Multicenter Survey of Endoscopic Treatment of Vesicoureteral Reflux Using Polyacrylate-Polyalcohol Bulking Copolymer (Vantris)

Stanislav Kocherov, Ibrahim Ulman, Sergey Nikolaev, Juan Pablo Corbetta, Yuriy Rudin, Andjelka Slavkovic, Zafer Dokumcu, Ali Avanoglu, Ludmila Menovshchikova, Semen Kovarskiy, Tatiana Skliarova, Santiago Weller, Juan I. Bortagaray, Juan C. Lopez, Víctor Durán, Carol Burek, Cristian Sager, Maruhnenko Dmitriy, Tatiana Garmanova, Aliev Djamal, Zorica Jovanovic, Nikola Vacic, Wael Abu Arafeh, and Boris Chertin

OBJECTIVE To evaluate an outcome of endoscopic correction of vesicoureteral reflux (VUR) using Vantris (Promedon, Cordoba, Argentina) in terms of its effectiveness and morbidity in a multicenter study.

MATERIALS AND METHODS From 2009 to 2013, 611 patients (210 boys and 401 girls) with a mean age of 3.56 years (range, 1 month-18 years) were treated at 7 centers worldwide endoscopically with Vantris injection. VUR was unilateral in 413 and bilateral in 198 patients comprising 809 renal refluxing units (RRUs). Of these, primary VUR was present in 674 RRUs (83.3%) and 135 (16.7%) were complex cases. Reflux was grades I-V in 24 (2.96%), 123 (15.2%), 451 (55.8%), 158 (19.5%), and 53 (6.6%) RRUs respectively. The follow-up continued from 6 to 54 months.

RESULTS Reflux resolved in 759 RRUs (93.8%) after first Vantris injection, in 26 (3.1%) after second, and in 6 (0.7%) after third injection, respectively. VUR improved to grade I after 1 or 2 injections in 5 ureters (0.6%), which needed no further treatment. Thirteen ureters (1.6%) failed endoscopic correction and required ureteral reimplantation. Vesicoureteral junction obstruction requiring ureteral reimplantation developed in 6 ureters (0.7%) and in 4 (0.5%) required stent insertion. Twenty-three patients (3.8%) suffered afebrile urinary tract infection. Seven (1.2%) developed febrile urinary tract infection. None of the studied patients demonstrated VUR recurrence on voiding cystourethrography.

CONCLUSION The results of this multicenter survey confirm that endoscopic subureteral Vantris injection is a simple, safe, and effective outpatient procedure for treating all grades of VUR. UROLOGY 84: 689–693, 2014. © 2014 Elsevier Inc.

Since the introduction of subureteral transurethral injection almost 3 decades ago, and over the last 10 years since the approval of dextranomer/hyaluronic acid copolymer (Dx/HA; Deflux; Q-Med Scandinavia, Uppsala, Sweden) for the treatment of vesicoureteral reflux (VUR) by the Food and Drug Administration, the endoscopic management of VUR has emerged as a first line treatment in all grades of reflux in some centers. The overall success rates, which were reported by the different groups of the authors, ranged between 68% and 92%, depending mainly on the VUR grade.[1-3] The complication rate after this procedure was infrequent and relates mainly to the obstruction of ureterovesical junction (UVJ) and the development a new contralateral VUR after treatment of unilateral VUR.[4-6] The concept of the endoscopic correction of VUR offers a minimally invasive treatment in the management of urinary tract infection (UTI) or renal parenchymal damage associated with reflux.[7-12] As endoscopic treatment of VUR has enjoyed a high rate of success in the short-term follow-up, it is extremely important to address the issue of the long-term efficacy of the used tissue-augmenting substance. Recently, very intriguing data regarding the very high incidence of VUR recurrence after

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From the Department of Pediatric Urology, Shaare Zedek Medical Center, Jerusalem, Israel; the Ege University Faculty of Medicine, Izmir, Turkey; the Filatov Pediatric Hospital, Moscow, Russia; the Pediatric Hospital, Buenos Aires, Argentina; the State Research Institute of Urology, Moscow, Russia; the Clinical Center, Nis, Serbia; and the St Josef Hospital, East Jerusalem, Palestinian Authority

Reprint requests: Boris Chertin, M.D., the Department of Pediatric Urology, Shaare Zedek Medical Center, Jerusalem 91031, PO Box 3235, Israel. E-mail: boris.chertin@gmail.com

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successful Dx/HA were presented by some authors.[13,14] These results, which show an overall recurrence rate of up to 21%, are extremely sobering. These findings lead us to believe that other tissue-augmenting substances may be needed to address the long-term efficacy of endoscopic treatment of VUR. Some suggested that the biodegradable nature of Dx/HA is responsible for the later VUR recurrence.[13] Polyacrylate-polyalcohol bulking copolymer (Vantris, Promedon, Córdoba, Argentina) is a new non-biodegradable tissue-augmenting substance, which may lead to the better stability of the injectable material and avoid VUR recurrence.[15-17] Some of us have recently reported that endoscopic correction of VUR is an effective outpatient procedure for all grades of VUR and is not associated with any significant morbidity.[15] Furthermore, prospective follow-up of 3 years showed no VUR recurrence in primary and complex cases of successfully treated VUR.[16] In this study, we have reviewed an outcome of endoscopic treatment of VUR in the large group of patients who were treated by different surgeons around the globe in terms of its effectiveness, long-term follow-up, and morbidity.

MATERIALS AND METHODS

A total of 21 pediatric urologists and/or pediatric surgeons at 6 centers worldwide answered an inquiry regarding experience with Vantris injection in VUR. Data were collected from an adopted completed standard questionnaire (Appendix 1).[18] The demographic data on the reviewed patients are listed in Table 1. Briefly, from 2009 to 2013, 611 patients (210 boys and 401 girls) with a mean age of 3.56 years (range, 1 month-18 years) were treated endoscopically with Vantris injection. VUR was unilateral in 413 and bilateral in 198 patients, comprising 809 renal refluxing units (RRU). Of these, primary VUR was present in 674 (83.3%) RRUs and 135 (16.7%) were complex cases. More than 135 ureters presented as complex cases. Of those, 77 RRUs (57%) had duplex system, 23 (17%) required reflux correction after failed ureteral reimplantation, 19 (14.1%) recurred reflux after previous endoscopic correction using different tissue-augmenting substances, and the remaining 16 (11.9%) had reflux secondary to the neurogenic bladder. Reflux was grades I-V in 24 (2.96%), 123 (15.2%), 451 (55.8%), 158 (19.5%), and 53 (6.6%) RRUs respectively. The main indication for endoscopic correction was febrile UTI in 482 of 611 patients (79%). The remaining 129 (21%) underwent surgery because of high-grade VUR or following parental request. In most patients, Vantris injection was performed on an outpatient basis. Patients were monitored with voiding cystourethrography (VCUG) and renal ultrasonography (US) at 3 months, 1 year, and 3 years. The follow-up continued from 6 to 54 months.

RESULTS

The outcome of the endoscopic correction is presented in Table 2. In brief, VUR resolved in 759 RRUs (93.8%) after first Vantris injection, in 26 (3.1%) after second, and in 6 (0.7%) after third injection, respectively. VUR improved to grade I after 1 or 2 injections in 5 ureters (0.6%), which needed no further treatment. Subureteral injection failed to correct reflux in 13 ureters (1.6%), which were then treated with ureteral reimplantation. The patients reviewed here did well also in terms of the reflux resolution after a single Vantris injection with almost 99% success rate in grade III patients (Table 3). More than 60% of patients have been followed for more than 2 years. One hundred and forty patients (23%) were followed >3 years. Of those 106 (76%) underwent VCUG as a part of the routine protocol to evaluate radiologic rate of VUR recurrence. None showed VUR recurrence. One patient demonstrated de novo reflux. US demonstrated normal appearance of kidneys in all but 10 patients (1.2%). Vesicoureteral junction obstruction requiring ureteral reimplantation developed in 6 ureters (0.7%; Clavien grade IIIb). Four RRUs (0.5%) required stent insertion because of the deterioration due to hydronephrosis, which resulted in complete resolution of obstruction (Clavien grade IIIb). Twenty-three patients (3.8%) suffered afebrile UTI (Clavien grade I). Seven patients (1.2%) developed febrile UTI (Clavien grade II). All those patients underwent VCUG. None demonstrated VUR recurrence on VCUG.

Table 1. Demographic data and patient characteristics

	n
No Gender	
Male	210
Female	401
No VUR cases (RRUs)	809
Primary, n (%)	674 (83.3)
Complex, n (%)	135 (16.7)
Mean age, range (mo-y)	3.6 (1-18)
No laterality (pt)	
Unilateral	413
Bilateral	198
No grade (RRUs), n (%)	
I	24 (2.96)
II	123 (15.2)
III	451 (55.8)
IV	158 (19.5)
V	53 (6.6)
Indications for surgery, n (%)	
Breakthrough UTI	482 (79)
High-grade VUR	89 (14.6)
Parent's request	40 (6.5)
Mean injected volume, mL, (range)	0.4 (0.2-1.3)

No, number; Pt, patients; RRU, renal refluxing units; UTI, urinary tract infection; VUR, vesicoureteral reflux.

COMMENT

This large multicenter survey confirms that subureteral Vantris injection is a simple and effective outpatient procedure for all grades of vesicoureteral reflux. Children return to full activity on the day of surgery and the procedure is well tolerated. No clinically untoward effects were reported in any patient from the use of Vantris used to correct reflux. The only significant complication of this procedure has been failure to resolve reflux at the initial injection. Reflux resolves in approximately 94% of refluxing ureters after first Vantris injection and an additional 3.8% require >1 injection. The main factor that

Table 2. Outcome of endoscopic correction of VUR in 809 RRUs

Endoscopic Injection	Outcome, n (%)
Correction after 1st injection	759 (93.8)
Correction after 2nd injection	26 (3.1)
Correction after 3rd injection	6 (0.7)
Downgrading of VUR	5 (0.6)
Failure and ureteral reimplantation	13 (1.6)

Abbreviations as in Table 1.

Table 3. Outcome of endoscopic correction in 809 RRUs with regards to the initial VUR grade after single injection

VUR Grade	No RRU	Resolved VUR (No RRU), n (%)
Grade I	24	24 (100)
Grade II	123	122 (100)
Grade III	451	448 (99.3)
Grade IV	158	150 (94.9)
Grade V	53	39 (73.6)

Abbreviations as in Table 1.

influenced success rate in our series and required in some cases a repeat injection or led to the ureteral reimplantation was the initial reflux grade. As it was expected, the patients with grade 5 required in some cases >1 injection to cure VUR; although, 73% success rate after single injection was acceptable in the endoscopic setting of VUR treatment. Another concern, which has been raised recently with the use of Vantris is ureteral obstruction after injection.[19] The UVJ obstruction rate in our series of 809 injected ureters was 1.2%. The obstruction was resolved after internal stent injection in 4 ureters (0.5%) and the remaining 6 (0.7%) required reimplantation. In one of the largest series of endoscopic correction of reflux in more than 12,000 ureters published by Puri and Granata[18] demonstrated that only 0.33% of all treated with Teflon ureters required ureteral reimplantation after obstruction. The previously reported figures regarding ureteral obstruction with Deflux injection ranged between 0.7% and 1.3%. However, recently Mazzone et al[6] presented some disturbing figures which showed that 9.3% patients treated with Deflux injection presented with UVJ obstruction and required ureteral reimplantation or stent insertion in half of the obstructed ureters. Some researchers blamed nonbiodegradable nature of Vantris with regards to the UVJ obstruction. However, aforementioned obstruction rate after Deflux injection significantly challenges these conclusions. We speculate that the underlining ureteral pathology may lead to the UVJ obstruction after Vantris injection. As we have treated a large population of patients with refluxing megaureters, it is possible that some of our patients presented initially with obstructing refluxing ureters and the injection solved the reflux on one hand and increased the obstructive component on the other, which finally led to the surgical reimplantation. In fact, the pathological reports from the patients who required reimplantation from one of the participating study centers demonstrated the obstructive segment in the intramural part of the ureter with minimal surrounding Vantris implant reaction. The possibility of UVJ obstruction after endoscopic correction cannot be brushed aside, and in some cases, earlier than 1 month after injection US is required to avoid renal damage after obstruction.

Over the last years, the management of VUR has become more controversial. Recently published by AAP subcommittee on Urinary Tract Infection, the 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 a rather benign homogenous condition. Some pediatric urologists 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. The main indication for surgery (79%) in the group of patients reported here was febrile UTI while on antibiotic prophylaxis. After successful correction of reflux, only 1.2% patients went on and demonstrated febrile UTI in spite of reflux correction. These prospective data are supported by our previous retrospective analysis and further iron out that endoscopic correction of VUR in selective group of patients might avoid further pyelonephrithis.[10,11,20-23]

Repeat VCUG was performed in 76% of those patients who completed 3 years of follow-up. The rest of the patients refused suggested follow-up VCUG because of infection-free status, absence of any clinical symptoms, and normal follow-up US. It is worth to stress it out that those 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 patient gender. None of our patients have had voiding problems before reflux correction. More than half of our patients who underwent 1 and 3 years VCUG had grade 3-5 VUR before endoscopic correction; therefore, we feel that the Vantris characteristics have contributed to the long-term success.

Some study limitations should be mentioned. The endoscopic correction of VUR was performed by numerous numbers of surgeons with different levels of expertise in endoscopic reflux correction. The study protocol was slightly different in some centers. We did not obtain VCUG in all patients who completed 1 and 3 years of the follow-up. However, it is worth mentioning that all participating center have monitored prospectively all 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 US examination. So far, we have performed ureteral reimplantation only in a small number of patients who were previously injected with Vantris. Therefore, we do not have enough data to comment on any specific difficulties in these patients and 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 no recurrence during prospective follow-up.

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APPENDIX

Vantris Follow-up Multicenter Study

- Period of study.....
- No of patients..... Female..... Male.....
- Mean age..... Age range.....
- No of primary renal refluxing units (RRU).....
- No of complex cases.....
- (Specify: Duplex, Post reimplantation etc).....
- Mode of presentation (UTI, Antenatal, Others).....
- Indications for surgery.....

1. Outcome of primary VUR

VUR Grade	No of Injections and Success (%)					
	RRU No	1st Injection		2nd Injection		3rd Injection	
		No	%	No	%	No	%
I							
II							
III							
IV							
V							

2. Outcome of complex VUR

VUR Grade	RRU No	No of Injections and Success (%)					
		1st Injection		2nd Injection		3rd Injection	
		No	%	No	%	No	%
I							
II							
III							
IV							
V							

- No of ureters failed and required reimplantation.....
- Follow-up length months mean (range).....
- VCUG after 3-6 months.....
- Follow-up VCUG if any (to specify when).....
- Follow-up US (to specify period).....
- VUR recurrence if any (to specify when).....
- Febrile UTI during follow-up.....
- Afebrile UTI during follow-up.....
- Complications.....
- Comments if any.....