RESEARCH PAPER

Endoscopic Management of Vesicoureteral Reflux and Long-term Follow-up

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Objectives: To report our experience with endoscopic management of vesicoureteral reflux (VUR) by injection of a tissue bulking substance – Dextranomer/ hyaluronic acid co-polymer at vesicoureteric junction.

Design: Retrospective analyses of case records.

Setting: Pediatric Surgery department in a tertiary care government Institute.

Participants: 500 children (767 renal units) consecutively referred to the out-patient department with vesicoureteral reflux noted on micturating cysto-urethrogram (MCU) over a period of 13 years (2004-2016).

Intervention: Preoperative VUR grading and renal scars on radionuclide scans were documented. Dextranomer hyaluronic acid copolymer was injected through a cystoscope at the vesicoureteral junction as a day care procedure under short anesthesia. Patients were followed (average duration 27.3 mo) with clinical assessment, periodic urine cultures and renal scans.

Main outcome measure: Cessation of VUR and symptomatic relief / clinical success postoperatively at 3 months.

Results: Complete symptomatic relief was obtained in 482 (96.4%) patients. In 681 units where MCU was available, 614 (90%) units showed resolution of VUR.

Conclusion: Endoscopic injection of tissue bulking substances at vesicoureteric junction to stop VUR seems to be an effective intervention

Keywords: *Dextranomer, Renal scars, Urinary tract infection.*

Vesicoureteral reflux (VUR) is a major cause of renal morbidity in children causing recurrent urinary tract infections (UTI), renal scars, hypertension, effect on somatic growth, and renal failure. Conventional treatment consists of either long-term administration of antibiotic prophylaxis or surgical ureterovesical reimplantation in selected cases. Increase of antibiotic resistance, non-compliance with long-term antibiotics, and the fact that antibiotics may not prevent development of renal scars [1] are concerns in the conservative management of VUR [2]. In this communication, we present our experience on a large cohort of Indian children with VUR, most of them symptomatic, presenting to a tertiary-care center.

Methods

This was an analysis of case records of children with VUR referred consecutively to the outpatient Pediatric Surgery department of a tertiary-care government hospital in Chandigarh, India from the year 2004 to 2016. Data were entered in a proforma at referral and during all follow-up visits. Being a referral Institution, all the children were referred to us with a VUR positive micturating cysto-urethrogram (MCU) for management. The diagnosis of VUR was based on a MCU performed both in the filling and voiding phase with an adequately filled bladder. The International system of radiographic grading of VUR was used. Ethical clearance and waiver of informed consent were obtained from the institutional ethics committee for reporting this retrospectively collected data.

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Apart from clinical assessment, urine culture, blood urea, serum creatinine, ultrasonography of kidney, ureter, bladder (USG KUB), and dimercaptosuccinic acid (DMSA) cortical scans to document renal scars were performed pre-operatively in all patients. The clinical criteria for considering the VUR as symptomatic were: fever, lower urinary tract symptoms, documented UTI, abdominal pain (especially in the flank), hypertension, features of renal failure, and effect on appetite and growth. Bowel dysfunction, constipation, UTI, and voiding dysfunction were treated aggressively preoperatively before being offered endoscopic treatment.

Patients with secondary VUR were included in the study only after the predisposing cause was treated satisfactorily. The treatment for neurogenic bladder

included clean intermittent catheterization and use of anticholinergics such as oxybutynin or tolterodine. Treatment of posterior urethral valve (PUV) comprised initial fulguration of valves, which was repeated if the patient continued to have poor stream and/or had a dilated posterior urethra on repeat MCU after three months. Persistence of VUR was reassessed a year after fulguration by which time a majority of VURs are expected to subside. The adequacy of treatment of PUV, urethral stricture, hypospadias and neurogenic bladder was confirmed by MCU showing normalization of urethra and bladder as well as absence of postvoid residual on USG. Patients who had not been treated adequately for any predisposing cause as above as well as VUR associated with ectopic ureteric orifice and obstructing megaureter were excluded. Those who could not afford the drug for injection and those who preferred surgical reimplantation or conservative management with uroprophylaxis were excluded. Once the above criteria were met, and recent urine culture was sterile, endoscopic treatment was offered as a day care procedure after a pre-anesthesia check up and informed consent from the parents.

Under short general anesthesia, with the patient placed in the lithotomy position, a pediatric cystoscope with a side channel was inserted visualizing the local anatomy. Dextranomer hyaluronic acid copolymer paste (Deflux, Q-Med AB, Uppsala, Sweden) available as a sterile 1 mL prefilled syringe of dextranomer microspheres in a 1% sodium hyaluronic acid solution was used. A special long sterile needle was introduced through the side channel of the scope and inserted 2-3 mm below the affected ureteric orifice at the 6 o'clock position and advanced a few mm so as to inject the paste submucosally until a volcanic bulge lifted up the orifice and made it crescent shaped (sub-ureteral Teflon injection or STING technique). The patients were discharged home a few hours later and advised to continue uroprophylaxis as before. The MCU was repeated 3 months later. DMSA renal scans were done in the postoperative period first at 6 months and later as required. Patients were followed-up periodically with clinical assessment and urine cultures. Repeat MCU in late follow-up was performed only if the patient became symptomatic again, had laboratory evidence of UTI or had new scars on DMSA scan.

The cessation of VUR and symptomatic relief/clinical success was analyzed postoperatively at 3 months. Complete success was defined as complete cessation of VUR on repeat MCU at 3 months. If there was no VUR, antibiotics were stopped and the child remained on periodic follow-up. Partial success included downgrading of VUR. Symptomatic relief was taken as clinical success. Persistence of same grade of VUR was considered as failure of the procedure. If VUR persisted, the child was offered a repeat injection therapy or surgical reimplantation unless the renal function was below 10% when a nephrectomy was advised in the presence of renal scars or hypertension.

RESULTS

Case records of 500 children (767 renal units) during the 13-year study period were analyzed. No patient was withdrawn because of adverse effects. There were 385 boys (M:F ratio 3.3:1). The age ranged from 2 to 156 months (Mean 45.1 mo; SD 41.3 mo) with a median age of 27 months.

Associated problems/anomalies were present in 241 (48.2%) of 500 patients. Apart from genito-urinary conditions in 184 (36.8%) patients (***Table* I**), associated conditions in other systems were gastrointestinal in 19 (3.8%) patients: anorectal malformation (15), Hirschsprung's disease (1), gall stones (1), esophageal atresia with tracheo-esophageal fistula (1), and malrotation (1); neurological in 7 (1.4%) patients: spinal dysraphism (6) and seizure disorder (1); Cardiac (congenital heart disease) in 4 (0.8%) patients; and miscellaneous in 27 (5.4%) patients: congenital talipes equinovarus (2), syndromic findings (9), failure to thrive (2), hypertension (13) and renal rickets (1).

Majority of the patients were symptomatic ***(Table* II)**, with some patients having more than one symptom. Of the

TABLE I ASSOCIATED GENITO-URINARY CONDITIONS IN CHILDREN WITH VESICOURETERAL REFLUX (N=500)

Associated genito-urinary conditions	*No. (%)*
Single kidney	47 (9.4)
Posterior urethral valve and Anterior urethral valve	39 (7.8)
Uretero pelvic junction obstruction	32 (6.4)
Duplex system	15 (3)
Hypospadias	11 (2.2)
Urethral stricture	8 (1.6)
Undescended testes	7 (1.4)
Neurogenic bladder	7 (1.4)
Previous failed reimplantation	6 (1.2)
Bilateral renal parenchymal disease	3 (0.6)
Vaginal atresia	2 (0.4)
Renal calculi	2 (0.4)
Horse shoe kidney	2 (0.4)
Others*	3 (0.6)

**Crossed renal ectopia, bladder exstrophy and meatal stenosis in one child each.*

WHAT IS ALREADY KNOWN?

- VUR may be managed by long term antibiotic prophylaxis or by surgical reimplantation in failed cases.

WHAT THIS STUDY ADDS?

- Endoscopic management of VUR with injection of tissue bulking substances at the vesicoureteral junction may be offered as an effective first line of management.

25 children who were asymptomatic, 17 were aged below one year, 14 had renal scars at presentation, five had associated ureteropelvic junction obstruction, four had a single kidney and two had previously been treated for posterior urethral valve (PUV).

The VUR was present bilaterally in 265 (53%), on the left side in 139 (27.8%), and on the right side in 96 (19.2%) children; majority of patients had grade IV-V VUR (***Table* III**). The cohort included 148 (29.6%) children who were less than 1 year old (Grade I: 6, Grade II: 13, Grade III: 40, Grade IV: 89 and Grade V: 82).

TABLE II PRESENTING SYMPTOMS IN PATIENTS REFERRED WITH VESICOURETERAL REFLUX

Symptoms	*No. (%)*
Recurrent urinary tract infections	475 (95.0)
Recurrent febrile episodes	248 (49.6)
Straining at micturition, frequency, urgency, dysuria, dribbling	105 (21.0)
Pain in abdomen	48 (9.6)
Poor appetite/poor weight gain	43 (8.6)
Bed wetting	18 (3.6)
Vomiting/Headache	16 (3.2)
Incontinence of urine	9 (1.8)
Hematuria	8 (1.6)
Excess crying	7 (1.4)
Hypertensive encephalopathy	4 (0.8)
Constipation	2 (0.4)
Others*	3 (0.6)

**Seizure disorder (1), renal rickets (1) and periorbital puffiness (1).*

TABLE III RESOLUTION RATE IN DIFFERENT GRADES OF VESICOURETERAL REFLUX AFTER ENDOSCOPIC DEXTRANOMER INJECTION

Grade of VUR	*Number of Units*	*MCU available*	*VUR resolved*
I	26	26	26 (100%)
II	47	42	41 (97%)
III	164	146	131 (90%)
IV -V	530	467	416 (89%)
Total	767	681 (89%)	614 (90%)

MCU: micturating cysto-urethrogram; VUR: vesicoureteral reflux.

Scars were present preoperatively in 396 of 767 kidneys (51.6%); among them 25% were in infants. Renal function tests (blood urea/serum creatinine) were deranged preoperatively in 45 (9%) children.

In all the patients, STING technique was used. Two injections were given in 101 units and three injections given in five units. In all others, only one injection was given.

Complete symptomatic relief was obtained in 482 (96.4%) patients during follow-up. In 681 units where MCU was available, 614 (90%) units showed resolution of VUR (***Table* III**). The mean duration of post-injection follow up was 27.3 months (range 1-156 months). In the kidneys which were interpreted to have pyelonephritic changes (but not as scars) on renal scans preoperatively, 8 units (1%) developed renal scars postoperatively. There were no significant complications except failure to stop the VUR. Among the failed cases, 15 underwent surgical reimplantation. Another five children (2 with bilateral VUR) underwent one side nephrectomy. These moieties had poor function (5-20%) to start with at referral, and all of them had multiple scars. In the early part of the study on parental insistence, endoscopic treatment was given. As patients remained symptomatic 2-4 years later, laparoscopic nephrectomy was performed following which there was resolution of symptoms.

DISCUSSION

In recent decades, endoscopic management with injection of tissue bulking substances has gained popularity in the Western world [3-7]. This technique has not yet gained momentum in Indian circumstances [8,9]. In this study, we report our experience with 500 children with VUR (767 renal units) from a single Institution in India who underwent endoscopic injection treatment with Dextranomer/hyaluronic acid copolymer.

The main limitation of the study was the inability to perform MCU 3 months postoperatively in all the patients, mostly due to parental reluctance to get the procedure done

when the patient had become asymptomatic. Moreover, in this report we have not evaluated this intervention in the form of a proper controlled trial. There was no comparison group in our study. Retrospective nature of data based on case records is another limitation.

Our results are in consonance with previously reported studies that there was no difference in the cure rate of different grades of VUR by endoscopic management with the resolution rate being equally good in higher grades (89%) as in lower grades (90-100%) of VUR [10].

In another study, Health related quality of life improved in patients in whom VUR could be successfully eliminated by endoscopic management [11]. The endoscopic treatment has also been shown to be more predictable than antibiotic prophylaxis with less social costs [12]. Fresh development of contra lateral reflux [13], distal ureteral obstruction [14,15], and postoperative misdiagnosis as distal ureteral calculi [16] are some of the complications reported in the literature. With moderate usage of only 1 mL injection technique each time, we did not come across these complications in our series. Though the material is expected to degrade after 3-4 years of injection, in this series, we observed only six late recurrences after many years, and all were managed by repeat injection therapy.

We conclude that endoscopic management of VUR alleviates inconvenience of many years of antibiotic therapy, and may be preferred as first line of management in symptomatic VUR. High upfront cost of injection is, however, a major concern for the parents.

Contributors: KLNR, PM: made substantial contributions to the concept and design of the study and acquisition, analysis and interpretation of the data and drafted the work; RS, JKM, MB, MAM: helped in acquisition of data and critically revised the content; BRM: critically apprised nuclear medicine scans of the study patients. All authors approved the final version of manuscript, and are accountable for all aspects of the work.
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