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Endoscopic treatment of grades IV and V vesicoureteral reflux with two bulking substances: Dextranomer hyaluronic acid copolymer versus polyacrylate polyalcohol copolymer in children☆,☆☆,★,★★

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ABSTRACT

Purpose: We aimed at evaluating the efficacy and complications of two bulking substances: dextranomer/hyaluronic acid copolymer(Dx/Ha;Dexell®) versus polyacrylate polyalcohol copolymer(PPC;Vantris®) in subureteric injection treatment of children with high grades (grades IV-V) vesicoureteral reflux(VUR).

Methods: Data of patients undergoing endoscopic treatment of high grade VUR (January 2009–August 2015) were retrospectively investigated. Patients with high grade VUR caused by posterior urethral valve, duplex system, paraureteral diverticula and neurogenic bladder were excluded. Classical subureteric injection method (STING) was used. Seventy-three children (45 girls and 28 boys) who had 88 refluxing renal units (RRUs) with grades IV-V VUR ($n = 64/n = 24$) underwent endoscopic treatment using Dx/Ha ($n = 63$ RRUs) and PPC ($n = 25$ RRUs).

Results: Mean age of patients in Dx/Ha and PPC groups were 6 (3) and 6 (3.75) year ($p = 0.81$), and volumes of these substances given were 1.3 (1) and 1 (0.5) mL ($p = 0.003$), respectively.

Overall, for the first endoscopic injection, success rate of grades IV-V VUR per RRU was 53.9% with Dx/Ha, compared to 80% in PPC-injected group, ($p = 0.024$). Late ureterovesical junction obstruction developed only in one patient in PPC-injected group. No ureteral obstruction was observed in Dx/Ha-injected group.

Conclusions: Endoscopic injection of PPC resulted in significantly higher success rate, compared to Dx/Ha in subureteric injection treatment of children with high grade VUR.

However, the development of late ureterovesical junction obstruction should also be taken into account in PPC injection.

Vesicoureteral reflux (VUR) is a common problem in childhood period, and its prevalence in normal children has been estimated to be between 0.4% and 1.8% [1]. Endoscopic treatment of primary VUR by subureteral injection (STING) is a modality used in children in the last three decades [2]. Because of being a relatively easy and minimal invasive procedure, STING is an alternative method to open surgery and long-term antibiotic prophilaxis. However, the most significant negative side of endoscopic treatment is that its success rate is lower, especially in high grade VUR than open surgery. In order to increase the success rate of endoscopic treatment, additional injections may be required [3]. Additionally, the experience of the surgeon, the content of substance used for injection, submucosal stability of injected substance, and the grade of VUR are the factors known to affect the success of procedure [4,5].

The aim of our study was to evaluate the efficacy and complications of two bulking substances: dextranomer/hyaluronic acid copolymer (Dx/Ha; Dexell®) versus polyacrylate polyalcohol copolymer (PPC; Vantris®) in endoscopic treatment of children with grades IV and V VUR.

1. Materials and methods

The data of patients undergoing endoscopic treatment of high grade VUR between January 2009 and August 2015 were retrospectively reviewed. Patients with grades IV and V reflux were considered high grade reflux. The following were included into the study as parameters we analyzed: sex, age when the first injection was given, grade and laterality of VUR, number of injections, volume and type of substances used for injection, ureteral orifice configuration, complications after surgery and outcome. Endoscopic treatment was performed in 73 children (45 girls and 28 boys) who had 88 refluxing renal units (RRUs) with

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Table 1
Demographic data and distribution of patients' characteristics.

		Dx/Ha	PPC	P value
Patients		53	20	
	Boys n	23 (43%)	5 (25%)	.149[a]
	Girls n	30 (57%)	15 (75%)	
	Bilateral n	22 (41.5%)	12 (60%)	.158[a]
	Unilateral n	31 (58.5%)	8 (40%)	
Median intraoperational age (year) (IQR)		6 (3)	6 (3.75)	.810[b]
RRUs		63	25	
	Grade IV n	44 (70%)	20 (80%)	.335[a]
	Grade V n	19 (30%)	5 (20%)	
Median volume of injected substance (mL) (IQR)		1.3 (1)	1 (0.5)	.003[b]
Orifice configuration n		15(23.8%)	11(44%)	.061[a]
	Lateral pillar defects n	2	5	
	Stadium-shaped n	5	3	
	Golf hole n	8	2	
	Form of horseshoe n	-	1	

Dx/Ha, dextranomer/hyaluronic acid copolymer; PPC, polyacrylate polyalcohol copolymer; IQR, interquartile range; RRUs, refluxing renal units.
[a] chi-square test.
[b] Mann–Whitney U test.

grades IV and V VUR using Dx/Ha and PPC, injected as a total of 63 and 25 RRUs, respectively. Of total 88 RRUs, 64 were grade IV VUR while 24 were grade V. The demographic data and distribution of patients' characteristics are presented in Table 1.

The selection of substance was dependent on the availability of the material in the hospital, in accordance with the reimbursement conditions of the social security system in Turkey. VUR was diagnosed by voiding cystourethrogram (VCUG) and classified under the International Classification System constituted by the International Reflux Study Committee [6]. Our indication of endoscopic treatment was high grade VUR along with breakthrough urinary tract infection (UTI), progressive renal scarring and nonresolution of VUR only in a few pre-school children. Patients with high grade VUR caused by posterior urethral valve, duplex system, ectopic ureter, paraureteral diverticula and neurogenic bladder were excluded. Children who had symptoms of dysfunctional voiding or constipation were treated conservatively before endoscopic correction. Endoscopic treatment was performed under general anesthesia with a pediatric cystoscope (9.5 F and 11 F Olympus®), and a Williams cystoscopic injection needle of 3.7 F, 23 gauge and 35 cm (Cook®) was used for the injections by a single surgeon (C.K.) through STING, a technique similar to that described in literature [7,8]. The usual technique of STING with the needle introduced submucosally under the ureteral orifice at 6-o'clock position was used in all patients, except for four patients with a widely open orifice in whom the injection was performed with the hydrodistention implantation technique. The injection of bulking substances was continued until the *volcanic* bulge was observed, raising the ureteral meatus onto the dome of the mound. In most of the patients, endoscopic injection was performed as an outpatient procedure. Antibiotic prophylaxis was used perioperatively and after STING, continued until the reflux was documented to resolve on postoperative cystogram. Control VCUG was performed at the third postoperative month. Preoperative evaluation consisted of urinalysis and culture, renal and bladder ultrasonography, dimercaptosuccinic acid scan, and videouro-dynamic studies. Postoperative studies included renal and bladder ultrasonography, urinalysis and urine culture performed on the 10th day, and at the 1st, and 3rd months after the procedure. The success of STING was defined as the elimination of VUR with a single injection. After the VUR was resolved, these children were followed up clinically and radiologically with renal ultrasound at 1st year and every 2 years. Complications were classified as UTI, progressive ureteral dilatation and neocontralateral VUR.

Statistical analyses were performed using SPSS for Windows 15.0 (SPSS, Chicago, IL). The appropriateness of variables to normal distribution rates was evaluated with visual histogram and probability graphics using analytic methods such as the Kolmogorov–Smirnov and Shapir–Wilk tests. Descriptive analyses were shown using median and interquartile range (IQR) for abnormal variables, and frequency tables for ordinal variables. The univariate analyses to identify variables associated with patient outcome were investigated using the chi-square, Fisher's exact, and Mann–Whitney U tests where they were appropriate. In multivariate analyses, the possible factors identified with univariate analyses were further entered into the logistic regression analyses to determine independent predictors of patient outcome. The receiver operating characteristic (ROC) curve analysis was performed to determine optimal cutoff values related to ages. $P < 0.05$ was considered statistically significant. An ethical approval was obtained from the ethical committee of Meram Medical School of Necmettin Erbakan University in Konya, Turkey.

2. Results

Median intraoperational age (IQR) was 6 (3) years (range 10 months–13 years) for Dx/Ha-injected group and 6 (3.75) years (range 2,5–14 years) for PPC-injected group.

For the first endoscopic injection, the success rates per RRU for grades IV and V VUR were 53.9% (34/63) in those injected with Dx/Ha, compared to 80% (20/25) in those with PPC ($p = 0.024$) although the success rates were found as 64% (41/64) for grade IV VUR and 54% (13/24) for grade V VUR. After the first injection, while a complete resolution was obtained in 24 of 44 grade IV VUR in Dx/Ha-injected group, 17 of 20 grade IV VUR in RRUs in PPC-injected group displayed a complete resolution ($p = 0.019$). For grade V VUR after the first injection, although a complete resolution was obtained in 10 of 19 RRUs in Dx/Ha-injected group, three of five RRUs in PPC-injected group displayed a complete resolution ($p = 0.769$) (Table 2). We were able to find no difference in the distribution of such parameters as sex (boy vs girl, via chi-square test, $p = 0.149$), median age at the first injection (Dx/Ha group vs PPC group, via Mann–Whitney U test, $p = 0.81$), ureteral orifice configuration (normal cone vs shapes of stadium, horseshoe,

Table 2
Outcome of endoscopic correction of VUR after first injection (chi-square test).

	Dx/Ha		PPC		P value
	RRU n	Success n (%)	RRU n	Success n (%)	
Grade IV	44	24 (54.5)	20	17 (85)	.019
Grade V	19	10 (52.6)	5	3 (60)	.769
Total	63	34 (53.9)	25	20 (80)	.024

Dx/Ha, dextranomer/hyaluronic acid copolymer; PPC, polyacrylate polyalcohol copolymer;