Endoscopic Correction of VUR Using Vantris as a New Non-biodegradable Tissue Augmenting Substance: Three Years of Prospective Follow-up

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OBJECTIVE
To evaluate the efficacy of Vantris in children with vesicoureteral reflux (VUR) after 3 years of prospective follow-up.

MATERIAL AND METHODS
Over the last 3 years, 109 children (72 girls and 37 boys) with a mean age of 6.2 ± 3.4 years (mean ± SD) underwent endoscopic correction of reflux using Vantris. VUR was unilateral in 53 and bilateral in 56 patients comprising 165 renal refluxing units (RRUs). Of these, primary VUR was present in 139 RRUs (84.2%) and 26 (15.8%) were complex cases. Ultrasound scan was performed 1 month, 1 year, and 3 years after injection, and voiding cystourethrogram (VCUG) was performed 3 months, 1 year, and 3 years after endoscopic correction.

RESULTS
The reflux was corrected in 153 RRUs (92.7%) after a single injection and in 7 RRUs (4.2%) after a second injection. In 5 RRUs (3.1%), VUR downgraded to grade I (3 RRUs) and grade II (2 RRUs) and they were taken off antibiotic prophylaxis. Two patients (1.8%) had afebrile urinary tract infections (UTIs) and 2 patients (1.8%) developed febrile UTI. VCUG was performed in 32 of 71 children (39.1%) who completed 1 year and in 6 of 15 (40%) who completed 3 years of follow-up. None showed VUR recurrence. Ultrasound scan demonstrated normal appearance of kidneys in all but 2 patients (1.8%). One patient required stent insertion because of deterioration of hydronephrosis that resulted in complete resolution of obstruction and another patient required ureteral reimplantation.

CONCLUSION
Our data show that Vantris injection provides a high level of reflux resolution with good clinical outcome during prospective follow-up. UROLOGY - - , 2013. © 2013 Elsevier Inc.

Since the introduction of subureteric transurethral injection almost 3 decades ago, and approval by the Food & Drug Administration of dextranomer/hyaluronic acid (Dx/HA) copolymer (Deflux, Q-Med Scandinavia, Uppsala, Sweden) for the treatment of vesicoureteral reflux (VUR), the endoscopic management of VUR has emerged as a first-line treatment for all grades of reflux in some centers around the world. The overall success rate reported by different groups of authors ranges between 68% and 92%, depending mainly on the VUR grade.1-3 Complications after this procedure are infrequent and related mainly to obstruction of the vesicoureteral junction and development of a new contralateral VUR after treatment of unilateral VUR.2

The concept of the endoscopic correction of VUR offers a minimally invasive treatment for the management of urinary tract infections (UTIs) and possible prevention of renal damage; therefore, it is extremely important to address the issue not only of the short-term success rate but also the long-term efficacy of the tissue augmenting substance used for endoscopic correction. Recently, intriguing data regarding the recurrence rate after successful Dx/HA treatment was presented.4,5 These results, which show an overall recurrence rate of up to 21%, are extremely sobering, and lead us to believe that another tissue-augmenting substance may be needed to achieve long-term efficacy in the endoscopic treatment of VUR. Some authors have suggested that the biodegradable nature of Dx/HA is responsible for the eventual VUR recurrence.4

Polyacrylate polyalcohol bulking copolymer (PPC, Vantris, Promedon, Cordoba, Argentina) is a new nonbiodegradable tissue-augmenting substance.6,7 We have conducted a prospective study aiming to evaluate the efficacy of Vantris in children with VUR in the short
and long term. Our preliminary results with a single injection of Vantris for the treatment of all grades of VUR were encouraging and were similar to the previously published data on Delflux. Herein, we present our data on up to 3 years of prospective follow-up of patients after Vantris injection.

**MATERIAL AND METHODS**

Over the last 3 years, 109 children (72 girls and 37 boys) with a mean age of 6.2 ± 3.4 years (mean ± SD) underwent endoscopic correction of reflux using Vantris and were followed prospectively. Reflux was diagnosed as a result of UTI in 88 of the patients (81.5%), in 14 (13.2%) after evaluation of antenatal hydronephrosis, and in the remaining 7 (5.3%) because of unrelated causes. We have previously published our standard protocol for evaluation and endoscopic correction of reflux. The reflux grade was based on the voiding cystourethrogram (VCUG) before and after surgery or during conservative treatment, according to the International Classification System (International Reflux Study Committee). Dimercaptosuccinic acid renal scan was used to assess renal scarring. The scan was performed at least 6 months after the last febrile UTI. Kidney uptake of 45%-55% of total renal activity was considered normal. Relative renal function of 20%-45% was considered moderate and renal function below 20% of relative renal function was considered poor.

The indications for endoscopic correction in the majority of cases were persistent high-grade VUR or breakthrough infections while on antibiotic prophylaxis. However, in some patients, reflux correction was performed according to guardian request. Of the studied patients, 104 renal refluxing units (RRUs) (63.4%) had normal renal function, 52 (31.6%) had moderate renal function, and the remaining 9 (5%) had poor renal function. Children who had symptoms of dysfunctional voiding or constipation were allocated to conservative treatment before endoscopic correction until full resolution of the voiding symptoms was achieved and preoperative reassessment including repeat VCUG was performed. As we have already stated, we have adopted in our practice a dysfunctional voiding symptoms survey for the evaluation of dysfunctional voiding. None of the children in this series had voiding dysfunction at the time of injection. All patients received antibiotic prophylaxis until VCUG was performed spontaneous resolution or definitive cure of the VUR. The technique of endoscopic correction used was similar to that described in the literature. In patients with grade I-III VUR, we used the usual technique of subureteric transurethral injection, with the needle introduced submucosally under the ureteral orifice at the 6 o’clock position. In patients with grade IV and V VUR or in those with a widely open orifice, the injection was performed inside the orifice, as published previously. Grade 1 VUR was treated only in children with contralateral high-grade VUR. Recurrent febrile UTI served as the only indication for surgery in 86 patients (81.5%), grade V VUR in 14 (13.2%), and in 9 (7.9%) reflux correction was performed on parental request. All injections were performed by a single surgeon (B.C.) as part of the study protocol. All families gave fully written informed consent regarding the procedure and tissue-augmenting substance used for reflux correction as part of our routine protocol. According to our standard practice, an ultrasound scan was performed 1 month after injection in order to identify hydronephrosis, obligatory VCUG was performed 2 months after injection, and renal function was considered poor. Moderate renal function was considered poor.

<table>
<thead>
<tr>
<th>Variables</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
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<tr>
<td>Male</td>
<td>37</td>
</tr>
<tr>
<td>Female</td>
<td>72</td>
</tr>
<tr>
<td>No. of VUR cases (RRUs)</td>
<td>165</td>
</tr>
<tr>
<td>Primary</td>
<td>139 (84.2%)</td>
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<tr>
<td>Complex</td>
<td>26 (15.8%)</td>
</tr>
<tr>
<td>Mean age (y) ± SD</td>
<td>6.2 ± 3.4</td>
</tr>
<tr>
<td>No. of laterality</td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>53</td>
</tr>
<tr>
<td>Bilateral</td>
<td>56</td>
</tr>
<tr>
<td>No. grade (RRUs)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>10 (8.5%)</td>
</tr>
<tr>
<td>II</td>
<td>23 (18.6%)</td>
</tr>
<tr>
<td>III</td>
<td>110 (40%)</td>
</tr>
<tr>
<td>IV</td>
<td>13 (25.4%)</td>
</tr>
<tr>
<td>V</td>
<td>9 (8.5%)</td>
</tr>
<tr>
<td>Indications for surgery</td>
<td></td>
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<tr>
<td>Breakthrough UTI</td>
<td>86 (78.9%)</td>
</tr>
<tr>
<td>High-grade VUR</td>
<td>14 (13.2%)</td>
</tr>
<tr>
<td>Parents’ request</td>
<td>9 (7.9%)</td>
</tr>
<tr>
<td>Mean injected volume (mL)</td>
<td>0.7 (range 0.2-1.1)</td>
</tr>
</tbody>
</table>

RRUs, renal refluxing units; UTI, urinary tract infection; VUR, vesicoureteral reflux.

3 months after endoscopic correction, and antibiotic prophylaxis was stopped if VCUG showed no reflux. Reflux was considered cured if VCUG did not demonstrate VUR of any grade. We have performed ultrasound scan 1 year and 3 years after injection as a part of the prospective follow-up. After the same regimen of the prospective follow-up, we have suggested to perform VCUG 1 year and 3 years after endoscopic correction.

**RESULTS**

The demographic data and indications for surgery are presented in Table 1. In brief, VUR was unilateral in 53 and bilateral in 56 patients comprising 165 RRUs. Of these, primary VUR was present in 139 RRUs (84.2%) and 26 (15.8%) were complex cases. Complex cases consisted of 11 duplex systems (42.3%), 13 (50%) after failed endoscopic correction with Delflux, 1 (3.8%) Prune Belly syndrome, and 1 patient (3.8%) with transplanted ureter.

VUR was grade I in 10 RRUs (8.5%), grade II in 23 RRUs (18.6%), grade III in 110 RRUs (40%), grade IV in 13 RRUs (25.4%), and grade V in 9 RRUs (8.5%), respectively. The reflux was corrected in 153 RRUs (92.7%) after a single injection and in 7 RRUs (4.2%) after a second injection. In 5 RRUs (3.1%), VUR was downgraded to grade I (3 RRUs) and grade II (2 RRUs) and they were taken off antibiotic prophylaxis. As it was expected, excellent results in terms of reflux resolution were demonstrated after a single injection in patients with grades I-III VUR (Table 2). Mean injected volume of Vantris per ureter was 0.7 mL (range 0.2-1.1 mL).

Two patients (1.8%) had afebrile UTI, 2 (1.8%) developed febrile UTI, and no VCUG showed reflux recurrence.

VCUG was performed in 32 of 82 children (39.1%) who completed 1 year and in 6 of 15 (40%) who...
completed 3 years of follow-up. In those 52 RRUs, initial VUR grade before the endoscopic correction was grade I in 1 RRU (1.9%), grade II in 13 (25%), grade III in 31 (59.6%), grade IV in 5 (9.6%), and grade V in 2 RRUs (3.8%), respectively.

No patient showed VUR recurrence. One patient demonstrated de novo reflux. Ultrasound scan demonstrated normal appearance of kidneys in all but 2 patients (1.8%). One patient required stent insertion because of deterioration of hydronephrosis that resulted in complete resolution of obstruction and another patient required ureteral reimplantation.

DISCUSSION

The concept of the endoscopic correction of VUR offers a minimally invasive treatment in the management of UTI or renal parenchymal damage associated with reflux.2,3 A recent meta-analysis of injection therapy considering outcomes from Dx/HA, polytetrafluoroethylene, collagen, polydimethylsiloxane, and chondrocytes suggested fewer subsequent UTIs than previously noted with open surgery or antibiotic prophylaxis, with an overall incidence of 6% (range 2.74%-14.15%) and febrile infection was observed in only 0.75% of the patients.5 Because endoscopic treatment of UTI has enjoyed the high rate of success in the short-term follow-up, it is extremely important to address the issue of the long-term efficacy and the subsequent UTI incidence after endoscopic correction of UTI. In the past, Kirsh et al1 have demonstrated that by using their technique of hydrodistention implantation technique injection, the short-term results with the endoscopic correction may be close to those results after open surgery, and, in the case of low reflux degree, even similar to those after open reimplantation. The same group recently published their experience with the patients who underwent double hydrodistention implantation technique and completed mean clinical follow-up of 19 months.10 The overall clinical success rate meaning that the 95% of the patients were UTI-free. The radiological success rate was also 93%. However, even those patients who demonstrated presence of VUR after endoscopic correction at 1 year VCUG were infection-free.

Over the last years, the management of VUR has become more controversial. Recently published American Academy of Pediatrics subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management guidelines for the diagnosis and management of initial UTI in febrile infants and children 2 to 24 months, have made an impression for the practicing pediatrician and pediatric urologist that VUR is rather a benign homogenous condition.11 Some pediatric urologists, we included, feel that these guidelines do not reflect the real world of possible renal damage associated with VUR and UTI and might put a patient in unjustifiable risk in terms of acquired renal scarring.

The main goal of treatment of VUR is to prevent febrile UTI and possible renal damage. In this study, the main indication for surgery (79%) in the group of patients was febrile UTI while on antibiotic prophylaxis. After successful correction of reflux, only 1.8% of the patients went on and demonstrated febrile UTI in spite of reflux correction. This prospective data is supported by our previous retrospective analysis and further iron out that endoscopic correction of VUR in a selective group of patients might avoid further pyelonephritis.5,12

As we have aforementioned, the recent manuscript by the Atlanta group brushed aside some concerns regarding long-term durability of Deflux as the ultimate choice for endoscopic correction.10 However, these findings are not completely consistent with other publications. Lee et al4 retrospectively studied VUR recurrence verified by VCUG, which was performed 1 year after successful Deflux injection. The initial experience with Dx/HA was similar to the existing studies, with a postoperative VCUG success rate of 73%, but at 1 year there was a recurrence rate of 26%. These findings lead the authors to believe that other studies, if re-evaluated beyond the initial VCUG, would yield similar findings. The working group on pediatric urology of the German Association of Pediatric Surgeons published the results of a multicenter prospective trial, which aimed to evaluate the long-term efficacy of endoscopic treatment of VUR using Dx/HA. A total of 284 patients (424 RRUs) were treated endoscopically with Deflux injection5; reflux was corrected in 68% of the RRUs, 46% of the patients completed 3 years of follow-up, and in 21% of RRUs, a recurrence of VUR was diagnosed between 6 months and 3 years. Based on this data, the authors strongly recommend continuing to follow patients after a successful injection beyond the first 3 years after surgery. Radiographic failure was also high in the Sedberry-Ross et al13 publications (27%) and Swedish Reflux Study14 demonstrated extremely high radiographic recurrence of 38%; however, 77% of these patients were infection free.

The authors blamed the biodegradable nature of Deflux for VUR recurrence.4,15 PPC is a new nonbiodegradable substance of synthetic origin belonging to the acryl family. The particles of PPC have an average diameter of 300 nm, thereby reducing the risk of local and distant migration.6,7 Once injected, the implant is also stable through time. Our preliminary results showed high efficacy rate of PPC (Vantris) in terms of reflux resolution after single injection in children with all grades of VUR.
and were similar to the previously published series on the endoscopic treatment of VUR. Reflux was cured with a single injection in 92.1% of all patients. It is of note that the failures occurred in patients from the group of complex cases.6

The data presented here reflect our 3-year prospective experience with the proved evidence of long-term durability of Vantris. All patients in our study have had ultrasound scan examination over a 3-year period. Although the Vantris implant was barely seen on ultrasound scan, we were able to monitor renal parenchymal change and hydronephrosis. Two patients demonstrated hydronephrosis deterioration requiring release of obstruction. One patient who underwent open reimplantation actually moved abroad so we do not have exact information regarding surgical indications for open surgery. In the other patient, a single kidney stent insertion resolved the obstruction and she is doing well since then.

Repeat VCU was performed in 40% of those patients who completed 1 and 3 years of follow-up, respectively. The rest of the patients ruled out suggested follow-up VCU because of free infection status, absence of any clinical symptoms, and normal follow-up ultrasound scans. It is worth it to stress that those 4 patients who presented with both afebrile and febrile follow-up UTI were radiologically reflux free. Some might argue that the VUR recurrence is depended not only on the material used for the endoscopic correction but also on the initial reflux grade, presence of the dysfunctional voiding, or the sex of the patient. None of our patients have had voiding problems before reflux correction. Moreover, 74% of our patients who underwent 1 and 3 years VCU had grade III-V VUR before endoscopic correction; therefore, we feel that the Vantris characteristics have contributed to the long-term success.

Some study limitations should be mentioned. We did not obtain VCU in all patients who completed 1 and 3 years of the follow-up. However, it is worth mentioning that we have prospectively monitored all our patients and were able to track all incidences of UTIs or other adverse effects. We do not have data on the characteristic appearance of Vantris on computed tomography, but we do know that it is barely seen on ultrasound scan examination. So far, we have performed ureteral reimplantation only on 1 patient who was previously injected with Vantris. Because he needed bladder surgery for different from VUR indications, and eventually required ureteral reimplantation on previously cured reflux, we excluded this patient from our study. We have not encountered any specific difficulties in this patient during surgery, however, on this very limited experience we are not able to comment whether it will be difficult to perform a ureteral reimplantation in patients after failure of VUR correction with Vantris. These questions are to be addressed in future studies.

CONCLUSION

Our data show that Vantris injection provides a high level of reflux resolution with a good clinical outcome during prospective follow-up. Multicenter studies on use of Vantris in patients with VUR with extended long-term follow-up are required.

References