

# Long-Term Results of Dexell Endoscopic Treatment of Vesicoureteral Reflux: An Option for the Management of Recurrent Urinary Tract Infection

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## Abstract

**Background:** Recurrent urinary tract infection (UTI) due to vesicoureteral reflux (VUR) is common in Iraq. Endoscopic treatment of VUR is used with advantages over antibiotic prophylaxis and ureteral reimplantation.

**Objectives:** This study was performed to assess the efficacy of a new agent, Dexell, for treating patients with VUR and its ability to manage recurrent UTI.

**Materials and Methods:** This research was a prospective study recruiting 156 patients with VUR treated by endoscopic subureteric injection of Dexell.

**Results:** VUR were unilateral in 87 cases and bilateral in 69 cases. VUR grades II-V were 18.7%, 28%, 32%, and 21.3%, respectively. The success rates were 64% after the first injection, 82.7% after second injection, and 93.3% after third injection. All patients with grades II and III were resolved completely while the success rates in higher grades were 91.7% for grade IV and 87.5% for grade V. No significant difference was noted between males and females regarding the success rate of endoscopic treatment (92% vs 91.6%,  $P > 0.05$ ). Recurrent UTI did not occur throughout the study period after the operation.

**Conclusions:** Cystoscopic injection of Dexell is an effective method for treating patients with VUR. It is a safe day case procedure that can prevent recurrent UTI in patients with VUR.

**Keywords:** VUR, Dexell, Recurrent UTI, Duhok, Iraq

## 1. Background

Urinary tract infections (UTIs) are common bacterial infections with an estimation of 150 million episodes in the world per year. The community-acquired uncomplicated lower UTI is the most common form that is often handled in primary care units (1). VUR is one of the most common urological abnormalities in paediatric population affecting 1-3% of children and 30-50% of patients diagnosed with UTI (2, 3). It has also been blamed for causing recurrent UTI and renal scarring (3, 4). In a study conducted in the USA, it was found that less virulent bacteria caused infection such as cystitis in subjects with neurogenic bladder, nonneurogenic bowel, and bladder dysfunction. On the other hand, bacteria with higher virulence determinants cause more severe UTI in patients with primary vesicoureteral reflux (5). To prevent VUR-related complications, patients can be managed by continuous antibiotic prophylaxis (CAP), surgical ureteral reimplantation, or endoscopic treatment by injecting bulking agents (2). Continuous and long-term use of antibiotics might be associated with increased levels of antibiotics resistance (6, 7). Recently, American urology

association (8) guidelines stated that patients over 1 year of age who received CAP and developed febrile breakthrough UTI should be considered for open surgical ureteral reimplantation or endoscopic injection of bulking agents (8). Many authors recommended endoscopic treatment (ET) as the first line of treatment (9-15). Dexell is a new product, which is biochemically similar to Deflux but with different molecular size. Deflux has dextranomer microspheres ranging in size from 80 to 250 microns (an average size of 130 microns) while the size of Dexell dextranomer microsphere is 80 to 120 microns. Therapeutically, no significant difference in the outcome of these two agents has been found (16, 17). The ideal injectable bulking agent should be durable, effective, safe, stable, none migrating, biocompatible, none-antigenic, and none-carcinogenic (18, 19).

## 2. Objectives

This study was performed to assess the efficacy of Dexell in treating patients with VUR of grades II-V and subsequent effect on recurrent UTI. The study setting was Heevi

hospital, Duhok, Kurdistan region, Iraq.

### 3. Materials and Methods

#### 3.1. Study Design

This was a prospective study conducted on 156 patients with VUR to assess the efficacy of Dexell therapy. All patients had recurrent UTI and received at least one shot of antibiotic suppression therapy. The study conducted at pediatric surgery department in Duhok, Kurdistan region from January 2012 to January 2015. Patients with grades II-V VUR with febrile breakthrough UTI were enrolled in the study. Those with previous failed ureteral reimplantation and patients with pre-existing or associated urological anomalies were also included in the study.

The procedure was performed on an outpatient basis and all patients received preoperative prophylactic antibiotics. Cystoscopy was performed under general anaesthesia and the bladder, urethra, and ureteric orifices were evaluated and any abnormality was recorded. Dexell was used for the injection through a rigid fine needle. Subureteric transurethral injection technique was performed on 150 patients. Six patients with grade V and hugely dilated ureteric orifice underwent hydrodistension implantation technique. All patients were discharged on the same day. The ET took 1 to 3 sessions depending on the success of operation. Patients were followed up postoperatively at the first and second month with clinical evaluation and urine analysis (to exclude UTI). Three months after operation, voiding cystourethrography were conducted on all patients to assess their responses. Patients with persistent reflux were scheduled for another session while those who responded to ET were evaluated after 1 year for the recurrence of reflux and frequency of UTI occurrences. Clinical evaluation, urine analysis and or urine culture was performed at each visit to exclude UTI.

#### 3.2. Ethics Statement

Written consents were taken from patients' guardians involved in the study. This study and method of attaining consent were approved by ethics committee of the University of Duhok, school of medicine, Kurdistan region, Iraq.

### 4. Results

VUR was unilateral in 87 cases and bilateral in 69 cases with a total of 225 refluxing ureters. VUR grades II-V were 18.7%, 28%, 32%, and 21.3%, respectively. Overall success rates after the first, second, and third injections were 64%, 82.7%, and 93.3%, respectively. Patients comprised 106 females and 50 males. Their ages ranged from 6 months to 13 years and mean follow-up period was 24 months. There were 10 patients with previous failed ureteral reimplantation, 24 patients with associated neurogenic bladder, and 2 have duplicated ureteral anomalies. The success rates were 64% after the first injection, 82.7% after the second

injection, and 93.3% after the third injection. All patients with grades II and III were resolved completely while the success rates in higher grades were 91.7% of grade IV and 87.5% for grade V ( $P > 0.05$ ). There was a failure of ET in 15 refluxing unit in 12 patients (6.7%) after the third injection, 6 of them had previous ureteral reimplantation, 1 with complex ureteral anomalies, 4 patients had neurogenic bladder, and 1 patient with gross hydroureteronephrosis. Recurrent UTI did not occur in patients with successful operations throughout the study. No significant difference was found between male and female patients regarding the success rate of ET (92% vs 91.6%). There was 1 postoperative ureteral obstruction presented clinically 48 hours after the procedure with severe loin pain, which was relieved by temporary insertion of a double J stent. The assessment 1 year after the first procedure showed that 6 patients developed recurrent VUR, 6 contralateral de-novo VUR, and 15 experienced a single attack of postoperative febrile UTI. Recurrent UTI did not occur throughout the study period after the success of the operation.

### 5. Discussion

UTI is the second most common infectious disease after respiratory tract infection (1). The etiology of such an infection differs in various parts of the world. VUR is a common urological problem in children and is associated with long-term complications (20). Although UTI damages the refluxing organ, renal scarring may occur in asymptomatic VUR and even the process could start antenatally (21, 22). Furthermore, studies have shown that the rate of scar formation was significantly higher in infants with VUR and febrile UTI than in those with febrile UTI alone (39.4% vs 7.5%) and the incidence of renal scar formation was significantly correlated with VUR grade (23). Mohanan et al. showed that renal scarring occurred in 9% of patients with VUR without UTI, while 29% of patients with UTI and VUR had renal scarring at the time of diagnosis (24). Watchful waiting for the possibility of spontaneous resolution of VUR was aimed with surveillance with or without antibiotics. VUR grades I to III resolved at 13% yearly during the initial 5 years of follow-up and then at 3.5% yearly during subsequent follow-up. On the other hand, grade IV to V reflux resolved at 5% rate yearly. Bilateral reflux resolved more slowly than unilateral reflux (25). Antibiotic prophylaxis has been used widely for the treatment of VUR but recent guidelines of American urology association showed that the incidence of febrile UTI in children receiving CAP was even greater than those not receiving it (8). Several studies have shown that CAP may have no benefit in treating patients with VUR (26-29). Renal scarring developed in 17% of patients who were treated by CAP (8), while patients with VUR who were treated with ET did not show new scar formation (30).

The second classical option of treatment is the ureteral reimplantation which is a major procedure with significant risk of post-operative complications. Open surgery

is suggested to be reserved only for 10% - 15% of children with failure of ET or has severe ureteral anomalies. Although Ureteral reimplantation provided a high success rate of 98%, lower success rate has been reported with reimplantation of VUR grade V (8). In addition, complication rate of up to 19.5% has been reported (31).

Since FDA approval of Deflux in 2001, ET has been widely used all over the world. It is minimally invasive, well tolerated, and provides cure rates in 85% of patients (32). In some publications, the success rate of ET approached those of ureteral reimplantation (14, 30). Recently a similar compound (Dexell) has been produced, which is biochemically similar to Deflux with a different molecular size. Two articles documented the use of Dexell with comparable results with Deflux, indicating the indifference of their molecular sizes in the success rate of ET (16, 17).

In our study, ET success was evaluated both clinically and radiographically. Clinical evaluation focused on the occurrence of UTI and its clinical symptoms. Radiological evaluation was performed on the third postoperative month as it was performed at the same time in the other studies (33, 34).

Overall success rates after the first, second, and third injections were 64%, 82.7%, and 93.3%, respectively, which were comparable to other studies (2, 30). However, the rate was less than the success rate obtained in Puri study (14). Possibly, this was due to the selection criteria of our patients which included failed reimplanted ureters and more importantly due to the level of experience and learning curve. It was thought that surgery should be preserved for grade V (the least responsive grade to treatment) and the ET offered the best result in grades II-IV only. However, recent studies showed that ET for grade V offered higher success rate than open reimplantation with only 3.6% failure rate and 5.4% recurrence rate (35). Such a success rate was higher than found after open ureteral reimplantation for grade V which was shown to be 80.7% with higher complication rate (36, 37). In a study conducted by Tsai et al. cases who developed failure to ET had associated risk factors (21). Factors associated with a lower success rate were neuropathic bladder (32, 33) and mound morphology (38). Also, site of the ureteric orifice showed to be important as lateral ureteric orifice decreased the efficacy of endoscopic injection (39). In addition, associated complex VUR caused lower success rate (40). In contrast to a study conducted by Capozza et al. who reported 76.9% success rate of ET in patients with failed reimplantation, we recorded the lowest success rate (40%) in such a group (41).

In comparison to surgical reimplantation, complications after endoscopic injection were rare and minimal (33). In this study, only 1 patient developed postoperative severe loin pain due to ureteral obstruction which was relieved by the temporary insertion of double J stent for 2 weeks.

Long-term result of ET was favourable as only 6 refluxing unit developed recurrence (3.8%), one of them was

grade I requiring no further treatment while the others were grades II and III which corrected by another session of ET. Chertin et al. reported 5% recurrence after ET and those recurrences with grade II or more can be candidates for repeated injections (30).

De-novo contralateral VUR occurred in 6 refluxing unit (3.8%), requiring ET for the new refluxing ureter. Kirsch et al. similarly reported 4.5% occurrence of contralateral VUR. The exact cause for this problem is unknown but it was thought to be due elimination of pop off mechanism (34).

All subjects involved in our study had recurrent UTI. After successful operation, none of the subjects had recurrent UTI. Apart from short course of antibiotics postoperatively, no subject needed antimicrobial therapy in the period of study. Therefore, screening of the people with recurrent UTI for VUR is recommended and this might offer a cost-effective option for the treatment of recurrent UTI in patients with VUR.

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