

Single Institutional Study on the Effectiveness of Cystoscopic Injection of the Tissue Bulking Agent-Dextranomer/Hyaluronic Acid Copolymer (Dx/HA) as a Treatment of Primary Vesicoureteral Reflux (VUR) in Children.

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ABSTRACT

Objective: To evaluate the effectiveness of cystoscopic subureteric injection of Dextranomer/Hyaluronic Acid as are the liable and safe substitute to prophylactic antibiotic therapy and open surgical treatment in cases of primary vesicoureteral reflux (VUR) in children

Materials and Methods: Retrospective study designed at Queen Rania Hospital for Children in Amman, Jordan between August 2015 and March 2018.

Sixty-three children were included in this study. Twenty-seven are males and 36 are females. Mean age of patients is seven years. Eighty-nine refluxing ureters were injected.

Reflux grades in the 89 ureters were one in five children (5.6%), II in 16 children (17.9%), III in 29 children (32.5%), IV in 23 children (25.8%) and grade V in 16 children (17.9%). The cystoscopic subureteric injection was performed using Dextranomer/Hyaluronic Acid as a tissue bulking agent.

Results: Vesicoureteral reflux was resolved after the first cystoscopic injection of Dextranomer/Hyaluronic Acid in 73 ureters (82%), downgraded in six ureters (6.7%) and never changed in 10 (11.2%) ureters. Those results were obtained via a follow-up Micturating Cystourethrogram (MCUG) done after three months of injection. None of the patients in this study has experienced significant complications.

Conclusions: Cystoscopic subureteric injection of Dextranomer/Hyaluronic Acid is a safe and effective method of treatment in the management of vesicoureteral reflux (VUR) in children. We recommend this minimally invasive, the short timed, ambulatory procedure as an excellent option for patients with primary vesicoureteral reflux giving a long term follow up to confirm the found results.

Keyword: Cystoscopy, Dextranomer/Hyaluronic Acid, Subureteric injection, Vesicoureteral reflux

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Introduction

Vesicoureteral reflux (VUR) is one of the most common urologic abnormalities seen in children. It is defined as the retrograde flow of urine from the urinary bladder to ureters that sometimes extending up into the kidneys. VUR is divided into Primary and secondary when it comes to its causes. Primary reflux which is the concern of this study refers to the situation where there are no major predisposing anatomical abnormalities; rather it is thought to be due to a minor structural anomaly or immaturity of the vesicoureteric orifice. Secondary reflux is associated with outlet obstruction, for example, posterior urethral valves or a neurogenic bladder. Reflux Nephropathy (RN) is a result of abnormal renal development leading to focal or extended renal dysplasia. In children with VUR and UTI, the incidence of renal scarring is 30-56%.⁽¹⁾ The prevalence of primary VUR (PVUR) is 1%- 6% with dominant inheritance and variable penetrance,⁽²⁾ while this is likely an

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underestimate because of phenotypic heterogeneity and the lack of noninvasive and non-dangerous diagnostic tools. VUR is detected most commonly during voiding, when intravesical pressure rises, but may occur any time in the voiding cycle, particularly when bladder function is abnormal.

Low-grade VUR (grades I to II) frequently resolves with medical treatment consists primarily of prophylactic antibiotics, whereas intermediate and high-grade VUR (grades III to V) usually persists and warrants surgical intervention. Before the introduction of cystoscopic subureteric transurethral injection (CSTI) therapy, the mainstay therapy of surgical treatment for VUR was the open ureteric reimplantation. In one study, the cure rate for open reimplantation was 98.1%.⁽³⁾ Open reimplantation surgery has a painful postoperative incision, required hospitalization, temporary insertion of Foley's catheter, and possible damage of the anatomy of the urinary bladder. The cystoscopic, minimally invasive injection of a tissue bulking agent as in Dextranomer/Hyaluronic acid has overcome some of the disadvantages of open reimplantation and currently becomes the preferred method of treatment due to higher success rates and low complication risks.⁽⁴⁾

On 2001, the United States (US) Food and Drug Administration (FDA) approved Dextranomer/Hyaluronic acid copolymer for the treatment of VUR. In this study, we evaluated the efficiency of injecting Dextranomer/Hyaluronic acid in intermediate and high grades VUR.⁽⁵⁾

Methods

This study is a single-institutional, retrospective study performed at Queen Rania Hospital for Children (QRHC) in Amman, Jordan between August 2015 and March 2018. Both paper and electronic medical records of 63 patients were reviewed. Ages of children in this study were from 2-12 years, a mean of seven years. 27 of patients are males and 36 are females. 89 refluxing ureters were injected (26 patients had bilateral injections whereas, 37 had the unilateral right or left injection). Mean injected volume was 0.6 mL of Dextranomer/Hyaluronic acid. Preoperative reflux grades in the 89 ureters were one in five (5.6%), II in 16 (17.9%), III in 29 (32.5%), IV in 23 (25.8%) and V in 16 (17.9%).

Every child has a recent preoperative Micturating Cystourethrogram (MCUG) and dimercaptosuccinic acid (DMSA) renal scan to document grading of the VUR and scarring of the kidney. Also, Preoperative urine cultures were obtained and analyzed from all patients, and no bacterial growth was confirmed before patient's-cystoscopic injection. Secondary causes of VUR as in neurogenic bladder or posterior urethral valve were excluded from this study.

Postoperatively, all patients underwent a renal ultrasound at 1 week to exclude hydronephrosis due to vesicoureteral junction obstruction as a complication of injection. Also, they underwent MCUG at three months postoperatively to evaluate the correction and grading of the reflux.

Reflux Grade I or complete resolving of VUR at the follow-up evaluation was defined success.

The technique performed for injection was the standard subureteric transurethral cystoscopic injection technique operated by professional pediatric surgeons. The studied outcomes were the success of injection by resolving or downgrading of the VUR to grade I on postoperative MCUG. Complications of injection were also included in this series.

Results

A total of 63 patients' underwent transurethral cystoscopic subureteric injection of Dextranomer/Hyaluronic acid. VUR was unilateral in 37 and bilateral in 26, comprising 89 refluxing ureters. VUR was Grade I in 5 ureters, Grade II in 16 ureters, Grade III in 29 ureters, Grade IV in 23 ureters and Grade V in 16 ureters. Vesicoureteral reflux (VUR) was resolved after the first trial of cystoscopic transurethral subureteric injection of Dextranomer/Hyaluronic Acid in 73 ureters (82%), downgraded in 6 ureters (6.7%) and persisted in 10 (11.2%) ureters. None of the patients in this series experienced any significant anaesthetic, surgical or medical complications as hydronephrosis or febrile Urinary Tract Infection (UTI). Patient's demographics and results are demonstrated in (Table I).

MCUG results at three months postoperatively are summarized in (Table II).

Table I: Patient's demographics and results

	Resolved	Downgraded	Failed
Male	27		
Female	36		
Bilateral	26		
Unilateral	37		
Refluxing UNITS	89		

Scarred	36			
Grade 1	5	5	0	0
Grade 2	16	12	0	4
Grade 3	29	24	3	2
Grade 4	23	20	2	1
Grade 5	16	12	1	3
Age	2-12Years	Mean=7 Years		

Table II: MCUG results at 3 months postoperatively

Resolved	73
Downgraded	6
Failed	10

Discussion

Vesicouretric Reflux disease is being considered among pediatric urologists as one of the most frequently encountered diseases of childhood. Management of the disease either medically or surgically is being discussed over the decades. Reflux nephropathy, scarring and non-functional kidneys are the end results of untreated bacterial VUR [6]. Usually, surgical intervention during the first year of life is not indicated as half of discovered VUR cases during this first year are having the chance for spontaneous resolution.⁽⁷⁾ After the first year of life, spontaneous resolution odds are being significantly decreased especially for intermediate and high grades VUR (Grades III-V) which warrants surgical intervention techniques.⁽⁸⁾ Our protocol management of VUR is to start the patient on prophylactic antibiotics for a long period of time to prevent bacterial reflux to kidneys and protect it from ESRD. This protocol has been found to be expensive and put the additional burden to parents and health care personnel. For that, surgical intervention has been claimed by many pediatric urologists especially for intermediate and high grades VUR on the early time of the disease.⁽⁹⁾ Surgical options to treat VUR are either open ureteric reimplantation or minimally invasive transurethral cystoscopic subureteric injection of bulk-forming agents.

The latter technique was found to be advantageous over open surgery due to many reasons. Speed recovery, day-case procedure, and minimal post-operative and anaesthetic complications besides its high acceptance rates among parents.^(10,11)

Detranomer/Hyaluronic acid (Dx/HA) is one of the commonly used injected bulk-forming agents. Other agents are beyond the scope of this study. Dx/HA copolymer is being used in endoscopic treatment since 1993.⁽¹²⁾ Dx/HA is a durable material with no risk of particle migration and tissue reaction.⁽¹³⁾

In our study, small-sized 0.6 mL of Dx/HA injection was performed to 89 ureters of 63 children with VUR and overall success rate was 82% from the first trial. Second or third trials were not an option due to the limited availability of the agent.

Subureteric Dx/HA injection has very low complication rates in literature and the most common complication is the ureteral obstruction.⁽¹⁴⁾ In our study, all patients were evaluated with ultrasonography one week after the operation to rule out obstruction and no complications were seen. Three months following injection, patients were reevaluated via MCUG study. According to findings on the MCUG, classifications of results were retrieved and classified as a success, downgrade or failure. Despite the current controversies on routine post-operative MCUG. We do it routinely at three months post – injection as it still the standard of care at our institution. We have compared our results to international results and found mild varieties in outcomes due to routine standards of postoperative follow up methods. But, in general, our results were comparable to international results and we are recommending the cystoscopic injection over open ureteric reimplantation.

Conclusion

VUR is a common disease between children but its pathophysiology is not fully understood yet. Options of management are plenty swinging from observation especially during the first year of life, continuous antibiotic prophylaxis, cystoscopic and laparoscopic injection of bulk-forming agents, and finally, open surgical ureteral reimplantation.

Cystoscopic transurethral subureteric injection of Dx/HA has become widely accepted as an alternative technique to open ureteric reimplantation for advantages of easy application, low complication rates, and high success rates.

We believe that further studies designed with more patients and longer follow-up duration can reveal the effectiveness and complication rates of this minimally invasive technique.

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