

Clinical Study

Subureteral Injection with Small-Size Dextranomer/Hyaluronic Acid Copolymer: Is It Really Efficient?

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The aim of this study was to evaluate the clinical results of patients with vesicoureteral reflux, which were treated with subureteral injection of small-size (80–120 μm) dextranomer/hyaluronic acid copolymer (Dx/HA). Data of 75 children (105 renal units) who underwent STING procedure with small-size Dx/HA for the treatment of vesicoureteral reflux (VUR) in our clinic between 2008 and 2012 were retrospectively analyzed. Preoperative reflux grade and side, injection indication, postoperative urinary infections and urinary symptoms, voiding cystourethrogram, and renal scintigraphy results were evaluated. The success rate of the procedure was 100% in patients with grades 1 and 2 reflux, 91% in patients with grade 3 reflux, and 82.6% in patients with grade 4. Overall success rate of the treated patients was 97%. Endoscopic subureteric injection with Dx/HA procedure has become a reasonable minimally invasive alternative technique to open surgery, long-term antibiotic prophylaxis, and surveillance modalities in treatment of VUR in terms of easy application, low costs and complication rates, and high success rates. Injection material composed of small-size dextranomer microspheres seems superior to normal size Dx/HA, together with offering similar success with low cost.

1. Introduction

Vesicoureteral reflux (VUR) is the most urologic abnormality in children. VUR is the backflow of the urine from bladder to the ureters or kidney [1]. It is seen in 1–3% of children [2]. VUR is more frequent in younger children because of the short submucosal portion of ureter [3]. VUR coexists in 30–40% of children with urinary tract infection (UTI) [4]. This ratio is 29% in boys and 14% in girls [3]. It is more frequent in male children in antenatal period but with rising age girls are affected more [2]. The relationship between VUR, UTI, and renal parenchymal injury is clearly identified recently. Reflux nephropathy is one of the most frequent causes of childhood hypertension and it can lead to growth retardation and renal deficiency [5]. The aim of treating reflux is preventing febrile infections and avoiding renal injury thus decreasing the morbidity rate of both disease and treatment.

Previously, in children with recurrent UTI attacks despite low dose antibiotic therapy, the treatment was open surgery

but recently endoscopic subureteric transurethral injection (STING) procedure is preferred because of high success rates and low complication risks [6, 7]. In 1981, Matouschek [8] first described the subureteric injection technique and O'Donnell and Puri [9] reported the first clinical series in 1984. STING technique was developed since then and many injection materials such as Teflon, bovine collagen, and macropastique are used for this purpose. However concerns about efficacy and safety have limited their usage [2, 10, 11]. Since the approval of dextranomer/hyaluronic acid copolymer (Dx/HA), endoscopic management of VUR has become an established alternative treatment [4].

Both dextranomer and hyaluronic acid are biocompatible, and a serious tissue reaction is not expected. Hyaluronic acid naturally exists in tissue [1]. Dx/HA has different commercial names, according to the size of the contained microspheres. Deflux contains 80–250 μm dextranomer microspheres and in products like Urodex® Dexell has a size of 80–120 μm [12].

TABLE 1: The demographic features of patients.

	The degree of VUR before treatment				<i>p</i>
	Grade 1 (<i>n</i> : 1)	Grade 2 (<i>n</i> : 9)	Grade 3 (<i>n</i> : 38)	Grade 4 (<i>n</i> : 27)	
Age (mean)	11	7,1 (2–14)	7,1 (1–12)	5,5 (1–12)	0,155
Follow-up (months)	20	21,8 (5–48)	10,8 (1–36)	9,8 (1–40)	0,012
Sex					
Male (<i>n</i> : 19)	0	3 (4%)	6 (8%)	10 (13,3%)	0,219
Female (<i>n</i> : 56)	1 (1,3%)	6 (8%)	32 (42,7%)	17 (22,7%)	
VUR side					
Left	0	3 (4%)	12 (16%)	6 (8%)	0,077
Right	1 (1,3%)	6 (8%)	10 (13,3%)	7 (9,3%)	
Bilateral	0	0	16 (21,3%)	14 (18,7%)	
Treatment indication					
Infection	1 (1,3%)	9 (12%)	22 (29,3%)	15 (20%)	0,075
Scar	0	0	16 (21,3%)	12 (16%)	

In this study, the aim was evaluating the efficiency of subureteral small-size Dx/HA injection treatment in children with VUR.

2. Patients and Methods

Data of 75 children who underwent subureteral small-size Dx/HA injection treatment for the treatment of VUR in our clinic between 2008 and 2012 were retrospectively analyzed. Injection was performed to 105 renal units in 75 patients. Preoperative reflux grade and side, injection indication, postoperative urinary infections and urinary symptoms, voiding cystourethrogram (VCU), and renal scintigraphy (if available) results were evaluated retrospectively. The indications for injection procedure were febrile infections despite antibiotic prophylaxis or renal cortical scars diagnosed in renal scintigraphy.

Small-size (80–120 μm) Dx/HA (Urodex) was used as the treatment agent. All procedures were performed under general anesthesia and in lithotomy position. With 9.5 F pediatric cystoscope, bladder and ureteral orifices were inspected. Procedure was performed like the injection technique described by O'Donnell and Puri [9]. Urodex was injected submucosally with 3.7 F needle inside the ureter orifice or inferior to the orifice. Injection proceeded until a volcano type bulge is seen and distal ureter was elevated with orifice. In most of the patients, one injection point was sufficient but if the ureteric bulge was not enough, another injection was performed into another suitable point. All injections were performed by a single experienced surgeon.

All patients were discharged from the hospital at the day of the procedure. Renal ultrasonography was performed to all patients one month after injection to eliminate the possibility of obstruction. In first year after operation, all patients were followed up with monthly urine analysis and culture. Three months and one year after the operation all patients underwent renal ultrasonography. Renal scintigraphy was performed to see if a new renal cortical scar formation existed in all patients six months after injection. Voiding

cystourethrogram was not performed routinely, and the patients were followed up according to the clinical signs. VCUs of patients evaluated were performed by other medical centers postoperatively. If the patient experiences new febrile infections or a new cortical scar formation was diagnosed in scintigraphy after injection, the procedure was accepted as unsuccessful. The rest of the procedures were accepted as successful. No repeat injection was performed.

Chi-square and Mann-Whitney *U* tests were used for statistical analysis. *p* values less than 0.05 were accepted as statistically significant.

This study was approved by Gazi University Ethical Committee (no. 2015/07A).

3. Results

Mean age and follow-up were 6.59 (1–14) years and 30.1 (12–48) months, respectively. 19 (25.3%) of patients were male and 56 (74.7%) were female. Injections were performed to left ureter in 21 (28%) patients, to right ureter in 24 (32%) patients, and bilaterally in 30 (40%) patients. Before treatment, reflux degree was 1 in 1 (1.3%) patient, 2 in 9 (12%) patients, 3 in 38 (50.7%) patients, and 4 in 27 (36%) patients. Treatment indications were cortical scar in renal scintigraphy in 28 (37.3%) patients and febrile urinary tract infections despite antibiotic prophylaxis in 47 (62.7%) patients. The demographic features of patients were demonstrated in Table 1.

The success rate of the procedure was 100% in patients whose reflux grades were 1 and 2 before treatment according to the preoperative VCU. Subureteral small-size Dx/HA injection procedure was successful in 91% of patients with 3rd grade VUR before treatment and 82.6% of patients with 4th grade of VUR. Overall success rate of the treated patients was 97%. The success rates were demonstrated in Figure 1.

The patients with unsuccessful procedure were all female. Success rate of the procedure was insignificantly different between male and female patients (*p*: 0.303). When grades 1 and 2 VUR were referred as mild-moderate reflux and grades 3 and 4 VUR were referred as severe reflux, the

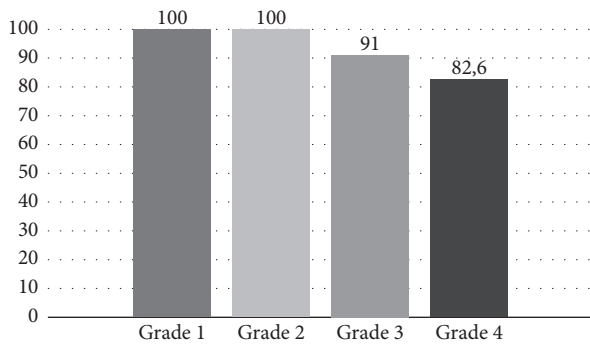


FIGURE 1: The success rates according to VUR grade (%).

differences in success rate between mild-moderate and severe groups were insignificant ($p: 0.440$). When the success rates were compared according to the injection indications, no statistically significant difference was present in febrile infection group and cortical scar group ($p: 0.284$). And the side of the injection was also not influential in the success of the procedure ($p: 0.259$). No complications occurred during or after the operations.

4. Discussion

VUR is one of the most frequent diseases of childhood and its treatment is being discussed since it is described. It causes destruction in renal parenchyma if not diagnosed and treated in early ages. It is not clear to state which treatment is most suitable for this disease. Infants are more vulnerable for renal scar formation and infections are frequent in these patients [13]. In the first year of life, with 50% possibility, VUR can recover spontaneously but this ratio is 15% in whole life. A child with VUR can heal without treatment within an average of 5 years [14]. Male infants with grade 4 or 5 reflux can heal spontaneously in 1 year with 29% possibility but after the first year this ratio decreases to 9% [15]. McLorie et al. [16] reported that in 93% of children with grade 4 reflux and 83% of children with grade 3 reflux the disease remained after 2 years of follow-up without treatment. After 5 years these ratios decreased to 70% and 50%, respectively. These findings show us that if antibiotic prophylaxis program is planned for a child with reflux, it means that this child will receive these drugs for a long time and it will cause concern about compliance to the treatment and the child will face problems about breakthrough infections and side effects of the drugs used for a long time period. Besides, many radiological imaging techniques will be performed to this child for follow-up and it will raise expenses, be invasive, and cause risk about infection due to catheterization [17]. Previously, only alternative to antibiotic prophylaxis was open surgery. With the development of endoscopic techniques and widespread use of different injection materials, the subureteric injection technique became a feasible alternative to open surgery [18, 19]. This technique is also more acceptable for parents. In a study, 80% of parents preferred endoscopic treatment rather than open surgery and antibiotic prophylaxis [6].

Many agents were used for subureteric injection until now. Polytetrafluoroethylene (Teflon) is an effective agent but

its usage is limited because of frequent particle migration and granulation formation in tissue [20, 21]. Polydimethylsiloxane (silicone, macroplastique) also lost its popularity because of similar reasons [22]. In addition, it is likely that silicone can lead to malign transformation [23]. Bovine collagen (Zyderm, Zypast) was considered as an alternative material to polytetrafluoroethylene but it lost its popularity too because the collagen vanishes from the tissue in long term and loses its effectiveness. Besides, it has a high risk of allergic reaction [24].

Dx/HA copolymer (Deflux) is being used in endoscopic treatment since 1993 [25]. Dx/HA is a durable material with no risk of particle migration and tissue reaction. In a study, which compares the long-term effectiveness of injection materials, Stredle et al. [26] performed subureteric injection treatment to 229 ureter units in 135 children. For this purpose, they used collagen, polydimethylsiloxane, and Dx/HA. The success rates with single injection are 52%, 55%, and 81.5%, respectively. Moreover, the children treated with Dx/HA experienced less infections during the follow-up period. When Urodex is being used as the injection material, it can be applied with a 3.7F needle by means of the small-sized microspheres in this material. Urodex includes positive loaded dextranomer, so the material causes a durable tissue reaction with immediate collagen formation and can remain in the tissue for a long time. Besides, Urodex is quite cheaper than Deflux in Turkey [12]. The price of Deflux is 300\$ and those of Urodex and Vurdex are 150\$ in Turkey. Urodex and Vurdex contain exactly the same ingredient.

Stenberg and Lackgren [27] first reported the results of injection treatment with Dx/HA in 1995 and many series indicating the success rates of this material were published since then. In literature, different success rates were reported about Dx/HA. The main reason of this difference is the variation of patient numbers and the criteria used for defining the successful application. In these studies the success rates differ from 63% to 100% but in recent studies these rates are usually over 85% [28–30]. In a large study published by Puri et al. [4] in 2012, subureteric Dx/HA injection was performed to 1551 children (790 bilateral) and after the 1st, 2nd, and 3rd injections, they saw that 87.1%, 11.3%, and 1.6% of reflux were recovered, respectively. No complications were seen and only 4.6% of these patients had febrile urinary infections in their follow-up. Biočić et al. [1] reported a recent study, which has similar results. They performed Dx/HA injection to 396 ureter units of 282 children with reflux, and they received 76%, 93%, and 94% of successful application rates after the 1st, 2nd, and 3rd injections, respectively. Aydogdu et al. [12] compared the materials, Dexell (Urodex) and Deflux. With this purpose, they applied Dexell to 56 patients and Deflux to 60 patients in subureteric injection. They found no difference in effectiveness between these two agents but in Dexell (small-size Dx/HA) group the treatment expenses were less when compared to Deflux group. Pogorelić et al. [31] published a brand new study in 2016, comparing the effectivity of Deflux and Vurdex in 104 children treated for VUR. Overall success rate for patients treated with Deflux was 93.3% and for patients treated with Vurdex 94.8%. There was no difference in effectivity of these two bulking agents.

All these studies support the findings of our study. In our study, small-size Dx/HA (Urodex) injection was performed to 105 ureters of 75 children with VUR and overall success rate was 97%. In our study, quite higher success rates were achieved when compared to literature. These values cannot be considered as real success criteria because in our study postoperative VCU was not performed routinely and patients were followed up according to their clinical findings. It means that clinically insignificant unsuccessful cases were possibly missed in which the reflux remains after injection but regresses to a circumstance that does not cause any breakthrough infection and new renal cortical scar. Recently, studies have begun to question the benefit of VCU to assess the success of the treatment [32]. In addition, cystography is not without morbidity. Standard fluoroscopic VCU exposes a child to approximately 0.93 mGy of radiation [33]. There is also an economic burden of this technique. Bisignani and Decter [32] have previously reported that eliminating VCU in uncomplicated patients after ureteroneocystostomy could save up to 2.8 million dollars annually in the United States alone. Grossklaus et al. [33] studied the benefit of postoperative VCU in evaluating the success of ureteral reimplantation. They found that the addition of VCU to the postoperative evaluation and the information provided by VCU was not predictive of patients with febrile urinary tract infections. Patients in whom persistent reflux was identified were all asymptomatic. Harper et al. [34] published their experiences about the endoscopic correction of vesicoureteral reflux, for whom no routine postoperative cystography was performed. They found that febrile urinary tract infections were not correlated with postoperative VCU findings. Bomalaski et al. [35] reported a study about comparing the initial postoperative imaging to radiological imaging throughout follow-up. They found that children with abnormal preoperative ultrasound or dysfunctional voiding were identified as a high-risk group for postoperative hydronephrosis or recurrent reflux. All other patients received little benefit from postoperative imaging, suggesting that further evaluation of this group is necessary only in the presence of a postoperative urinary tract infection.

Subureteric Dx/HA injection has very low complication rates in literature and most common complication is ureteral obstruction [36, 37]. In a study in which the complication rates are relatively higher, Mazzone et al. [38] applied Dx/HA injection to 87 ureters in 44 patients and they saw obstruction in only 5 (5.7%) patients' 5 (9.3%) ureters after operation. They suspected obstruction with the clinical findings of pain, infection, and deterioration in renal functions. Four of these 5 patients' obstruction relieved spontaneously with ureteral stent or nephrostomy catheter. Although it is not frequent, the clinician must be aware of the risk and symptoms of obstruction after injection. In our study, all patients were evaluated with ultrasonography one month after the operation to rule out obstruction and no complication was seen.

5. Conclusion

Endoscopic subureteric injection with Dx/HA procedure has become a reasonable minimally invasive alternative

technique to open surgery, long-term antibiotic prophylaxis, and surveillance modalities in treatment of VUR in terms of easy application, low costs and complication rates, and high success rates. Urodex, which has smaller dextranomer microspheres than Deflux, seems superior together with offering similar success with low cost. We think that further studies designed with more patients and longer follow-up duration can reveal the effectiveness and complication rates of this smaller microspheres technique more clearly.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

Serhat Gürocak carried out the data collection and application of procedures. İyimser Üre carried out the data collection and statistical analysis. Özgür Tan participated in study design and application of procedures. Amirali Farahvash participated in the design of the study and performed the statistical analysis. Cem Senol conceived of the study and participated in its design and coordination and helped to draft the manuscript. Hüseyin Gümüstas carried out the data collection. İrfan Atay participated in study design and data collection. Nuri Deniz drafted the manuscript. All authors read and approved the final manuscript.

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