New Tissue Bulking Agent (Polyacrylate Polyalcohol) for Treating Vesicoureteral Reflux: Preliminary Results in Children

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Abbreviations and Acronyms

Dx/HA = dextranomer/hyaluronic acid copolymer

FDA = Food and Drug Administration

HIT = hydrodistention implantation technique

PDMS = polydimethylsiloxane

PPC = polyacrylate polyalcohol copolymer

VCUG = voiding cystourethrography

VUR = vesicoureteral reflux

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Study received approval of committee of ethics of research protocols of the hospitals involved.

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Purpose: We report the preliminary results of endoscopic treatment of vesicoureteral reflux in children using polyacrylate polyalcohol copolymer.

Material and Methods: We performed a prospective multicenter review of pediatric patients treated with subureteral injection of a new nonabsorbable substance. Only patients with 1 year of followup were included.

Results: A total of 83 patients underwent injection of polyacrylate polyalcohol copolymer at our institutions between 2005 and 2006. Among this group 18 males and 43 females with a median age of 58 months (range 9 months to 18 years) completed 1 year of followup. Reflux was bilateral in 27 patients (44.3%) and unilateral in 34 (55.7%). Number of injected ureters was 88. Reflux grade was V in 3 ureters (3.4%), IV in 12 (13.6%), III in 41 (46.6%) and II in 32 (36.4%). Mean ± SD injected volume per unit was 0.76 ± 0.43 ml. Median followup was 20 months (range 16 to 24). Complications after injection included dysuria in 6 patients (9.8%), fever in 3 (4.9%) and lumbar pain in 4 (6.6%). Reflux was eliminated in 78 renal units (88.6%), decreased to grade I in 6 (6.8%) and persisted in 4 (4.5%). Ureteral obstruction developed in 1 patient and was treated operatively. Overall success rate was 83.6%.

Conclusions: Polyacrylate polyalcohol copolymer can be used to treat vesicoureteral reflux with comparable efficacy to other substances currently used, with a low rate of complications.

Key Words: acrylic resins, endoscopy, injections, Vantris, vesico-ureteral reflux

SPONTANEOUS resolution of vesicoureteral reflux is common, with rates of nearly 100% in grade I and II disease, and 20% to 60% in grade III to V disease.[1] Despite these figures, surgical and endoscopic treatment can be considered in the presence of breakthrough urinary infections or noncompliance while on antibiotic prophylaxis, presence or development of new renal scars or persistent reflux after several years of followup, or based on parent preference.[2]

Subureteral injection of biocompatible agents produces a mass effect, changing the shape and anatomy of the ureterovesical junction, preventing reflux. We previously used a newly developed, nonabsorbable, biocompatible injection bulking substance to eliminate VUR.[3] We describe the preliminary results of a prospective multicenter study of PPC (Vantris®) in children with VUR.

MATERIALS AND METHODS

PPC, a new nonbiodegradable substance of synthetic origin belonging to the acrylic family, leads to formation of a fibrotic capsule that can result in better stability and

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long-term durability in treating VUR. PPC particles are flexible, have an irregular shape and are highly malleable when compressed. The substance is easy to inject and can be manually extruded using 23 gauge needles. Most of the particles have an average diameter of 300 μm and, therefore, the risk of local or distant migration is reduced.[2] The substance is also stable through time.

This protocol was approved by the committee of ethics of research protocols of the hospitals involved, and parents signed an informed consent for each patient. PPC has been subjected to various biocompatibility tests according to the International Organization for Standardization 10993-1 standard,[4] and was approved for clinical trial at the involved institutions. The protocol allowed treatment of children with primary unilateral or bilateral VUR (grade II to V) confirmed by VCUG and related renal function of the involved unit greater than 10% according to dimercapto-succinic acid or diethylenetriamine pentaacetic acid scan. Most patients (92%) were included because of breakthrough infections or noncompliance with antibiotic prophylaxis. Patients were treated at 6 different hospitals in 2 countries (Argentina and Brazil). Sterile urine was a precondition for the procedure. Exclusion criteria consisted of neurogenic bladder, reflux secondary to other anatomical malformation of the urinary tract (obstruction, complete duplicated pelvicaliceal system), previous surgical or endoscopic procedures, and suspected or confirmed dysfunctional voiding by clinical findings or abnormal results (irregular bladder wall, diverticulum) on VCUG. Postoperative studies included urinalysis, renal and bladder ultrasound, and VCUG after 1 year of followup.

Endoscopic treatment was performed with the patient under general anesthesia with a 10Fr Storz® cystoscope using subureteral injection or HIT (intraureteral), or a combination of both techniques, depending on the anatomy of the ureteral meatus and surgeon experience.[5,6] All senior investigators involved in the protocol had long previous experience with subureteral injection using other tissue bulking agents, including Dx/HA, collagen, hydroxyapatite and PDMS (Macroplastique®). Antibiotic prophylaxis was used perioperatively and maintained for 10 days postoperatively, when it was suspended following a normal urinalysis.

Table 1. *Patient demographics at baseline*

No. gender (%):	
M	18 (29.5)
F	43 (70.5)
No. ureters:	
Rt	41
Lt	47
Mean age (range)	58 Mos (9 mos–18 yrs)
No. laterality (%):	
Unilat	34 (55.7)
Bilat	27 (44.3)
No. grade (%):	
II	32 (36.4)
III	41 (46.6)
IV	12 (13.6)
V	3 (3.4)
Mean ± SD injected vol (ml)	0.76 ± 0.43

Table 2. *Resolution of reflux at 1-year followup*

Grade	No. Ureters	No. Improved (grade I)	No. Treatment Failures	% Successes	p Value
II	32	0	0	100	<0.011*
III	41	3	2	87.8	0.049†
IV	12	2	2	66.6	0.003†
V	3	1	0	66.6	0.085†
	—	–	–		
Totals/av	88	6	4	88.7	

* Chi-square test comparing grade II with grades III to V.
† Fisher's exact test comparing grade II with each grade.

RESULTS

A total of 83 patients underwent injection of PPC at our institutions between 2005 and 2006. Of the patients 61 had at least 1 year of followup (mean 20 months, range 16 to 24) and VCUG results available. Patient demographics are outlined in table 1 and followup results are summarized in table 2. Of the 5 patients (6 ureters) who had reflux improve to grade I none received further treatment but all were followed clinically by their local pediatrician. Reflux persisted in 4 patients, of whom 2 were treated surgically (vesicoureteral reimplantation in 1, nephrectomy due to 10% related renal function in 1), 1 underwent reinjection with good results and 1 was lost to followup. Statistical analysis demonstrated that lower preoperative VUR grade was a determinant of improved results, with success in grade II significantly better compared to higher grades.

All patients were maintained on 25 mg/kg oral cephalexin daily for 10 days after endoscopic treatment. Postoperative complications included fever greater than 37.5C in 3 patients (4.9%), dysuria in 6 (9.8%, soon after the procedure related to cystoscopy in 4, and at 2 and 4 months in 2), lumbar pain in 4 (6.6%, of whom 2 underwent ultrasound, which revealed mild pyelectasis in 1 with resolution at 1 week) and afebrile urinary tract infection in 1 (1.6%). One female underwent extravesical ureteral reimplantation elsewhere 6 months after endoscopic injection because of progressive hydronephrosis on ultrasound after a urinary infection. In this patient VCUG was negative for VUR, and the final and retrospective diagnosis after anatomical examination of the distal ureter was primary obstructive megaureter with associated VUR. The final success rate was 83.6%.

DISCUSSION

Endoscopic treatment of VUR was first described in 1981 by Matoushek,[5] and began gaining popularity following a report on its use by O'Donnell and Puri.[6] Since Dx/HA was approved in 2000 by the FDA,[7] the number of children with VUR treated with subureteral injection has steadily increased,[8] and Dx/HA has become the first line endoscopic treatment. Its use has gained popularity worldwide because of its

simplicity, ease of application and good results. Many additional substances have been developed and used in the last 20 years for the endoscopic treatment of VUR.[9–13]

The results in this preliminary study using subureteral injection of PPC to treat VUR are satisfactory, with success in 88.6% of ureteral units and 81.9% of patients. These rates are comparable to those obtained with other substances currently in use. For example in a study of 228 patients with grade III to V reflux treated with Dx/HA Lackgren et al reported a cure rate of 96% at 1 year of followup.[14] However, at 5 years the recurrence rate was 13%. This recurrence could be related to the biodegradable nature of Dx/HA, as suggested in a prospective study by Oswald et al, who compared endoscopic treatment with Dx/HA to PDMS in a study comprising 114 ureters equally divided into 2 treatment groups.[15] At 1-year followup reflux was cured in 80.9% of ureters treated with PDMS and 67% of those treated with Dx/HA. This difference could be related to the nonbiodegradable nature of PDMS. However, PDMS is more difficult to use and requires a special device for injection because of its viscosity.[10]

Lorenzo et al reviewed a 6-year experience with PDMS at the Hospital for Sick Children in Toronto, performing a multivariate analysis of data showing overall success by renal units and patients of 65% and 72%, respectively, and stressing the importance of surgeon experience with subureteral injection as a statistically significant factor.[16] Recently Lee et al published their experience with Dx/HA from 2002 to 2006.[17] They repeated VCUG at 1 year postoperatively only in patients initially cured and observed VUR recurrence in 26% of patients, particularly those with grade III to V reflux. Thus, they recommend continuous followup despite initial success with Dx/HA. The higher success in our patients 1 year after the procedure could be related to the large experience of the pediatric urologists involved and the nonbiodegradable nature of the bulking agent.

We hypothesized that subureteral injection with a permanent bulking agent could be a primary option for treatment in these clinical scenarios, avoiding late recurrence of reflux caused by bulking agent resorption, although there is no clear evidence that resorption is associated with a deleterious effect on the renal parenchyma.[18] As could be expected, most cured cases (ureters) were associated with lower reflux grades. Additionally success rates with subureteral injection in grade II cases (100%) were significantly better than in grade III to V as a group ($p < 0.011$), especially compared to grade IV ($p = 0.003$), as observed in most published studies.[9,14,16,17] This disparity constitutes a limitation to obtaining comparable results between subureteral injection and open surgery in all grades of VUR. In this study we excluded patients with dysfunctional voiding because this condition could contribute to subureteral injection failure, as suggested by Sedberry-Ross[19] and Capozza[20] et al. To evaluate the effectiveness of PPC only in primary VUR, we also excluded complete pyeloureteral duplication and complex cases (posterior urethral valves, prune belly syndrome, neurogenic bladder), although Perez-Brayfield[21] and Lackgren[22] et al have proposed subureteral injection as an initial step to manage VUR in such cases.

Probably the most worrisome complication of this procedure is ureteral obstruction as described by Vandersteen et al, who observed that obstruction always resolved with ureteral stent placement, although VUR developed in 50% of patients after relief of obstruction.[23] Although transient lumbar pain developed in some of our patients, there was no confirmed obstruction in the immediate postoperative period. The only patient with ureteral obstruction was diagnosed 6 months later by ultrasound performed elsewhere because of a urinary tract infection. Postoperatively (ureteral stenting was not intended) anatomical examination confirmed a primary megaureter, as described by Aaronson et al.[24] Although uncommon, this condition must be suspected when there is a permanent preoperative megaureter on repeat ultrasound examinations, and a ureteral meatus smaller than expected for reflux grade and ureteral dilatation are present on cystoscopy, as observed retrospectively in our patient.

We attempted to analyze whether the injected volume of PPC had a role in the development of obstruction or failure of the procedure. However, the small number of patients did not permit a valid statistical analysis.

Despite the limitations of our study, such as the relatively short followup (1 year), lack of a control group and lack of comparison to other substances injected by the same pediatric urologists, the results obtained with PPC injection are encouraging. Review of the literature demonstrates that our results are similar to large studies of other antireflux substances. Additionally PPC has the advantage of being nonbiodegradable and durable through time, and does not require special equipment for injection, as does PDMS. Thus, PPC fulfills the criteria for the ideal implantable material and possesses some advantages over other bulking substances.

CONCLUSIONS

PPC eliminated vesicoureteral reflux in 83.6% of cases. It has a low number of complications and its effectiveness at eliminating reflux is comparable to other substances currently used in pediatric urology. Given the nonbiodegradable nature of the material, the antireflux effect will probably persist through time and become permanent. Thus, PPC is an attractive material for initial treatment in those patients with VUR who have few possibilities of spontaneous cure.

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EDITORIAL COMMENTS

The authors describe their initial experience using an acrylic tissue bulking substance (PPC) for endoscopic treatment of VUR. Their results appear promising and are similar to other agents, including Dx/HA. Everyone reading this comment should be encouraged by these results but may wonder if the product is more cost effective. Given the enormity of this question, and the rigor and cost of the FDA approval process, marketing etc, this issue was not addressed.

Unlike most published series using other agents, the authors obtained VCUGs 1 year postoperatively and achieved a patient success rate of 84%. It is noteworthy that the success rate for high grade VUR was 67%, the average injected volume was 0.8 ml and the injection technique varied through time. This series is similar to our initial experience using Dx/HA. The uniform application of double HIT using increased volume (average 1.3 ml) resulted in a 90% radiographic patient success, albeit at 3 months, and a long-term clinical success of 95% (similar to the current series). We have seen no difference in success up to grade V reflux. I would anticipate the same improvement in radiographic success using PPC injected in a more standardized fashion. However, it is unknown what effect its use may have on the rare development of ureteral obstruction (1.2% in current series and 0.3% in our experience).

One of the attractive aspects of using Dx/HA (in addition to its being the only FDA approved agent) was that it was believed to degrade with time and, thus, not pose any long-term risks. However, our experience monitoring the volume of Dx/HA during a 3-year period revealed that measured volume (after the initial 20% loss of hyaluronic acid within 2 weeks) was quite stable for at least 3 years.[1] Those who have explanted Dx/HA at ureteral reimplantation have noted that the procedure is not difficult,

the product is encased by a fibrous capsule and there is little change to the consistency of the dextranomer even after several years. Although I would not expect any major differences with PPC, it would be important for the authors to share their experience through the long term regarding reoperation (endoscopic and open) and the appearance of PPC on radiographic studies, since Dx/HA has a characteristic appearance on computerized tomography and has been shown to mimic ureteral stones.[2]

From a purely technical standpoint the high viscosity of PPC requires a pump type syringe that is quite easy to use. While the tactile "feel" of the injection method is lost due to the syringe design, I have injected PPC using double HIT in several complex cases while in South America and have been informed that the success rate was 100%. I remain encouraged and look forward to more publications by the authors.

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This multicenter study of 61 children resulted in an admirable 1-year success rate of 84%. However, the data are from a relatively small noncomparative case series and, as such, should be regarded as preliminary. Given the study design, it is impossible to compare the success rate in this series with other injectable agents. Thus, the importance of the physical properties of PPC (eg its lack of biodegradability) remains unclear.

Similarly it is unclear whether the 1.6% obstruction rate (1 of 61 cases) in this series is significantly different from the 0.3% to 0.7% reported with other injectable agents (reference 22 in article).[1] However, the occurrence of symptomatic ureteral obstruction requiring surgical intervention in such a small series is worrisome, particularly since lumbar pain developed postoperatively in 4 additional patients (6.6%). Future protocols of PPC injection should consider warning patients that the risk of obstruction, although low, may be increased with this agent. Nevertheless, these data overall are interesting, and further trials comparing PPC and other VUR treatment modalities would appear worthwhile.

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REPLY BY AUTHORS

We agree that with the available data it is impossible to say if our obstruction rate is higher than that reported for other agents. We have experience with other agents and find PPC easy to inject. The syringe is not a pump and tactile sensation during injection is good.