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Factors affecting the success of endoscopic treatment of vesicoureteral reflux and comparison of two dextranomer based bulking agents: does bulking substance matter?

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Abstract *Introduction:* Among the interventional treatment modalities for vesicoureteral reflux (VUR), endoscopic subureteric injection seems to be the least invasive method with acceptable outcomes when applied in appropriate patients.

Objective: The aim of the presented study is to investigate the parameters which may affect the outcomes of endoscopic injection and to compare the efficacy of two different bulking agents both composed of dextranomer-hyaluronic acid copolymer.

Study design: The data of patients who underwent endoscopic VUR treatment between 2003 and 2012 were retrospectively reviewed. Patients with history of previous open antireflux surgery, more than one failed endoscopic treatment for reflux, VUR caused by posterior urethral valve, duplex system and overt spinal dysraphism were excluded. Surgical technique was the classical STING method. One of the dextranomer-hyaluronic acid copolymer agents was used (Deflux in 109 and Dexell in 131 patients). Both agents were composed of similar amounts of hyaluronic acid gel (15 mg in Deflux versus 17 mg in Dexell) but different sized dextranomer microspheres (80–250 μ m in Deflux and 80–120 μ m in Dexell). During the follow-up, ultrasonography was performed with 3-month interval, antibiotic prophylaxis was continued until the control voiding cystourethrography (VCUG) was taken. Patient based success was defined as the disappearance of reflux on control VCUG performed 3–6 months after the operation.

Results: Data were available for 240 patients. Mean age and mean postoperative follow-up were 78 ± 41 months and 19 ± 18 months. The overall success rate was 73.2%. Gender, laterality, grade of VUR, presence of voiding dysfunction, renal scar and preoperative breakthrough infection (BTI) were not found to affect the outcome, whereas age younger than 54 months and previous history of failed

endoscopic injection were found to negatively affect the outcome both in univariate and multivariate analysis. The postoperative UTI (5 febrile and 43 nonfebrile) rate was 20%. Both univariate and multivariate analysis showed that postoperative UTI was more common in patients with persisting reflux, with preoperative breakthrough infections and in girls. Patient characteristics, treatment outcome and postoperative UTI rate were similar regarding the used bulking agent. No ureteral obstruction was experienced within the follow-up period.

Discussion: Our success rate for second injection is about 60%, which is significantly lower than for the patients who underwent first injection. We could not find any affecting factor for this difference. Contrary to the literature, our success rates were similar in different reflux grades. We can explain this finding that we value the intraoperative orifice configuration more than the grade which can be accepted as a patient selection bias. The lower success rate in children younger than 54 months can be explained by unstabilized bladder dynamics and higher voiding pressures in this age group, who are still in the toilet-training phase. Despite successful endoscopic treatment, UTI might occur. Postoperative UTI was more common in patients with persisting reflux, preoperative BTI and girls. The similar success rates of both bulking agents proved that dextranomer size does not affect the clinical outcome. Limitations of our study can be counted as follows: 1. the data do not include the number of patients in whom conversion to open surgery was decided intraoperatively because of the unfavorable orifice configuration, 2. our data do not include the injected volume records.

Conclusion: Endoscopic treatment of VUR has satisfying outcomes in properly selected cases. Younger age (<54 months) and previous history of failed injection history were found to be related to unfavorable results. Postoperative UTI occurs more frequently in patients with persisting reflux, preoperative breakthrough infection history and girls. The choice of one of the dextranomer-based substances does not affect the surgical outcome and postoperative UTI development.

KEYWORDS

Vesicoureteral reflux;

Endoscopic;

Treatment;

Outcome;

Infection;

Bulking material

Table. Comparison of treatment success regarding several factors (chi-square test)

Male vs female	%66 vs 75.4	$p=0.174$
Age <54 m. vs >54 m.	%65.7 vs 78.5	$p=0.043^{**}$

Unilateral vs bilateral	%77.5 vs 67.6	$p= 0.087$
Grade 1–2 vs 3 vs 4–5	%77.9 vs 73 vs 67.4	$p=0.455$
Grade 1–2-3 vs 4–5	%74.7 vs 67.4	$p= 0.311$
VD, no vs yes	%80 vs 78.1	$p= 0.774$
Scar, no vs yes	%72 vs 72.4	$p= 0.941$
BTI, no vs yes	%73 vs 74.5	$p= 0.806$
Deflux vs Dexell	%75.2 vs 71.8	$p=0.545$
Previous failed STING, no vs yes	%75.9 vs 59.5	$p= 0.038^{**}$

BTI = breakthrough infection; VD = voiding dysfunction.

Introduction

Vesicoureteral reflux (VUR) is one of the most important causes of pediatric nephropathy in many countries including ours [1,2]. Understanding the physiopathology and course of the disease has led to conservative management of most patients. However, there remains a group of patients with recurrent febrile urinary tract infections (UTI) under antibiotic prophylaxis, whose chance of spontaneous resolution is unlikely and whose kidneys are scarred, who require interventional treatment modalities [3,4]. The interventional modalities include open, endoscopic and laparoscopic approaches. Among these, endoscopic subureteric injection seems to be the least invasive method with acceptable outcomes when applied in appropriate patients [5,6].

The aim of the present study is to investigate the parameters which may affect the outcomes of endoscopic injection, and to compare the efficacy of two different bulking agents both composed of dextranomer-hyaluronic acid copolymer.

Materials and methods

We reviewed the data of patients who underwent endoscopic injection between 2003 and 2012 for treatment of VUR. Patients with history of previous open antireflux surgery, more than one failed endoscopic treatment for reflux, secondary VUR caused by posterior urethral valve, duplex system and overt spinal dysraphism were excluded. Data were available for 240 patients, and these were recorded to a standard sheet. Preoperative patient characteristics are given in Table 1. Reflux was classified as low (grade 1–2), moderate (grade 3) and high (grade 4–5). Voiding dysfunction was defined as the presence of lower urinary tract symptoms (presence of urge, incontinence, weak stream, hesitancy, frequency and urinary tract infections, but without overt uropathy or neuropathy) in children older than 5 years evaluated by symptom score [7] or urodynamic study. Behavioral modification and/or medical treatment were given appropriately before any intervention.

Surgery was indicated in patients with recurrent febrile urinary tract infections under antibiotic prophylaxis, whose chance of spontaneous resolution is unlikely, whose kidneys are scarred and with parental decision. Surgical technique was the classical STING method performed by or under supervision of one of the pediatric urologists (S.T and H.S.D) [8]. One of the two dextranomer-hyaluronic acid copolymer agents (Deflux in 109 and Dexell in 131 patients) was used. Both agents used in this series were highly viscous and were composed of similar amounts of hyaluronic acid gel (15 mg in Deflux versus 17 mg in Dexell) but different sized dextranomer microspheres (80–250 μm in Deflux and 80–120 μm in Dexell). The selection of the agent was dependent on the availability of the material in the hospital, in accordance with the reimbursement conditions of the social security system. As ours is a referral center, most of our patients live in other geographic areas of the country. Therefore, after the procedure patients were hospitalized for an average of 1 day (0–2). During the follow-up, ultrasonography was performed with 3-month interval, antibiotic prophylaxis was continued until the control voiding cystourethrography (VCUG) was taken. Patient-based success was defined as disappearance of reflux on control VCUG, which was performed 3–6 months after the operation.

Effects of several parameters were examined on outcome. The SPSS 15.0 software program was used to perform statistical analysis. Mann-Whitney, chi-square and *t* tests were used where appropriate and logistic regression analysis was used for multivariate analysis. A *p* value <0.05 was used for determination of statistical significance. Multicollinearity status between the parameters found to be significant in multivariate analysis was investigated by collinearity statistics. A calculated variance inflation factor (VIF) value of more than 5 indicated a multicollinearity problem.

Ethical approval was not required for this study.

Results

Mean age of the patient and mean postoperative follow-up was 78±41 months and 19±18 months. The overall success rate was 73.2%. The postoperative UTI (5 febrile and 43 nonfebrile) rate was 20%. As shown in Table 2, gender, laterality, grade of VUR, presence of voiding dysfunction, renal scar and preoperative breakthrough infection were not found to affect the outcome, whereas age younger than 54 months (identified by ROC curve, AUC 0.603, *p* = 0.02) and previous history of failed endoscopic injection (37 patients) were found to negatively affect the outcome both in univariate and multivariate analysis (binary logistic regression, *p*<0.001).

Postoperative UTI was present in 20% of patients. As we analyzed the possible predictors for postoperative UTI, univariate analysis showed that it was more frequent in patients with persisting reflux (14.7% vs 36.1%, chi-square test, *p*<0.001), with preoperative breakthrough infections (11.3% vs 32%, chi-square test, *p*<0.001) and in girls (2% vs 25.5%, chi-square test, *p*<0.001), and multivariate analysis with binary logistic regression method revealed these three factors were significant (*p*<0.001).

The odds ratios of the detected significant factors for the surgical outcome and postoperative UTI are given in Table 3. Concerns regarding a likely multicollinearity problem between these significant factors were investigated by linear regression analysis. The collinearity statistics yielded a

value of variance inflation factor (VIF) approximately 1 for all significant factors, which dispels the doubts on a multicollinearity problem.

Deflux and Dexell were used in 109 and 131 patients, respectively, and treatment outcomes were similar. The distribution of preoperative patient characteristics was similar regarding the used bulking agent (Table 4). No ureteral obstruction was experienced within the follow-up period.

Discussion

Endoscopic subureteric injection technique is a minimally invasive modality, with a short learning-curve allowing surgeons to use it extensively [9,10]. It can be repeated in failed cases and necessitates a very short hospitalization period. Besides these advantages, selection of the appropriate patient is of utmost importance. The literature has sufficient data to select the patients who will benefit most. The literature states a success rate of about 70% [5,6]. Our overall patient-based success rate is 73%, which is comparable with the literature. As mentioned previously, the techniques has a short learning curve and within a 10-year period, the success rate did not differ significantly. Although this result was achieved in an educational institute, consistency can be explained as the procedures were performed by or under supervision of one of two experienced pediatric urologists (S.T/H.S.D). The literature also reports a success rate of about 68% in second and 34% in third sessions [5]. Our success rate for second injection is about 59.5%, which is significantly lower than for patients who underwent first injection. We analyzed the parameters which might cause this difference; unfortunately, we were not able to find a difference in parameters between first and second injection cases. Our cohort does not include tertiary cases as our policy is to transfer to open surgery for patients with two previous failed endoscopic injections.

Several techniques have been described for endoscopic subureteric injection with the aim of increasing the success rates: HIT, double HIT, HIT plus STING [11]. Some authors reported improved success rates [8], whereas others did not detect a positive effect [12]. The effect of these

modifications on the outcomes is not clear, and therefore our preference is still to perform conventional STING technique.

The grade of VUR is one of the most important factors affecting the success rate. A meta-analysis revealed a decreasing success rate with increasing reflux grade [5]. However, our study did not show this inverse correlation and success rates were similar in different reflux grades. We can explain this finding in that we value the orifice configuration more than the grade and intraoperative decision is established in this manner, which can be accepted as a patient selection bias. In our unit, we would still consider open reimplantation in the vast majority of high-grade refluxers (grades 4 or 5), but only in those with good orifice configuration and relatively longer submucosal tunnel during endoscopy would we consider endoscopic treatment. In other words, high success rates in high grades can be achieved with appropriate patient selection. On the other hand, the data do not include the number of patients in whom conversion to open surgery was decided intraoperatively because of the unfavorable orifice configuration. The absence of these data may be considered a limitation of the present study.

Neurogenic or idiopathic voiding problems have been claimed as the cause of failure [13-15]. Patients with neurogenic bladder problems were excluded in our study. Although voiding dysfunction was present in half of the patients older than 5 years, we did not detect a negative effect of voiding dysfunction on surgical outcome. Our policy in VUR patients older than 5 years is always to evaluate the presence of voiding dysfunction with noninvasive diagnostic tools (questionnaires, uroflowmetry) or videourodynamics if necessary. Patients with voiding dysfunction are given standard urotherapy and/or medical treatment. Therefore, in our patient group, voiding dysfunction is most of the time under control, and outcome of the injection therapy was not found to be affected. Thus, before application of any interventional treatment modality, we strongly recommend evaluation of status of voiding dysfunction as proposed by AUA guidelines [9,13,16].

An interesting finding of our study was the higher success rate in older patients. The success rate was 78.5% in children older than 54 months, whereas it was 65.7% in younger patients. This difference can be explained by unstabilized bladder dynamics and higher voiding pressures in the younger age group who are still in the toilet-training phase. Supporting this theory, we detected that the frequency of male gender (37.3% vs 16.4%, chi-square test, $p=0.001$) and bilateral disease (53.7% vs 35.2%, chi-square test, $p=0.01$) was greater in the younger age group.

The primary aim of anti-reflux interventions is to prevent reflux of urine to the kidney rather than preventing urinary tract infections. Despite a successful endoscopic or open anti-reflux procedure, urinary tract infections might occur. Although the number and incidence of urinary tract infections decrease, they never get to zero per cent [17]. Postoperative UTI was more common in patients with persisting reflux, preoperative BTI and girls.

Most of the time, there are no complications with endoscopic subureteric injection procedures. The only procedure-related important complication is postoperative obstruction of the ureteral orifice, which is usually transient and does not require intervention. Nonetheless, ureteral obstruction might be significant and require intervention in a very small percent of patients, reported to be less than 1% [18]. In the present series, there were no cases of obstruction.

Endoscopic treatment of VUR was first described by Matouschek, who used Teflon particles for this purpose [19]. The use of dextranomer-hyaluronic acid copolymer for subureteric injection was first reported in 1995 and since then it has become a serious alternative to conventional open surgeries with its non-immunogenic, biocompatible, non-allergenic, biodegradable, non-migrating and longlasting effect properties. The two materials used in this study resemble each other, with similar amounts of hyaluronic acid gel and dextranomer microspheres. Yet the polymer structure is different and there are some slight differences in structure/physiologic properties and the way they have been manufactured. In our study, patient characteristics were similar regarding the bulking

agent used. Success rates were similar for both bulking agents, proving that dextranomer size does not affect the clinical outcome. There is one previous study that reports similar success rates with these two agents in association with a difference between the average injected volumes of the material (0.9 ml for Deflux, 1.6 ml for Dexell) [20]. However, when cost analysis is considered, the former material is at least three times more expensive than the latter in the national market. One of the limitations of the present study was that our data do not include the injected volume records, hence we abstain from making a comment on this issue. Although we did not measure the volume injected per renal unit, our reimbursement records show that the number of syringes used for patients were similar with the two bulking agents, therefore we cannot really comment that you need to inject more with Dexell but we can comment that the amount used per patient does not differ and therefore the cost does not increase with increasing volumes of injection.

Conclusion

Endoscopic injection for treatment of VUR is widely used and has satisfying outcomes in properly selected cases. Younger age (<54 months) and previous history of failed injection history were found to be related to unfavorable results. Postoperative UTI may persist even in successful cases; however, it occurs more frequently in patients with persisting reflux, preoperative breakthrough infections history and girls. The choice of one of the dextranomer-based substances does not affect the surgical outcome and postoperative UTI development.

Conflict of interest

None.

Funding

None.

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Table 1. Patient characteristics

Sex (m/f), <i>n</i>	53/187
Unilateral/bilateral, <i>n</i>	138/102
Reflux grade (1-2/3/4-5), <i>n</i>	68/126/146
Breakthrough infection, %	47
Scar, %	44
Voiding dysfunction, %	49
Previous STING history, %	15.7
Deflux/Dexell, <i>n</i>	109/131

Table 2. Comparison of treatment success regarding several factors (chi-square test)

Male vs female	%66 vs 75.4	$p=0.174$
Age <54 m. vs >54 m.	%65.7 vs 78.5	$p=0.043^{**}$
Unilateral vs bilateral	%77.5 vs 67.6	$p=0.087$
Grade 1-2 vs 3 vs 4-5	%77.9 vs 73 vs 67.4	$p=0.455$

Grade 1-2-3 vs 4-5	%74.7 vs 67.4	$p=0.311$
VD, no vs yes	%80 vs 78.1	$p=0.774$
Scar, no vs yes	%72 vs 72.4	$p=0.941$
BTI, no vs yes	%73 vs 74.5	$p=0.806$
Deflux vs Dexell	%75.2 vs 71.8	$p=0.545$
Previous failed STING, no vs yes	%75.9 vs 59.5	$p=0.038^{**}$

BTI = breakthrough infection; VD = voiding dysfunction.

Table 3. Odds ratios and VIF values of the significant predictors for postoperative success and UTI

	Parameters	Significance ^a	Odds ratio	95% confidence interval (lower-upper)	Collinearity statistics, VIF value
Postoperative success	Age (<54 m. vs >54 m.)	0.044	0.497	0.252-0.980	1.014
	Previous failed injection	0.019	2.566	1.168-5.638	1.014
Postoperative UTI	Persisting reflux	<0.001	4.466	2.022–9.865	1.011
	Preoperative BTI	0.001	3.637	1.684–7.852	1.016
	Gender	0.007	17.112	2.201–133.046	1.027

^a Binary logistic regression analysis.

BTI = breakthrough infection; UTI = urinary tract infection; VIF = variance inflation factor (value more than 5 indicates a multicollinearity problem).

Table 4. Distribution of preoperative patient characteristics and postoperative outcome regarding the bulking agent types

Male/female, <i>n</i>	18/91	35/96	$p=0.058^a$
Unilateral/bilateral, <i>n</i>	61/48	77/54	$p=0.660^a$
Grade 1-2/3/4-5, <i>n</i>	31/62/16	37/64/30	$p=0.243^a$

Grade 1-2-3/4-5, <i>n</i>	93/16	101/30	$p=0.107^a$
VD, yes, %	47	51.3	$p=0.611^a$
Scar, yes, %	46.9	41.6	$p=0.425^a$
Preoperative BTI, yes, %	48.4	45.9	$p=0.712^a$
Previous STING history, yes, %	15.6	15.3	$p=0.944^a$
Operation age, months	86	80	$p=0.364^b$
Postoperative UTI, yes, %	23.6	17.6	$p=0.215^a$
Success, patient, %	75.2	71.8	$p=0.545^a$

^a chi-square test. ^b Mann-Whitney test.

BTI = breakthrough infection; VD = voiding dysfunction.

AUTHOR QUERIES

1. What is the significance of the asterisks in the tables?