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Surgery Alive

Modified unilateral periureteral injection technique in the treatment of patients with high-grade vesicoureteral reflux: A study of primary findings

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Vesicoureteral reflux

Abstract *Objective:* Although endoscopic treatment has been used by many pediatric urologists for the treatment of vesicoureteral reflux (VUR), it has no considerable success in high-grade VUR. We aimed to describe the primary outcomes of unilateral periureteral injection technique (PIT), as well as bilateral PIT in high-grade VUR.
Methods: In this prospective study, we examined 92 ureters in 45 boys and 40 girls from February 2010 to May 2018. Bilateral PIT and unilateral PIT were applied in 67 and 25 refluxing units, respectively. In the unilateral PIT, the subureteral injection site was only at the 5- or 7-o'clock position. However, in the bilateral PIT, the subureteral injection sites were at 5- and 7-o'clock position. Pre- and post-operative reflux grades were evaluated by voiding cystourethrography 6 months after surgery.
Results: Seven patients had bilateral reflux. Overall, 75 (81.5%) ureters showed Grade IV VUR, while 17 (18.5%) had primary Grade V VUR. The mean age of the subjects was 39.2 months. In unilateral PIT ureters, VUR was resolved in 23 (92.0%) refluxing units. It was downgraded to Grade III in one ureter (4.0%) and to Grade II in another ureter (4.0%). In addition, in bilateral PIT cases, VUR was resolved in 60 (89.6%) ureters; it downgraded to Grades II and III in 3 (4.5%) and 4 (6.0%) refluxing units, respectively.

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Conclusion: Unilateral PIT can be highly effective in the treatment of selected ureters of high-grade VUR. However, further studies are needed to confirm our results.

1. Introduction

Vesicoureteral reflux (VUR), as the most common pediatric anomaly of the urinary tract, affects approximately 1%–3% of all children and 30% of children with a history of febrile urinary tract infection (UTI) [1,2]. Endoscopic treatment, as an effective and minimally invasive approach, has been used by many pediatric urologists for the treatment of these patients [3]. Matouschek [4] first introduced this therapeutic approach in 1981, and Puri and O'Donnell [5] popularized it in the early 1980's. Generally, endoscopic treatment has many advantages over open surgery in VUR [6].

Although more than three decades have passed since the introduction of endoscopic treatment, no considerable success has been achieved in the treatment of high-grade VUR (Grades IV and V). Inevitably, ureteral reimplantation has become the standard therapy for high-grade VUR [7]. To overcome the shortcomings, we introduced a new modified endoscopic treatment, called bilateral periurethral injection technique (PIT) in a previous study and reported the primary outcome that had an acceptable success rate in patients with high-grade VUR [8]. In the bilateral PIT, injection is performed in the subureteral orifice at 5- and 7-o'clock positions.

In the present study, for the first time, we present the primary results of a unilateral PIT, in which subureteral injections were performed in the subureteral orifice only at 5- or 7-o'clock positions in selected ureters. Meanwhile, we report the primary outcomes of ureters in the bilateral PIT.

2. Patients and methods

2.1. Patients and ethics

In this prospective study, all patients with high-grade VUR, presenting to the Razi Educational Hospital of Guilan University of Medical Sciences, Rasht, Iran, from February 2010 to May 2018, were enrolled in the study. The parents were informed about the study protocol before entering the study, and written informed consents were obtained from all patients' guardians. The method of the study was approved by Medical Ethics Committee of the Guilan University with the study protocol (IR.GUMS.REC.1398.485).

The endoscopic injection was used in the cases antibiotic prophylaxis failed and UTI got worse. International Reflux Study Grading Systems were used to determine the reflux grading of patients enrolled in the study [9]. All patients had VUR according to voiding cystourethrography and only those with primary high-grade VUR were included in this study. In addition to voiding cystourethrogram, preoperative evaluation consisted of blood chemistry, urinalysis and urine culture, urinary system ultrasonography, and dimercaptosuccinic acid scan were taken before study.

The exclusion criteria were having a posterior urethral valve, neurogenic bladder, bladder or bowel dysfunction, and anatomic abnormalities, such as ureteral duplication, bladder diverticulum, secondary obstruction due to severe dilated and tortuous refluxing ureters, and chronic and congenital disease. In toilet-trained children, only bladder and bowel function were assessed. Based on a dysfunctional voiding scoring system, the score more than 6 for toilet-trained girls and more than 9 for toilet-trained boys were considered as bladder and bowel dysfunction [10].

Treatment success was defined as VUR disappearance as Grade 0.

2.2. Endoscopic technique

All procedures were carried out by only one senior surgeon (Asgari SA), under general anesthesia, using a 10 Fr cystoscope (Storz®, Tuttlingen, Germany). All patients received 50 mg/kg of cephalozin (Zydus Cadila Healthcare Ltd, Ahmedabad, India) intravenously as the preoperative antibiotic prophylaxis. As previously reported [8], Vanteris® (Promedon, Córdoba, Argentina) was injected submucosally below the ureteral orifice using a 23-gauge needle at 5- and 7-o'clock positions to create a prominent bulge and raise the distal ureter and ureteral orifice. The injection needles were parallel to each other; in other words, they did not cross each other and were not at an acute angle. The direction of the needles was carefully controlled during needle insertion and bulking agent injection. Injection was performed slowly by advancing the needle and holding it for 30 s. Through this injection, the ureteral orifice appeared completely coated and narrowed (Supplementary Video 1).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.ajur.2021.11.011.

On the other hand, in unilateral PIT cases, a subureteral injection was performed only in one side at 5- or 7-o'clock position. When visually satisfactory coaptation and narrowing of the ureteral orifice was achieved, no subureteral injection was performed on the opposite side (Supplementary Video 2).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.ajur.2021.11.011.

2.3. Postoperative management

Antibiotic prophylaxis was used preoperatively and continued for 1 week after the procedure unless the first

ultrasound showed ureteral dilatation. Urinary ultrasound was performed 4 weeks after injection to identify hydronephrosis and other complications. In addition, postoperative studies included urinary ultrasound, blood chemistry, urinalysis, and culture 1 and 4 weeks after injection and 3 and 6 months after the procedure. Finally, voiding cystourethrogram and dimercaptosuccinic acid scan were repeated at 6-month postoperative follow-up.

2.4. Statistical analysis

Chi-square test (categorical data) and independent sample *t*-test (numerical data) were used for comparisons. Data are given as mean±standard deviation (SD). Statistical analysis was performed using SPSS 24 software (IBM Corp., Armonk, NY, USA). The *p*-value $\leq$0.05 was regarded statistically significant.

3. Results

We evaluated a total of 85 children including 45 boys and 40 girls with high-grade VUR, including 92 ureters with 67 bilateral ureters. Out of 92 high-grade VUR ureters, Grades IV and V were reported in 75 (81.5%) and 17 (18.5%) refluxing units, respectively; these patients were treated by PIT injection of polyacrylate polyalcohol copolymer. The mean age of children was 39.2 (SD 8.4) months and range was from 8.0 to 126.0 months. The mean injection volume per ureter was 1.7 (range 1.0—4.2) mL in bilateral PIT and 0.9 (range 0.8—1.0) mL in unilateral PIT. The amount of injected material was determined based on the patient's age, ureteral orifice shape, and mound and coaptation location.

In bilateral PIT cases, VUR completely resolved in 60 (89.6%) renal refluxing units; VUR was downgraded to Grades II and III in three (4.5%) and four (6.0%) renal refluxing units, respectively. On the other hand, in unilateral PIT cases, VUR completely resolved in 23 (92.0%) refluxing units; it was downgraded to Grade III in one case (4.0%) and to Grade II in another (4.0%).

Continuous antibiotic prophylaxis was terminated in Grade II patients. With respect to treatment success, VUR completely resolved after bilateral PIT in 49 (65.3%) ureters with Grade IV VUR and in 11 (64.7%) ureters with Grade V VUR. On the other hand, in unilateral PIT cases, VUR completely resolved in 20 (26.7%) ureters with Grade IV VUR and 3 (17.6%) ureters with Grade V VUR.

All patients were followed up for a minimum of 6 months after surgery (range 6—17 months). Postoperative complications included fever in two (2.4%) patients with UTIs, transient dysuria in six (7.1%) patients, and mild to moderate flank pain in two (2.4%) patients 4 weeks after the procedure (Table 1). The mean surgery duration was 13 (range 8—15) min and 19 (range 14—21) min in unilateral PIT and bilateral PIT, respectively. It is found that unilateral PIT can be effectively performed in some patients, similar to bilateral PIT and there was no significant relation between unilateral and bilateral injection (p=0.734). No serious treatment-related complications, such as ureteral obstruction, were reported.

Table 1 The demographic and clinical characteristics of patients and study results.

Variable	Value
Mean age, mean±SD (range), month	39.2±8.4 (8.0—126.0)
Refluxing unit, *n* (%)	
Grade IV	75 (81.5)
Grade V	17 (18.5)
VUR completely resolved, *n* (%)	
Bilateral PIT (*n*=67)	60 (89.6)
Unilateral PIT (*n*=25)	23 (92.0)
Downgraded to Grade II, *n* (%)	
Bilateral PIT (*n*=67)	3 (4.5)
Unilateral PIT (*n*=25)	1 (4.0)
Downgraded to Grade III, *n* (%)	
Bilateral PIT (*n*=67)	4 (6.0)
Unilateral PIT (*n*=25)	1 (4.0)
Sex, *n* (%)	
Boy	45 (52.9)
Girl	40 (47.1)
Laterality, *n* (%)	
Left	33 (38.8)
Right	45 (52.9)
Bilateral	7 (8.2)
Post-surgery complications, *n* (%)	
Fever	2 (2.4)
Dysuria	6 (7.1)
Flank pain	2 (2.4)

PIT, periureteral injection technique; VUR, vesicoureteral reflux; SD, standard deviation.

4. Discussion

Endoscopic treatment of VUR has an acceptable success rate and low morbidity. This cost-effective approach causes no scars and can be applied as an outpatient procedure. It is recognized as a standard therapeutic method, especially for low-grade VUR because of its minimally invasive nature and high success rate similar to open surgery [11]. However, a major disadvantage of endoscopic management is the low success rate in patients with high-grade VUR. The most important factor affecting the success rate of endoscopic treatment is the grade of VUR [11].

A meta-analysis by Elder et al. [12] revealed that the success rate of endoscopic management decreases as the reflux grade increases. The reported success rates for Grades IV and V VUR were 63% and 51%, respectively. To overcome this major disadvantage and increase the success rate, endoscopic treatment was modified by Kirsch et al. [13]. In their technique, the needle was directly injected into the ureteral orifice [13]. The procedure was modified as a hydrodistention implantation technique (HIT) for greater ureteral wall coaptation, in addition to orifice closure [14]. Compared with the previous technique, this modified approach showed a success rate of more than 90% in all ureters with Grade I to Grade IV reflux; however, the difference was only significant for Grade III patients [15].

Although some researchers have reported excellent success rates with up to three injections for high-grade VUR

[16], others have only reported a success rate of 41% in patients with Grade IV reflux [17]. Only a few studies have addressed the overall success rate of treatment for high-grade VUR (Grades IV and V). Overall, the success rate for high-grade VUR ranges from 50% to 80% [16]. Conversely, higher success rates have been reported in some studies using HIT [18,19]. It should be noted that these studies were mainly carried out among Grade IV patients and reported controversial results [11,16,18]. In addition, other studies with a multivariate analysis method have failed to demonstrate any significant differences in patient outcomes between HIT and conventional ureteral orifice injection [15,20–22].

Endoscopic treatment for high-grade VUR has several disadvantages [11]. This is an inspiration for urologists that endoscopic treatment can compete well with open surgery treatment for high-grade VUR. In a preliminary report, we introduced a new modified endoscopic PIT with promising results [8]. Unlike others techniques, of which subureteral injection is performed at a 6-o'clock position, injections in PIT are done at 5- and 7-o'clock positions for high-grade VUR (Grades IV and V); this technique was called bilateral PIT with a success rate of 90%. We improved this technique by reporting more cases in the present study. In the modified approach, injections are performed only at 5- or 7-o'clock positions for the selected cases; this technique is called unilateral PIT with a success rate of 92%. Our findings showed that the primary outcomes of unilateral PIT are as promising as bilateral PIT.

The overall success rate of PIT (unilateral or bilateral) is 90%, and this technique can effectively downgrade high-grade VUR. In some cases, downgrading high-grade VUR can stop febrile UTI and result in a more spontaneous resolution of VUR. Accordingly, PIT can be regarded as an appropriate treatment for high-grade VUR [23]. It should be noted that downgrading VUR by at least two grades is considered a significant improvement [2].

We need to determine the important features of PIT, which result in its higher success rate. Generally, coaptation, along with lengthening, is more valuable than a volcano-shaped mound alone [24]. The advantages of our technique can be described that PIT is more convenient and no guide wire is needed unlike double HIT and high-grade VUR has a shorter intramural ureteral length; therefore, in double HIT of ureter, injection is usually done outside the intramural ureter. This can increase the risk of extravasation and migration since the wall thickness of the extramural ureter is significantly less than that of the intramural ureters [25]. However, PIT has enough tissue support and thickness due to subureteral injection, which decreases the risk.

In PIT, we could achieve coaptation of the ureteral orifice with better lengthening and narrowing, in addition to optimal mound morphology. The bulge created by the intraureteral or subureteral injection at 6-o'clock position cannot cover the lumen properly. It creates a crescent-shaped upper border and produces a roof gutter effect in the lateral aspect of the lumen, which allows urine efflux into the ureter. However, in PIT, there is no roof gutter effect on urine efflux. In addition, the ureteral orifice is coated and narrowed alongside the intramural ureter. In PIT, the bleb size and injection volume are correlated with treatment success [26].

In this technique, a larger bleb size can be achieved. Considering the advantages of PIT, we believe that our modification of this technique (unilateral or bilateral) can significantly improve the outcomes of high-grade VUR treatment. No serious complications, such as postoperative obstruction of the ureteral orifice, were reported. However, some of our patients experienced a few minor complications, such as postoperative flank pain ($n=2$, 2.4%), fever ($n=2$, 2.4%), and dysuria ($n=6$, 7.1%). The present study, which included more patients with high-grade VUR compared with our previous study [8], approved our previous findings regarding the high success rate of PIT in the treatment of high-grade VUR. However, as indicated earlier, we suggest a unilateral PIT when a visually satisfactory coaptation and narrowing of the ureteral orifice is achieved after a unilateral subureteric injection. Lastly, the most striking finding of this study is that we changed the conventional injection site (6-o'clock position) and obtained excellent results in the treatment of high-grade VUR.

Despite the valuable results of the present study and their important implications for future research, there are some limitations, such as the small sample size, short-term follow-up, and the use of a non-absorbable substance. It should be noted that the use of Vanteris® is approved in Iran, while in some countries, including the United States, it is prohibited.

5. Conclusion

Unilateral PIT, similar to bilateral PIT, can be effective in the treatment of selected cases of high-grade VUR. However, further research with a larger sample size and longer follow-up is needed to confirm our results.

Author contributions

Study concept and design: Seyed Alaeddin Asgari, Afshin Safaei-Asl, Mandana Mansour-Ghanaie, Seyed Mohammad Asgari, Seyed Ahmad Naseri Alavi.
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Conflicts of interest

The authors declare no conflict of interest.

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