in 133 ureters.

In the present study, the overall cure rate in patients younger than 5 years was similar to patients of 5 years or older. There was no significant difference between the cure rates of girls and boys. Of the patients, 69 had unilateral and 32 had bilateral reflux before the initial treatment, and the cure rates were similar in both of these groups. The

VUR was grade III in 54 (40.6%), grade IV in 57 (42.8%) and grade V in 22 (16.5%) ureters, and the mean grade of VUR was 3.8, preoperatively. The cure rates of injection therapy with Dx/HA was inversely correlated with the reflux grade ($P < 0.001$).

There were 13 patients with duplicated systems and all of them had high-grade (grade IV or V) VUR in the lower moieties. After endoscopic treatment with Dx/HA, the cure rates for patients with single system was 80%, compared to 15.3% for patients with duplicated renal unites ($P < 0.001$). The cure rate of patients with high-grade (grade IV or grade V) reflux and single system was 68.1% (45/66), and it was also significantly higher than those with duplex system ($P < 0.001$). Of the 133 refluxing ureters, 8 were normal cone ureteral orifices, 38 were golf-hole, 40 were horseshoe and 47 were stadium-type ureteral orifices. The cure rate in patients with golf-hole type orifices was significantly lower than that of the remaining patients ($P < 0.001$). On the other hand, the cure rate was also significantly lower in patients with normal nephroureteral unites compared to that of patients with hypoplastic nephroureteral systems ($P = 0.022$). The overall cure rates of Dx/HA injections in the different above-mentioned groups are shown in Table 2. We detected that there was also a correlation between cure rates and experience with surgery. Our overall success rate was 56.6% in the first 30 patients compared to 86.7% in the last 30 patients ($P = 0.005$). However, we detected that the cure rates of four study surgeons were similar.

NCVUR with low grade (grade I or II) was seen in five patients (7.2%) with unilateral VUR, who had neither history of VUR nor an abnormal-appearing ureteral orifice on cystoscopy. These patients were observed on antibiotic prophylaxis. The NCVUR resolved spontaneously during the first year of followup, and all these patients had repeat VCUGs to document that.

A total of 21 patients with 35 (26.3%) refluxing ureters, who failed Dx/HA injection, underwent open ureteral reimplantation. No treatment-related serious adverse event was encountered. Only minor complications were seen in three (2.9%) patients, including transient dysuria in two patients and mild hematuria lasting 1 day in one patient.

Table 1 Treatment results in 133 ureteral unites

	No. of injection (%)			Total no. (%)
	1	2	3	
Cure	73 (54.8%)	16 (26.7%)	9 (20.4%)	98 (73.6%)
Improved	32 (24.1%)	20 (33.3%)	15 (34.1%)	15 (11.2%)
Failure	28 (21.1%)	24 (40.0%)	20 (45.5%)	20 (11.5%)
Total	133	60	44	133

Table 2 The overall success rates following one or more courses of treatment in the different groups

		N	Success n (%)	P
Age	<5 years	62	44 (70.9%)	NS
	≥5 years	71	54 (76.1%)	
Sex	Female	68	55 (80.8%)	NS
	Male	33	25 (75.7%)	
Laterality	Unilateral	69	56 (81.1%)	NS
	Bilateral	32	42 (65.6%)	
Grade	III	54	51 (94.4%)	<0.001
	IV	57	41 (71.9%)*	
	V	22	6 (27.2%)**	
Single ureteral unite		120	96 (80%)	<0.001
Duplicated ureter		13	2 (15.3%)	
Orifice type	Normal	8	8 (100%)	<0.001
	Golf hole	38	14 (36.8%***)	
	Horshoe	40	34 (85.0%)	
	Stadium	47	42 (89.3%)	
Hypoplastic nephroureteral system		30	17 (56.6%)	0.022
Normal nephroureteral system		103	81 (78.6%)	

* $P < 0.001$ for grade IV vs. grade III and grade IV vs. grade V.
 ** $P < 0.001$ for grade V vs. grade III. *** $P < 0.001$ for Golf hole orifices vs. the other groups

Discussion

The success rates of endoscopic treatment of VUR using Dx/HA have varied from 63 to 100% [7, 8]. Overall success rates were reported as 70–80% for primary uncomplicated VUR [9, 10]. Most of our patients had primary VUR, but we also attempted endoscopic treatment of VUR in 13 patients with a duplex system. In our study, the overall cure rate was 73.6% for a significant number of patients with grade III–V VUR. Because repeat injections resulted in an acceptable cure rate, we suggest that patients who experience one failed Dx/HA injection may undergo one or two additional injections. These results were reported in some other studies [11, 12]. Although our cure rate was not as high as in some studies, it must be remembered that the majority (59.3%) of our patients had grade IV or grade V reflux, and 9.7% had duplicated systems that have lower cure rates with injection therapy. In addition, taking the improved patients into consideration, the overall success rates were 78.9 after the first and 84.9% after the third injection.

In our study, the mean injected volume of Dx/HA was 0.9 (0.5–4) cc for each orifice injection. In a recent meta-analysis including the four studies on Dx/HA injection, Elder et al reported that the mean injected volume was 0.69 cc [11]. Although our value was higher than this, in the first few cases, this value was higher than 1 cc and

declined as the time passed. Recently, we have observed that 0.5–0.6 cc Dx/HA is usually sufficient for success in noncomplex cases. The amount of material was decreased by the hydrodistention-implantation technique used in recent years, which was described by Kirsch et al. [13] and which optimizes ureteral coaptation.

With the wide use of Dx/HA, more treatment failures are being encountered. Therefore, the variables that influence the cure of Dx/HA injection should be identified and patients and their parents should be informed about the cure rate and significant predictors of injection therapy. However, there are few reports regarding the prognostic factors related to the treatment results of Dx/HA injection. The objectives of our analysis were to determine the success rates and to investigate whether various risk factors for treatment failure could be identified.

In the present study, there was not a significant difference between the cure rates of patients younger than 5 years old and the remaining patients. This result is consistent with previous studies [11, 13]. We found that gender was not a statistically significant predictor of vesicoureteral reflux correction and our result corroborates another study [14]. Moreover, the cure rates of patients with bilateral reflux and unilateral reflux were found to be similar in our study. Kirsch et al. [13] also reported that there was no statistically significant difference between the cure rates of unilateral VUR and bilateral VUR.

Our cure rates achieved with Dx/HA injection therapy were correlated inversely with VUR grade and the cure rate was significantly lower in patients with grade V. While similar findings have been reported in many studies [11, 15, 16], this relation was not observed in some other studies [9, 13]. Lavella et al. reported that mound morphology, but not other factors including grade, volume injected, endoscopic appearance after injection and presence or voiding dysfunction, was the only statistically significant predictor of a successful outcome [17]. In literature, a wide range of variable success rates were reported for patients with duplicated system, perhaps due to differences in the patients' characteristics, techniques, experience with surgery and the materials used. While some of the authors reported that the success rate was significantly lower for duplicated versus single system as in the present study [9, 11, 16], others reported that a duplex system did not attain significance [18–20]. In our study, caudal migration of the Dx/HA implant was the most common findings in repeated cystoscopy for patients with initial treatment failure. However, the number of patients with duplex system were small and, therefore, further studies are needed to find a definite conclusion in this matter.

In our study, the cure rate of Dx/HA injection therapy was significantly lower in patients with golf-hole orifice. Capozza and Puri reported similar results in their study

[3, 6]. However, 92.1% of our patients had high-grade (grade IV or grade V) reflux and, probably, the reason for failure of the injection therapy in this group is not merely the orifice but the grade of VUR, as well. Moreover, several studies have shown that injection therapy is not only feasible, but does give good results for these patients [19, 21]. In the present study, 56.6% of the hypoplastic renal unites undergoing Dx/HA injection were cured, which was similar to the incidence reported by some authors [6, 7]. This low cure rate may be a result of maldevelopment of nefroureteral unites in these patients. It is known that the cause of Dx/HA failure is usually due to an incorrect technique, principally an injection that is too deep with secondary migration of the material along the Waldeyer sheath [6, 18]. Consistent with this, our cure rate was low at the beginning, which was mostly due to incorrect injection, and it was improved by the time the experience with the technique increased. Following Dx/HA injection treatment, there was a NCVUR with low grades (grade I or II) in 8.1% renal unites in patients with unilateral VUR. It is noteworthy that the NCVUR was resolved spontaneously during the first year of followup.

The Dx/HA injection has been associated with minimal morbidity. Cystitis occurs in 6.4% of patients, bladder spasms in 2% and febrile urinary tract infection in 0.75% of patients [11, 12]. Ureteral obstruction rarely occurs [16, 22]. In our study, there was not any serious adverse event and only minor complications were seen in 2.9% of the patients.

Conclusions

Endoscopic injection of Dx/HA has a high cure rate and it is repeatable in failed cases. The main disadvantage of endoscopic therapy is failure of the method, which was seen in 26.3% of the patients in our study. If we return to the title, we may say “yes, there are some predictive factors for the outcome of endoscopic treatment of grade III to V VUR with Dx/HA.” The success rate of injection therapy with Dx/HA can be improved, in some patients with lower success rate, by careful and adequate patient selection, associated with surgical experience. However, more aggressive approaches such as open ureteral reimplantation are needed for patients, who have low success rates at the beginning. Based on the success rates in our study, we continue to offer Dx/HA as primary therapy for selected patients.

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