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Endoscopic correction of vesicoureteral reflux in children

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ABSTRACT

Introduction: Dextranomer/hyaluronic (Dx/HA) acid is the only tissue-augmenting agent approved by the Food and Drug Administration (FDA) for the vesicoureteral reflux (VUR) treatment.

Objectives: We aimed to evaluate short-term outcomes of the Dx/HA in patients who had undergone subureteric injection.

Patients and Methods: In this study, 30 patients with VUR diagnosis who had indications for open surgery were enrolled in the study. Patients underwent subureteric Dx/HA injection. Additionally patients underwent a one-year follow up period, subsequently. Follow up included urine analysis, urine cultures and kidney and urinary tract ultrasonography study.

Results: Of a total 30 patients, 8 patients (27%) were male and 22 patients (73%) were female. The mean age of patients was 25.19 ± 0.70 months. Postoperative VUR resolution was observed in 28 patients (93.3%). Moreover, during one year follow up, urinary tract infection (UTI) was not reported in patients. However, recurrent VUR was detected in 8 patients (27%) during ultrasonography follow up. Analysis showed no significant difference of recurrence in VUR between males and females ($P=0.285$) and VUR severity ($P=0.1$). There was a significant relationship between recurrent UTI history before intervention and VUR recurrence after subureteric injection ($P=0.007$).

Conclusion: Dx/HA acid subureteric injection provides acceptable resolution rate among VUR patients, but its biodegradability causes VUR recurrence during one-year follow up.

Implication for health policy/practice/research/medical education:
Dextranomer/hyaluronic acid subureteric injection provides acceptable resolution rate among vesicoureteral reflux (VUR) patients and this highlights the necessity for the strict implementation of it in VUR.

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Introduction

Vesicoureteral reflux (VUR) is a common problem in children, which increases the risk of the urinary tract infection (UTI), nephropathies and end-stage renal diseases. VUR is characterized by backflow of the urine from bladder toward the kidney, which affects 1%-3% of all children (1,2). While VUR pathophysiology leads to spontaneous resolution during first five years in most of the cases, some serious complications include recurrent UTI, renal injury and chronic kidney diseases (3-5). Three main therapy methods have been introduced for VUR treatment including observational therapy, prophylactic antibiotic administration, ureteroneocystostomy and endoscopic subureteral injection (1,6,7). Observational therapy emphasizes the spontaneous resolution of the VUR, however several studies showed incidence rate of

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approximately 15% in all children (8). In addition, some reports showed that prophylactic antibiotic not only cannot prevent pyelonephritis but also leads to UTI with antibiotic resistant organisms that make more challenging problems (9-11).

In 1981, Matouschek, firstly described the endoscopic subureteral injection for VUR treatment (12). Since 1984, O'Donnell and Puri popularized endoscopic sub-ureteral transurethral injection (STING) modality for VUR treatment. It has become one of the most attractive and first line therapy for children with VUR due to its high success rate, minimum aggression and few complications (13-16). Although, open surgery is still considered as gold standard for VUR treatment, however, STING has several advantages including simplicity, safety, quickness with low aggression which can provide an alternative treatment for open surgery (17,18). Since three decades ago, dextranomer/hyaluronic acid copolymer (Dx/HA) (Deflux) was the first tissue augmenting substance that was approved by the Food and Drug Administration to be used in VUR (19,20). Additionally, Dx/HA is a biocompatible, synthetic and non-immunogenic agent. Its biochemical characteristics make it susceptible to biodegradability (21). However, several studies reported the high rate of VUR recurrence in patients who had undergone STING by Dx/HA at long-term follow up, especially in patients suffering from high-grade VUR (22).

Objectives

This study was aimed to evaluate the Dx/HA (Deflux) efficacy and short-term complications in VUR patients who had undergone STING.

Patients and Methods

Target population

From February 2015 to March 2017, a prospective study was carried out in a single center in Urmia, West Azerbaijan, Iran. During this period, due to lack of the resources and follow up possibility, 30 children with age range of 7 months to 15 years old were enrolled in the study using convenience sampling. Before intervention, patients underwent kidneys and urinary tract ultrasonography study in order to evaluate hydronephrosis following VUR. Then patients underwent modified STING using rigid cystoscopy and 3.7 FR catheter to inject settled amount of the Dx/HA (Deflux). The amount of injected drug was recorded for each patient. The length of stay in hospitals and preoperative complications were recorded for all patients. Further, kidney and urinary tract ultrasonography were conducted during the first and third month after intervention as postoperative follow up. In addition, patients underwent voiding cystourethrogram (VCUG) to evaluate VUR during third month postoperative. Finally, one year after the intervention, patients had undergone last follow up session to evaluate STING success rate and postoperative complications.

Inclusion criteria were included as follows: 1. Children aged 1 to 5 years old with bilateral grade III-IV VUR without resolution during follow up, 2. Children aged 6-10 years old with unilateral grade III-IV VUR without resolution during observational therapy, 3. Children 6-10 years old with bilateral grade III-IV VUR, 4. Children aged 1-5 years old with unilateral or bilateral grade IV VUR that did not resolve during follow up, 5. Children aged 6-10 years old with grade IV VUR and 6. Children older than one year old with a renal injury during imaging. Exclusion criteria were included patients who had a previous history of anti-reflux surgery and secondary reflux.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. All process of the study and probable complication were described for the parents before any intervention and all parents gave their written informed consent. This study was approved by the ethics committee of Urmia University of Medical Science and the objectives of the study were explained to all parents of participants and all of them accepted to participate and were assured of the confidentiality of information as well as the voluntary nature of participating in the study.

Statistical analysis

All data were analyzed using SPSS software version 18 and descriptive statistics and independent *t* test were used. Dependent variables were described as mean ± standard deviation (SD) and independent variables were expressed as frequency and percentages. Chi-square, independent *t* tests and ANOVA were used to determine the relationship between independent and dependent variables. The level of significance was considered less than 0.05.

Results

In the current study, during one-year period, 30 patients with VUR diagnosis who had indications for open surgery were enrolled. Of 30 patients, 8 patients (27%) were male and 22 patients (73%) were female with the mean age of the 25.19 ± 0.70 months (range; 7 to 93 months). Positive family history for VUR was recorded in two patients. Regarding the physical examination, the most prevalent complaint was pain and crying (53%). Dysuria and hematuria were the other common symptoms. Eighteen patients (60%) had unilateral VUR, while 12 patients (40%) suffered bilateral VUR. Left kidneys (60%) were the most common refluxing renal unit (RRU) suffering VUR. Twenty-six patients (86%) had a positive history of the previous UTI, however, despite prophylactic antibiotic therapy, UTI was detected in 24 patients (80%) (Table 1). During preoperative and postoperative di-mercapto succinic acid (DMSA) scan study for evaluating renal dysfunctions following VUR, renal injury was detected in 26 (86.7%) and 14 patients (46%), respectively. Postoperatively, 28 patients (93.3%) had successful Dx/HA STING. However, regarding postoperative complications, postoperative vesicoureteral junction obstruction (VUJO) following Dx/HA STING was detected in 4 patients (13.3%). The mean amount of the injected tissue-

Table 1. Patients' data

Variable		No.	%
Type of VUR	Unilateral	18	60
	Bilateral	12	40
Gender	Boy	8	27
	Girl	22	73
Kidney	Right	18	60
	Left	12	40
History of UTI	Yes	28	86
	No	2	14
Renal Injury detected by DMSA	Preoperative	26	86.7
	Postoperative	14	46

Abbreviations: VUR, vesicoureteral reflux; UTI, urinary tract infection; DMSA, Dimercaptosuccinic acid.

augmenting agent was 0.73 ± 0.50 mm. Accordingly, postoperative urinary tract ultrasonography approved effective injection in all patients. The mean length of stay in hospital was 1.2 ± 0.4 days.

During follow up period, there was no report of the VUR recurrence or any other complication in first and third months. However, after one year, recurrent VUR was reported in 12 patients (42.8%) that detected during ultrasonography follow up in all patients.

The chi-square test showed no significant difference between female and male regarding the VUR recurrence ($P=0.285$). Considering the type of the VUR among patients with recurrent VUR, 5 patients had bilateral VUR before STING and 7 patients had suffered from unilateral VUR. In this study no significant difference was seen in VUR recurrence between the groups ($P=0.12$) (chi-square test). During one-year follow up, six patients (50%) had right RRU. Similarly, six patients (50%) had left RRU, while analysis by chi-square test showed no significant correlation between the sides of the involvement with VUR recurrence ($P=0.438$).

Eight patients (33.3%) with failed prophylactic antibiotic therapy experienced recurrent VUR one year after intervention, however, 4 patients with VUR recurrence did not have the failed antibiotic therapy history before intervention. Likewise, chi-square test showed a significant difference between the groups with a positive and negative history of the failed prophylactic antibiotic therapy regarding VUR recurrence ($P=0.007$).

Discussion

In the present study, the results showed high success rate (93.3%) for Dx/HA subureteral injection in VUR treatment during one-year follow up. In our study, 12 patients (42.8%) had recurrent VUR during ultrasonography follow up. We found no significant correlation between the patients' gender and RRU involvement with STING success rate. However, there was a significant relationship between recurrent UTI history and STING failure. Nonetheless, it can be estimated that history of the recurrent UTI before intervention may lead to higher probability of the STING failure in pediatrics.

Since three decades ago endoscopic sub-ureteric injection for VUR treatment was described for the first time. It has been a competitive alternative for open surgery, due to its acceptable success rate, safety and simplicity, less time consuming and short length of stay in hospital (12,20). Although the success rate for endoscopic interventions in VUR treatment varies between 70% and 90% in the literature, the optimal technique and bulking agent for STING are controversial (23,24). In addition, it is believed that the advantages of endoscopic intervention provide a possibility to repeat the procedure in case of failure or recurrence (25). For the first time, Matouschek used Teflon particles for injection (12). Stenberg and Lackgern were first persons to introduce Dx/HA as a bulking agent and tissue-augmenting agent to sub-ureteric injection using STING procedure and they reported cure rate of 68% during 3-month follow up (26). However, further reports using modified STING procedure had high cure rate (90%). The results were significant only in patients with grad III VUR. Among several bulking agents used for STING procedure in VUR treatment such as silicone, autogenous blood, chondrocytes and polydimethylsiloxane, Dx/HA acid was the only agent approved by the FDA for VUR treatment during STING procedure (19). According to previous studies, Dx/HA acid is a non-immunogenic material, which has no potential carcinogenic effects. Moreover, it has been reported to be durable, but some studies suggested that its biodegradability leads to lower durability and VUR recurrence following degradation (27,28). Although many studies suggest that appropriate selection of patients can lead to higher success rate, lower recurrence and complications, however biodegradable agents such as Dx/HA may cause VUR recurrence and failure during long-term follow up (25).

The reported success rate is 70% for VUR correction using STING procedure in the literature (8,23). In the current study, the success rate for endoscopic correction of the VUR using Dx/HA injection was 93.3%, which provides a higher rate compared to the literature. However, in a study by Wadie et al, the overall success rate was reported 77.4% during single Dx/HA injection (8). Several studies evaluated poly-acrylate polyalcohol copolymer (PPC) as an effective and safe material in VUR correction instead of Dx/HA and its success rate has been reported more than 90% (28,29). Therefore, it should be highlighted that appropriate selection of the patients to undergo endoscopic correction of the VUR, not only enhances procedure success rate, but also may provide better symptoms resolution.

Various preoperative factors including younger age before treatment and previous history of the failed endoscopic injection may be related to the intervention failure, which was detected by Serkan et al (25). On the other hand, some other studies suggested that preoperative history of dysfunctions and neurogenic disorders have a role in the failure of VUR endoscopic treatment (30-32). We found patients with the previous history of recurrent UTI significantly had the high rate of treatment failure. This

finding demonstrates the role of recurrent UTI before intervention as an unfavorable risk for results.

In previous studies, the incidence of the UTI after open surgery of VUR is approximately 10%. In the study of Lackgern et al, the incidence of the UTI in VUR patients who had recurrent VUR following endoscopic subureteric injection of the Deflux reduced to 8%, comparable to the study by Wadie et al. They detected 13% recurrent infection after endoscopic intervention in patients (8,33). However, in our study, none of the patients developed UTI after Dx/HA sub-ureteric injection during one-year follow up. On the other hand, VUR recurrence detected in none of the patients during ultrasonography studies at the end of the follow up. Therefore, our results showed recurrent UTI's eradication in 100% of the patients. Despite previous studies that evaluated Dx/HA sub-ureteric injection, none of the patients developed any significant signs or symptoms related to procedure complications in the present study.

Conclusion

Dx/HA acid is a non-immunogenic and safe material for sub-ureteral injection treatment of the VUR and provides acceptable resolution rate among patients, but its biodegradability causes VUR recurrence after one-year follow up, which leads to needing for the second injection in the future.

Limitations of our study

Our study had some limitations including; 1; inability to perform long-term follow up, 2; enrolling few patients to the study and 3; not evaluating the effect of injection amount on the results of the intervention. The small sample size of studies conducted in this field was the potential limitation of this study. There is still need to further studies to access additional information about this issue.

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Authors' contribution

MMR and SN designed the study. SF and SN generated the data collection sheet, performed the data collection, and wrote the discussion. RV and SF conducted the literature review and wrote the introduction. MH wrote the methods. MH and RV conducted the statistical analysis. All authors read, revised, and approved the final manuscript.

Conflicts of interest

There were no conflicts of interest to be declared.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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