



High success rate with new modified endoscopic treatment for high-grade VUR: A pilot study with preliminary report

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Summary

Purpose

Despite the benefits of the minimally invasive endoscopic treatment for vesicoureteral reflux (VUR) it has a major drawback which is low success rate in high grade VUR. For overcoming this problem, we introduce a new modified technique of endoscopic treatment called periureteral injection technique (PIT).

Materials and methods

In a prospective study a total of 37 ureters in 19 boys and 14 girls were treated, including 3 bilateral cases. Of 37 units, 30 (81.1%) had grade IV and 7 (18.9%) had grade V primary VUR (18 right, 13 left and 3 bilateral units). Subureteral injection of Vantris[®] was done at the 5-o'clock and 7-o'clock positions in which the direction of injecting needles were almost parallel. Pre- and post-operative eval-

uation included urinalysis, urinary tract ultrasonography, voiding cystourethrography (VCUG), dimercaptosuccinic acid scan and urodynamic studies.

Results

The median age was 38 months (range 8–125). At 6 months follow up period confirmed with VCUG, the VUR has been disappeared in 34 (91.8%) units and 3 units [2 (5.4%) grade II and 1 (2.7%) had grade III] had downgraded VUR. Complications included early fever due to urinary tract infection in 1 children, transient dysuria in 2 patients and low back pain in one patient (Summary Table).

Conclusion

The success rate of PIT for treatment of high grade VUR is high. However, further studies with more patients and longer follow up periods are needed to draw final conclusion.

Table Demographic and clinical characteristics of patients and study results.

Variables	Values	Grade of reflux after PIT	
		Completely disappeared	Downgraded
Mean age, months (range)	38 (8–125)	–	–
Refluxing unit, n (%)	36 (100.0)	–	–
Grade IV	29 (80.6)	27 (93.1)	2 (6.9)
Grade V	7 (19.4)	6 (85.7)	1 (14.3)
Gender, n (%)			
Male	19 (57.6)	–	–
Female	14 (42.4)	–	–
Laterality, n (%)			
Left	12 (36.4)	–	–
Right	18 (54.5)	–	–
Bilateral	3 (9.1)	–	–
Follow-up period, months	6		
Postoperative complications, n (%)			
Fever	1 (2.8)	–	–
Dysuria	2 (5.5)	–	–
Flank pain	1 (2.8)	–	–

PIT, periureteral injection technique.

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Introduction

VUR affects approximately 1–3% of all children [1], making it the most common pediatric anomaly of the urinary tract [2]. Endoscopic periureteral injection of different materials is an accepted treatment for low-grade VUR [3]. Endoscopic technique is non-invasive compared with open surgery. Once the reflux is successfully corrected, there is no need to administer long-term antibiotic prophylaxis. Surgical intervention may be necessary in patients with breakthrough infection despite continuous antibiotic prophylaxis (CAP), non-compliance with the prophylaxis medications [4], high-grade VUR (Grade IV and V) and presence of pyelonephritic changes in kidney or congenital abnormalities [5]. For high-grade VUR, ureteral reimplantation has proven to be the standard therapy [6]. However, open surgery is an invasive method with its own complications, and Grade V VUR has been reported to be resistant to treatment in 20% of cases after ureteral reimplantation [7].

Endoscopic treatment of VUR was introduced in 1981 by Matouschek [8], and popularized in the early 1980s by O'Donnell and Puri [9]. Endoscopic treatment is an effective and minimally invasive approach to treating children with VUR. As the injection evolved, the endoscopic treatment became the first option for the management of VUR [10]. But the most important disadvantage of this procedure, especially in high-grade VUR, was its lower success rates at long-term follow-up [11]. In this pilot study, a new, modified endoscopic treatment method has been introduced for treatment of high-grade (IV and V) VUR – it is called the periureteral injection technique (PIT).

Materials and methods

Between February 2010 and May 2013, 33 consecutive children (19 boys and 14 girls) with high-grade primary VUR were studied in a prospective manner. A total of 36 ureters, including three bilateral cases (Grade IV VUR in 29 and Grade V VUR in seven cases), were treated with polyacrylate polyalcohol copolymer (Vantris[®], Promedon, Cordoba, Argentina) injection using the PIT. The indication for treatment was recurrent UTI despite CAP. All of the subjects had high-grade VUR and febrile UTI while they were receiving CAP. Febrile UTI was defined as rectal fever ≥ 38 °C associated with a positive urine culture and biological inflammatory syndrome (leucocyte count $\geq 15,000/\text{mm}^3$ and/or C-reactive protein (CRP) ≥ 15 mg/l). Urine cultures with $>10^5$ colony forming units/ml were regarded as UTI. In children who were not toilet trained, urine specimens were collected via sterile bags. Reflux was graded according to the International Reflux Study grading system [12].

A single surgeon treated all patients. The presence of VUR was confirmed by VCUG. In addition to VCUG, pre-operative evaluation consisted of blood chemistry, urinalysis and culture, urinary system ultrasonography, DMSA scan, and urodynamic studies. Only patients with primary VUR were included. Patients with PUV, bladder and bowel dysfunction, and anatomic abnormalities such as ureteral duplication and bladder diverticula were excluded from the study.

In toilet-trained children, bladder and bowel function were assessed only. Bladder and bowel dysfunction was

defined as a score of >6 for toilet-trained girls and >9 for toilet-trained boys, based on a dysfunctional voiding scoring system [13]. Furthermore, children with a history of ureteral or endoscopic injection were excluded. Patients with treatment failures were not offered reinjection. Success was defined as the elimination of VUR (Grade 0) with a single injection. The parents were well informed about the study protocol and all of them gave their informed consent before commencement of the study. The Medical Ethics Committee of Guilan University of Medical Sciences approved the study protocol.

The endoscopic technique

Periureteral injection was performed under general anesthesia using a 10-French (F) cystoscope and double hydrodistention implantation technique (HIT), with some modification. In the classic double-HIT injection method, the needle is passed into the ureteral orifice (UO) and inserted at the mid-ureteral tunnel at the six o'clock position. Sufficient bulking agent is injected to produce a bulge, which initially coapts the detrusor tunnel, while a second implant within the most distal intramural tunnel leads to coaptation of the UO (double-HIT method).

In the modified technique, the needle was passed into the UO at two different positions (five and seven o'clock positions). The direction of the inserted needle in these two positions was parallel to each other. This direction was carefully controlled during needle insertion and bulking agent injection. In other endoscopic techniques the injection is usually being done in 6 o'clock, but in PIT, the injection is being done in two sites (5 and 7 o'clock), and a coapted and narrowed ureteral tunnel similar to a nonrefluxing ureter is achieved. It results in satisfactory coaption and narrowing of ureteral orifices. All patients received 50 mg/kg cephalotin intravenously as the pre-operative antibiotic prophylaxis. Half of or two-thirds of the bladder's capacity was filled. Through a 23-gauge needle, Vantris[®] was injected submucosally below the ureteral orifice at the five and seven o'clock positions to create a prominent bulge and raise the distal ureter and ureteral orifice. The injection needles were in parallel, flat and did not cross over each other, nor were they at an acute angle. The injection was carried out slowly, while the entire length of the needle was advanced and held for 30 s. The injection made the ureteral orifice appear completely coapted and narrowed (see video as supplementary material). This technique included two injection sites in one session. No second endoscopic injection was performed. The patients were kept on antibacterial prophylaxis for 1 week after the procedure, unless the first ultrasound showed ureteral dilatation.

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Follow-up

Urinary tract ultrasonography was performed 1 and 4 weeks after injection to identify hydronephrosis and other complications. In addition, postoperative studies included

urinary system ultrasonography, blood chemistry, urinalysis and culture 1 and 4 weeks after injection, and at 3 and 6 months after the procedure. DMSA scan, urodynamic studies and VCUG were repeated at the 6-month postoperative follow-up. Children with failure underwent cystoscopy. The cystoscopy was performed solely to identify possible causes of failure (i.e. mound migration).

Results

The median age was 38 months (range 8–125). The mean volume injected per ureter was 2.3 ml (range 2–3). The amount of injected material was determined according to the patient's age or shape of the ureteral orifice. Reflux completely disappeared in 33 (91.7%) renal refluxing units. In two (5.5%) renal refluxing units, VUR downgraded to Grade II and they were taken off CAP. VUR downgraded to Grade III in one (2.8%) renal refluxing unit. In a breakdown of treatment success by grade, VUR completely resolved after the first endoscopic injection in 27 (93.1%) ureters with Grade IV and in six (85.7%) ureters with Grade V reflux. Two patients (6.9%) with Grade IV VUR demonstrated downgrading to Grade II. In addition, in one patient (14.3%) with Grade V VUR, the reflux was also downgraded to Grade III.

All patients were followed up for a minimum of 6 months postoperatively (median 12 months, range of 6–17 months). All renal refluxing units had dilatation of the renal pelvis on an ultrasound performed at 1 week of treatment, which disappeared, except in five (13.9%), in the next follow-up after 4 postoperative weeks. Postoperative complications included: fever in one (2.8%) patient who developed a UTI (urine culture with *Escherichia coli* $\geq 10^5$ colony forming units/ml); dysuria in two (5.5%) patients soon after the procedure; and mild-to-moderate flank pain in one patient (2.8%) at the 4-week follow-up. The average time for the endoscopic treatment was 42 min. There were no significant complications related to treatment. The causes of failure were determined based on cystoscopic findings. One patient had mound displacement of injected material. In two patients, the injected materials migrated to a medial or caudal direction in relation to the ureteral orifice. There was no de-novo contralateral reflux.

Discussion

The endoscopic treatment of VUR provides an acceptable success rate, with lower morbidity and cost, plus no scars. Also, it can be performed as an outpatient procedure. The optimal endoscopic technique for VUR remains controversial, especially for high-grade VUR. In 1995, Stenberg and Lackgren first described dextranomer/hyaluronic acid (Dx/HA) implantation using the traditional sub-trigonal injection (STING) procedure of inserting the needle approximately 3 mm distally into the orifice and then advancing it under the orifice for injection to create a mound [14]. They reported a 68% cure rate at 3-months follow-up. Kirsch and colleagues subsequently reported a modified technique of placing the needle directly into the ureteral orifice for injection [15]. Then, they revised this procedure as the hydrodistention implantation technique (HIT) for more

ureteral wall coaptation, in addition to orifice closure [16]. They reported an overall success rate of 90%, but the differences were only significant for Grade III VUR.

The reported overall success rate of endoscopic correction of reflux is as high as 70% [17,18], but studies addressing the overall success rate for high-grade reflux (Grades IV and V) are scarce. The reported success rate for high-grade VUR is 50–80% [19]. However, higher success rates have been reported in some studies. The most important factor affecting the success rate of endoscopic treatment is grade of VUR. The chance of VUR disappearing is lower in higher grades [18,19]. Despite many advantages of endoscopic treatment of VUR compared with open surgery (95–100% success rate), its effectiveness for high-grade reflux still has drawbacks [7,20]. The outcomes were predominantly Grade IV. Kaye and colleagues studied 336 patients with primary VUR (Grades I–IV) who were treated with dextranomer/hyaluronic acid via the Double-HIT method [21]. Initial radiographic success rate (after one injection) was 90%. Lackgren and Kirsch [22] have also reported similar results. Shim and colleagues treated 63 patients with Grade IV or V reflux using the conventional STING method [23]; the overall resolution rate was 67% for Grade IV and 43% for Grade V. Dawrant and colleagues retrospectively studied the long-term efficacy and safety of endoscopic treatment in 642 high-grade refluxing units with Grade III–V disease [24]; overall, complete resolution of VUR occurred after a single injection in 69%.

Downgrading of high-grade VUR is also a reasonable option in the treatment of children with Grade IV–V reflux who develop breakthrough UTIs [25]. Sometimes downgrading of reflux will result in cessation of febrile UTIs and more spontaneous resolution of VUR. The modified new PIT has partly overcome this problem, and the outcomes are comparable with those reported for Grade IV with Double HIT by the Emory group [22,23].

In addition, bleb size correlates with treatment success. A measured volume >25% of the injected volume will result in 90% and 95% cure in HIT and double HIT methods, respectively [26,27]. In the PIT, larger bleb size can be achieved. In high-grade VUR, the lumen of ureteral orifice is more dilated than usual. Because of intraureteral or sub-ureteral injection, the created bulging does not cover the lumen properly. Therefore, it results in a crescent-shape of the upper border and makes a roof gutter effect in the lateral aspect of the lumen, which allows efflux of urine into the ureter. This could possibly explain the lower success rate of other methods of endoscopic treatment compared with the PIT. With the PIT, the ureteral orifice is coapted and narrowed alongside the intramural ureter.

In the current study, patients treated with Vantris[®] injection experienced few complications. One patient experienced postoperative flank pain, one developed fever, and two had dysuria. These findings are in agreement with previous studies [28]. Since age, gender, and bilaterality of VUR don't affect treatment outcomes [29], the correlations between these variables and treatment outcomes were not assessed.

This pilot study had some limitations. The most important ones were small sample size and a short-term follow-up period. Most notably, there were only seven Grade V ureters. This is too small to make definitive conclusions

about the success of this technique for Grade V VUR. Additionally, Vantris is not FDA approved for use in the USA. Moreover, urine specimens were collected via sterile bags in patients who were not toilet trained.

Superior success rates have been realized with the double HIT technique; but, there is no clear-cut documentation of any particular technique being superior, and selection of a given technique is typically individualized to the child at the discretion of the operating physician.

Conclusion

In this pilot study, the PIT had high success rates in improving high-grade VUR. However, further studies with larger sample sizes and longer follow-up periods are needed to confirm these findings.

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