

Can Peri-Operative Tolterodine Enhance the Success Rate Of Endoscopic Treatment For Primary Vesicoureteric Reflux? A Randomized Prospective Study

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Purpose: To assess the impact of bladder dysfunction on the success rate of endoscopic treatment (ET) of primary vesicoureteric reflux (VUR) and evaluate the ability of peri-operative tolterodine to improve the success rate of ET via stabilization of the detrusor.

Material and methods: Patients with primary VUR in need of ET were divided into two groups: Group A consisted of patients with elements of bladder dysfunction (Dysfunctional Voiding Symptoms Score (DVSS) >6 in females and > 9 in males) and Group B contained patients with "stable bladders".

Members of Group B were randomly assigned at their clinic follow up visit into two subgroups. Group B1 did not receive tolterodine. Group B2 was started on a prophylactic dose of tolterodine one week before ET and continued for a month thereafter.

Results: Forty four patients with a mean age of 5.2 years and with VUR were included in the study. In group B1, 18 of 24 (75%) ureters showed resolution of VUR. Among the 14 patients in group B2, 17 out of 23 (74%) refluxing ureters showed complete resolution. The overall success rate was 70% in all groups with 70 refluxing renal units.

No statistically significant difference in success rate was found between the three groups

Conclusions: We did not find a correlation between bladder dysfunction and the success rate of ET for VUR, and the presumed subclinical voiding dysfunctions do not appear to affect the outcome of ET for VUR, nor does prophylactic tolterodine treatment appear to enhance the success rate

Keywords: vesicoureteric reflux, bladder dysfunction

Introduction

Vesicoureteral reflux (VUR) is one of the most common urinary tract anomalies in childhood, affecting approximately 1% of all children¹. It must be treated properly to avoid the risk of upper urinary tract infections and long term kidney damage². Endoscopic injection of a bulking agent provides a high chance of immediate cure without the need for long term antibiotic prophylaxis, and unlike with open surgery, bladder function remains unimpaired^{3,4}.

There are contradictory results in the available literature regarding the relationship between voiding dysfunction and the success rates of endoscopic treatment (ET) of VUR. Some studies have reported that mild forms of lower urinary tract dysfunction do not influence the results of ET for VUR⁵, and others have indi-

cated that bladder dysfunction may contribute to ET failure⁶. However, most investigators are convinced of the need for prospective studies to delineate this phenomenon. We conducted a prospective study designed to investigate the relationship between ET of VUR and bladder dysfunction and at the same time to examine whether the use of peri-operative tolterodine can enhance the success rate of endoscopic correction in patients with primary VUR.

Materials and methods

All toilet trained children with VUR, as confirmed by a voiding cystourethrogram (VCUG), and seen in our clinic between 2005 and 2008, were evaluated for the presence of voiding dysfunction according to the Dysfunctional Voiding Scoring System⁹ (DVSS). They

were then divided into two groups, those with elements of bladder dysfunction (DVSS >6 in females and >9 in males) and those with "stable bladders" (DVSS <6 in females and <9 in males).

We included all patients who showed an indication for surgical intervention, such as breakthrough urinary tract infection despite antibiotic prophylaxis, intolerance and/or non-compliance to antibiotic regimens, no resolution of reflux after more than two years of follow up and high grade reflux with significant renal scarring. Patients with a lower anatomical urinary tract disease, such as posterior urethral valve, neuropathic bladder or a Hutch diverticulum, were excluded from the study.

The initial evaluation was based on the DVSS and included patient history, physical examination, VCUG, renal and bladder ultrasonography, urinalysis, and voiding diary.

Endoscopic correction was performed under general anesthesia and in the lithotomy position. All procedures were recorded on videotape.

Using a 10 F standard cystoscope with an offset lens, the ureteral orifice was hydrodistended while the bladder partially filled. We used dextranomer/hyaluronic acid copolymer (Deflux®) with the HIT technique¹⁰ for intraureteric injection modification with hydrodistention verification.

All children were enrolled in a bladder and bowel rehabilitation program that included the following: timed voiding every 2 to 3 hours, instructions for proper hygienic and positional measures during voiding (especially for girls), frequent fluid intake, and dietary changes to reduce carbohydrates and other non-residue diet items and replace them with increasing amounts of vegetables, fruits and other fiber forming elements to encourage at least one bowel movement per day of soft stool. Patients with bladder dysfunction according to the DVSS score, were started on anticholinergic medications, and ET was not done until we saw signs of improvement in bladder function.

Children in the stable bladder group were randomly assigned at their initial clinic visit into two subgroups: subgroup B1, in which only endoscopic correction was carried out, and subgroup B2, in which children were treated with a prophylactic dose of tolterodine starting one week before the procedure and continuing for a month thereafter.

Patients were evaluated 2 months after the procedure

by renal and kidney ultrasound to rule out an obstructed upper tract, and VCUG was performed to assess reflux status. Prophylactic antibiotics were continued until resolution of reflux was confirmed. Treatment success was defined as complete resolution of reflux. Cases with persistent reflux were considered treatment failures and were offered continued observation on prophylactic antibiotics and a second ET session.

Statistical comparisons of the different population variables and of the success of endoscopic treatment in all groups (patients with voiding dysfunction and patients with stable bladder either with or without tolterodine) were carried out.

Results

A total of 44 patients with 70 refluxing ureters were included in the study. Patient details are summarized in Table 1. All procedures were performed as day cases and patients received general anesthesia. All patients were taking a once-daily prophylactic antibiotic. No peri-operative complications were recorded. The grade of reflux ranged from 1 to 5 according to the International Reflux Study in Children classification¹¹; Grade 1 VUR was only treated when associated with contralateral VUR of higher grade. The overall success rate was 70% in all groups with the first injection.

In group one (patients with symptoms of bladder dysfunction, DVSS >6 in females and >9 in males), 15 patients with 23 refluxing ureters (8 patients had bilateral VUR) fulfilled the inclusion criteria and were managed with complete bowel and bladder rehabilitation before their endoscopic correction, together with anticholinergic medications. Out of these 23 refluxing ureters, 14 (60%) showed complete resolution of VUR with the first injection.

In group two (patients with stable bladders, DVSS <6 in females and <9 in males), 29 patients (47 refluxing ureters) were randomly and blindly assigned by card randomization into two groups. In group B1, 15 patients (24 ureters, 9 were bilateral) received only endoscopic injection, and of these 24 ureters, 18 (75%) showed resolution of VUR. In group B2, 14 patients (23 ureters, 9 were bilateral) received tolterodine, and 17 of 23 (74%) refluxing ureters showed complete resolution (Table 2).

No statistically significant difference in success rate was found between the three groups ($P=0.464$), between the two main groups ($P=0.254$) or between group B1 and B2 ($P=0.365$) (Table 3).

Table 1: Patient characteristics

	Number	Percentage (%)
Gender		
M	18	40.8
F	26	59.1
Age		
Mean	5.2	
Range	3 to 10	
Bilaterality	26	59.1
Grade of VUR		
G1	2	2.8
G2	22	31.4
G3	27	38.6
G4	12	17.2
G5	7	10

Table 2: Success rate among groups.

Group A: bladder dysfunction group; Group B1: stable bladder, no tolterodine; Group B2: stable bladder with tolterodine.

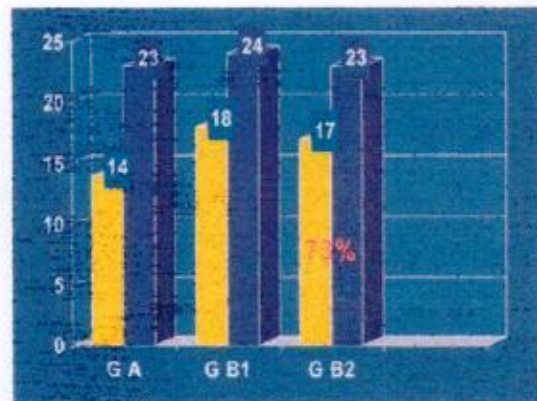


Table 3: Statistical significance.

Between the three groups	Between the two main groups, A and B	Between groups 1 and 2
(P = 0.464)	(P = 0.254)	(P = 0.365)

Discussion

The introduction of ET for VUR was a radical departure from the standard treatment of surgical intervention and observational management¹².

Despite the worldwide interest in this minimally invasive procedure and increasing experience, the overall long term success rates are still inferior to open surgery, ranging between 72% to 95% regardless of the primary pathology or the material used¹³. Therefore, investigators are continuing to look for different ways to enhance the success rate of this minimally invasive modality.

Proposed causes of treatment failure include leakage of the bulking agent to the bladder through the needle track¹⁴, mucosal ulceration above the injection site, and

displacement of the mound by possible bladder instability due to inherit voiding dysfunction¹⁵.

A relationship between bladder dysfunction and VUR is generally acknowledged, with a high proportion of children with VUR having overactive bladders or dysfunctional voiding⁷. Numerous reports implicate detrusor instability as the cause of VUR^{16,17}, while others suggest that children with bilateral reflux have a higher incidence of bladder dysfunction than those with unilateral reflux¹⁸. Regardless of whether reflux is caused by bladder dysfunction or not, a second important issue is the effect of this voiding dysfunction on the endoscopic treatment of VUR. This effect is not clear in the literature with some investigators claiming that voiding dysfunction is a negative factor that lowers the success rate of ET and others saying that it has no effect^{7,8}.

However, all of these studies were retrospective studies, and many investigators have noted the need for a prospective study to give a solid answer to this question^{7,19,20}.

We designed a prospective study that to our knowledge is the first to assess the relationship between bladder dysfunction and the success rate of ET for VUR.

The patient group with symptoms of bladder dysfunction was treated with proper bowel and bladder rehabilitation, and all patients were required to show signs of improvement before they were subjected to ET. Patients with no symptoms of bladder dysfunction (stable bladder group) were randomly assigned into two groups, one of which received tolterodine peri-operatively to assess the effect of using anticholinergic medications to abolish subclinical bladder dysfunction.

In our study, by statistically comparing the success rate of patients with bladder dysfunction with that of patients with stable bladders, we found that bladder dysfunction had no effect on the success rate of ET. At the same time, we found that peri-operative administration of an anticholinergic as a prophylactic had no significant effect in patients with primary VUR and stable bladders. For further confirmation, we compared the three groups and found no statistical difference in the success rate of ET. This finding offers further evidence of the lack of influence of bladder dysfunction on the success rate of ET in patients with VUR.

Our sample size was small, and further studies with

larger samples are needed to study this effect.

Conclusions

We did not find a correlation between bladder dysfunction and the success rate of ET for VUR. The presumed subclinical voiding dysfunctions do not appear to affect the outcome of ET for VUR, nor does prophylactic tolterodine treatment appear to enhance the success rate

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