

# Does the Diameter of Dextranomer Microspheres Affect the Success in Endoscopic Treatment of Vesicoureteral Reflux?

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<b>OBJECTIVE</b>	To evaluate whether the polymer microsphere diameter affects the success rate in the endoscopic treatment of vesicoureteral reflux.
<b>METHODS</b>	In our consecutive series, 56 patients underwent subureteral injection with Dexell and 60 patients were treated with Deflux. Patients were evaluated with pediatric lower urinary tract scoring system, uroflowmetry, and a residual urine volume and voiding diary at the time of injection and control. Patients with grade V reflux, duplex systems, paraureteral diverticula, or refractory lower urinary tract symptoms were excluded. The numbers of renal units with grade II-III vesicoureteral reflux were 78 and 73 in the first (Deflux) and second (Dexell) groups, respectively. The numbers of renal units with grade IV reflux were 24 and 17 in the first and second groups, respectively. The resolution rate was determined by voiding cystourethrogram at the third postoperative month. Postoperative febrile urinary tract infections and <i>de novo</i> scars in dimercaptosuccinic acid were noted. Groups were compared by the $\chi^2$ test.
<b>RESULTS</b>	Mean follow-up time and mean age of the children were not significantly different. The number of nondilating and dilating renal units was not significantly different. Resolution rates were similar between the groups (79.5 and 78%, respectively). There was no significant difference in terms of resolution rates when dilating and nondilating urinary systems were separately analyzed. The average volumes used per renal unit were 0.9 and 1.6 mL in the first and second groups, respectively ( $P < .005$ ). Postoperative febrile urinary tract infection and <i>de novo</i> scar formation rates were similar.
<b>CONCLUSION</b>	The diameter of dextranomer microsphere does not affect the short-term success rate in endoscopic treatment of vesicoureteral reflux. Multicentric, randomized and prospective studies are required for long-term clinical results. UROLOGY 80: 703–706, 2012. © 2012 Elsevier Inc.

Vesicoureteral reflux (VUR) is one of the most common urologic abnormalities in children.<sup>1</sup> It occurs in 1%-2% of the pediatric population and in 30%-40% of children with urinary tract infection (UTI).<sup>1,2</sup> Early and accurate management of VUR is crucial because the association of VUR, UTIs, and reflux nephropathy is well recognized.<sup>1,3</sup> The possible morbidity of pyelonephritis in the acute setting and the long-term potential for developing childhood hypertension and chronic renal failure secondary to renal scarring are major reasons for diagnosing and correcting reflux in children.<sup>4</sup>

Endoscopic correction of reflux is the first alternative if medical management with low-dose antibiotic treatment has failed.<sup>5</sup>

Various injectable agents, including polytetrafluoroethylene, bovine collagen, autologous chondrocytes, and silicone have been used for subureteral injections.<sup>1,5,6</sup> Because conflicting findings exist in the recent literature about the efficacy and safety of these substances, their substances is limited for the endoscopic treatment of VUR.<sup>4,7,8</sup> Use of dextranomer/hyaluronic acid copolymer (Deflux) has become an established alternative for the endoscopic treatment of reflux in children, since its first clinical use in 1995.<sup>5</sup>

Deflux consists of dextranomer microspheres averaging 80-250  $\mu\text{m}$  in sodium hyaluronic acid solution. Positively charged dextranomer (Dexell), used for comparison with Deflux in the recent study, consists of positively charged dextranomer microspheres with an average size of 80-120  $\mu\text{m}$ . Both materials are nonim-

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**Table 1.** Properties of Dexell and Deflux

	Dexell	Deflux
Dextranomer (mg/mL)	50	50
Hyaluronic acid (mg/mL)	15	17
Osmolality (mOsmol/l)	400	341
pH value	6.2	7.1
Diameter of dextranomer microspheres ( $\mu\text{m}$ )	80-120	80-250
Cost (€/cc) in Turkey	140	315

munogenic and biodegradable with no potential for malignant transformation.

We retrospectively compared the efficacy of Deflux and Dexell with different microsphere size and polarity in the subureteral injection treatment for VUR in children.

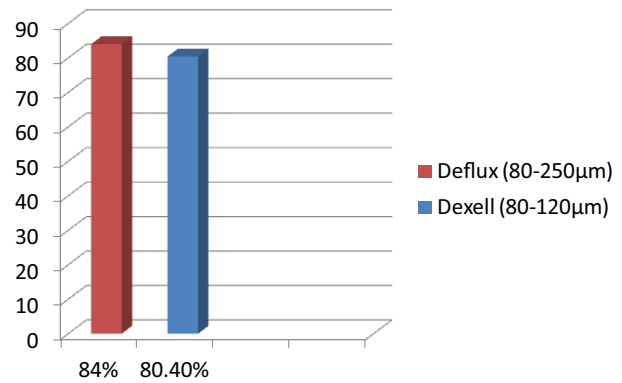
## MATERIAL AND METHODS

A total of 116 children with VUR were included in the study. All of the patients were identified postnatally, and the mean age of the patients was 4.3 years. Patients with grade V reflux, duplex urinary systems, paraureteral diverticulum, and refractory lower urinary tract symptoms were excluded from the study. All imaging studies were evaluated by a single radiologist who was blinded to the study groups. The numbers of renal units with grade II-III VUR were 78 and 73 in the first (Deflux) and the second (Dexell) groups, respectively. The numbers of renal units with grade IV reflux were 24 in the first group and 17 in the second group. Deflux with dextranomer microspheres 80-250  $\mu\text{m}$  in diameter had been used for 60 patients in 102 renal units between October 2009 and September 2010. Between October 2010 and August 2011, 56 patients (90 renal units) underwent subureteral injection with positively charged dextranomer (Dexell), which has dextranomer microspheres 80-120  $\mu\text{m}$  in diameter. Table 1 summarizes the properties of Dexell and Deflux.

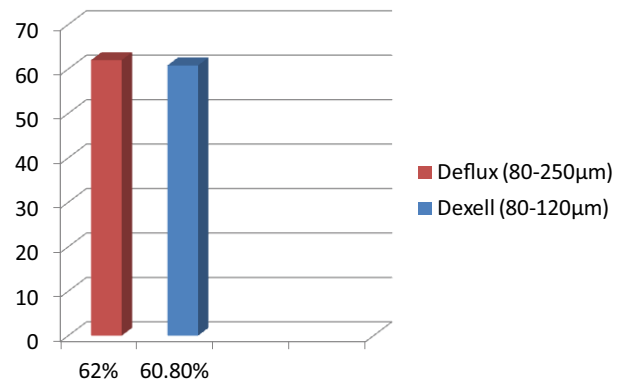
Patients were evaluated with a pediatric lower urinary tract scoring system (PLUTSS), uroflowmetry (UFM) and residual urine volume, and voiding diary at the time of subureteral injection and control at the third month after the procedure. All children were evaluated with voiding cystourethrogram (VCUG) for the resolution rate and with dimercaptosuccinic acid (DMSA) scan for *de novo* scar formation at the third postoperative month. Postoperative febrile UTIs have been noted. Statistical analyses were performed with  $\chi^2$  test, and statistical significance was set at a *P* value of  $< .05$ .

## RESULTS

A total of 60 children (10 male and 50 female) in the first (Deflux) group and 56 children (11 male and 45 female) in the second (Dexell) group were evaluated. There was no statistical difference between the 2 groups in terms of male/female ratio. The mean follow-up time (7.6 and 7.4 months, respectively) and mean age of the children (4.6 and 4.0 years, respectively) were not significantly different between the first and second groups. The mean number of UTIs before the surgery was 4.2 (range 2-7) and 4.5 (range 2-6) in the first and second groups, re-



**Figure 1.** Resolution rates evaluated with VCUG for nondilating (grade II-III vesicoureteral reflux [VUR]) urinary systems in both groups. (Color version available online.)



**Figure 2.** Resolution rates evaluated with VCUG for dilating (grade IV VUR) urinary systems in both groups. (Color version available online.)

spectively. No statistical difference was noted between the 2 groups in terms of UTI frequency. The number of nondilating urinary systems (grade II-III VUR) was not statistically significantly different when the 2 groups were compared (78 and 73 urinary systems respectively). Similarly, the number of dilating urinary systems (grade IV VUR) was not significantly different between the first and second groups (24 and 17 urinary systems, respectively).

None of the patients were maintained on prophylaxis in the postoperative period. Resolution rates evaluated with VCUG on the third postoperative month were similar between the groups (79.5% and 78% respectively) ( $P > .05$ ). There was no significant difference between the 2 groups in regard to resolution rates when dilating and nondilating urinary systems were separately analyzed (Figs. 1 and 2). Resolution was defined as no obvious VUR at VCUG at the third postoperative month.

Four of 60 patients in the first group and 2 of 56 patients in the second group presented with febrile urinary tract infection in the postoperative period, which subsided after intravenous antibiotic treatment ( $P > .05$ ). The rate of *de novo* scar formation on postoperative DMSA scan was not significantly different when the 2 groups were compared ( $P = .001$ ) (3 of 60 and 2 of 56

patients, respectively). All endoscopic procedures were performed by a single surgeon. The mean volume of subureteral injection material used per renal unit was 0.9 and 1.6 mL in the first and second groups respectively. The difference was not significantly different ( $P < .05$ ). None of the patients experienced ureteral obstruction, postoperative urinary retention, or gross hematuria. Mean hospitalization time was 22 hours (range 20-36 hours) in both groups. Mean operation time was 32 minutes (range 25-58 minutes) and 36 minutes (range 30-62 minutes) for Deflux and Dexell, respectively ( $P = .001$ ).

## COMMENT

Management of children with VUR consists of long-term antibiotic prophylaxis, endoscopic treatment, and open surgery. Long-term administration of prophylactic antibiotics implies the danger of bacterial resistance with promotion to breakthrough urinary tract infections, and its success relies on patient or parent compliance.<sup>1</sup> A previous study reported spontaneous resolution rates of 13% yearly for grade I to III VUR and 5% for grade IV to V VUR with antibiotic prophylaxis.<sup>9</sup> Capozza et al showed 69% and 38% success rates for endoscopic treatment and antibiotic prophylaxis, respectively, after 1 year of treatment.<sup>10</sup>

Although open surgery achieves a success rate of 92%-98%, it is an invasive procedure requiring longer hospitalization time.<sup>1,11,12</sup> Following modifications in the endoscopic procedure technique, such as the submucosal intraureteral injection, the reported success rates have made endoscopic treatment an attractive alternative to open surgical procedures.<sup>4,13</sup> A previous study observed a resolution rate of 79% for ureters with grades I and II, 72% with grade III, and 65% with grade IV reflux following 1 injection.<sup>11</sup> Kirsch et al previously reported short-term success rates in 92% of ureters after the first injection with the subureteral transurethral injection (STING) procedure.<sup>13</sup> Endoscopic treatment of high-grade VUR has been investigated previously, and success rates varying from 55% to 90% have been reported.<sup>5,14-16</sup> Capozza et al showed that 80% of parents prefer endoscopic treatment to antibiotic prophylaxis and open surgery when given a free choice after detailed information about all treatment options.<sup>17</sup>

Endoscopic treatment is a safe, easy, and minimally invasive procedure with advantages, including repeatability in cases of failure after the first injection and shorter hospitalization and operation times.<sup>1,15</sup> In case of failure after the first application, although the total anesthesia time increases, success rates improve with the repeated injections.<sup>15</sup> No increase in complication rates or decreases in resolution rates have been noted in open surgery after previous unsuccessful endoscopic treatment.<sup>18</sup> The most important factors affecting the success rates of endoscopic procedure in the management of children with VUR are the surgeon's experience and the

content of the injection material used.<sup>4,15</sup> All patients in this study were treated by a single surgeon. Endoscopic intervention introduces a new variable: the implanted material.<sup>4</sup>

Various agents have been used previously for endoscopic correction of VUR.<sup>1,5,6</sup> In a previous study, Elder et al showed no difference between different agents used for subureteral injection in terms of success rates.<sup>16</sup> However, currently, dextranomer seems to be the ideal agent because it is easy to inject, nonimmunogenic, nontoxic, biodegradable, does not migrate to other organs, and is associated with minimal local inflammation.<sup>1,4</sup>

Subureteral injection with Dexell, which consists of a smaller average microsphere size compared with that of Deflux, is a minimally invasive procedure since the material can be applied using a 3.7-Fr needle. Because Dexell includes a positively charged dextranomer, it potentially will have a more durable response, causing more rapid collagen tissue formation at the injection site. The cost of Dexell (€140/cc) is less when compared with the cost of Deflux (€315/cc).

In this study, we compared the success rates between use of 2 different dextranomer molecules with different microsphere sizes and polarities. We have noted no statistical difference between these 2 agents in terms of success rates. In addition, there was no significant difference between the 2 study groups in terms of resolution rates when dilating and nondilating urinary systems were separately analyzed. Febrile urinary tract infection rates, *de novo* scar formation on postoperative DMSA scan, operation time, and hospitalization time were similar for both materials used. Although the mean volume of subureteral injection material used per renal unit was less (0.9 mL) in the first (Deflux) group when compared with the second (Dexell) group (1.6 mL), mean cost was more in the first group (Table 1).

Limitations of our study include a short follow-up period. Our findings reflect the short-term resolution rates on VCUG at the third postoperative month. A longer follow-up period would be more helpful in interpreting our recent results.

## CONCLUSIONS

In our study, we showed that the diameter of dextranomer microsphere, widely used for the endoscopic treatment of children with VUR, does not affect the short-term success rate of the procedure. Multicentric, randomized, prospective studies with longer follow-up periods are required for long-term clinical results.

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