Comparison of dextranomer/hyaluronic acid based bulking agents in the treatment of vesicoureteral reflux in children: Deflux versus Vurdex

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Introduction: *The objective of this study was to compare the clinical efficacy of two similar tissue bulking agents, Deflux and Vurdex, used for a treatment of vesicoureteral reflux (VUR) in our institution.*

Material and methods: *The case records of 104 children, treated endoscopically for primary VUR from January 2010 to January 2015, were retrospectively reviewed. Most of the patients were treated with Deflux until 2012, when use of Vurdex was started.*

Exclusion criteria were patients with secondary reflux due to neurogenic bladder, duplicated refluxing ureters, primarily operated patients and patients operated after first or second injection.

Results: *Endoscopic treatment of vesicoureteral reflux using Deflux was performed in 65 children (106 ureters). There were 24 patients with unilateral and 41 patients with bilateral VUR. After first injection of Deflux success was achieved in 74 ureters (69.8%), after second injection in 91 ureters (85.8%) and after third injection in 99 ureters (93.3%). The same procedure using Vurdex was performed in 39 children (58 ureters). There were 20 patients with unilateral and 19 patients with bilateral reflux. After first injection of Vurdex success was achieved in 43 ureters (74.1%), after second injection in 52 ureters (89.6%) and after third injection in 55 ureters (94.8%).*

Conclusions: *Overall success rate for patients treated with Deflux was 93.3% and for patients treated with Vurdex 94.8%. No significant difference in success rates between two groups was found (p = 0.714). However, Vurdex has an advantage because of the significantly lower price, but with same treatment results as Deflux.*

Key Words: vesicoureteral reflux, dextranomer/hyaluronic acid, Deflux, Vurdex, cost-benefit analysis, children

Introduction

Vesicoureteral reflux (VUR) is an abnormal movement of urine from the bladder into ureters or kidneys. It may present before birth as prenatal ureterohydronephrosis, an abnormal widening of the ureter, or with a urinary tract infection or acute pyelonephritis.[1-3] In recent years, endoscopic subureteral injection has become a first-line treatment for children with VUR because of its high success rates and a very low incidence of complications.[1,4-6] Since Matouschek's initial description of the subureteral injection technique in 1981 and the first clinical series reported by O'Donnell and Puri in 1984, it has evolved into a therapeutic alternative to open surgery.[7] Open repair prevent reflux by increasing the length of the intravesical ureter, facilitating compression

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of the ureter against the detrusor muscle during bladder filling. These procedures generally require inpatient hospitalization for management of postoperative pain as well as temporary urinary catheter drainage. In contrast, endoscopic repair is an outpatient procedure with minimal postoperative pain and no need for urinary catheter. The reduced morbidity of endoscopic repair, however, may come at the cost of decreased surgical success. The estimated success rate of open surgery is 95%-98%, while the reported success rate of endoscopic surgery is 80%-95%.[6,8,9] Injectable agents, such as Teflon, bovine collagen and Macroplastique, have all been used; however, concerns about efficacy and safety have limited their use.[8] Since the approval of dextranomer/ hyaluronic acid copolymer, endoscopic management of VUR has become an established alternative treatment in children. Both dextranomer and hyaluronic acid are biocompatible, which means that they do not cause clinically important reactions within the body.[8] Endoscopic injection of dextranomer/ hyaluronic acid copolymer is a safe and effective management for pediatric patients with VUR. It is a simple 15 minute, outpatient procedure. In terms of effectiveness and long-term success Deflux is the most reliable injectable material for the endoscopic treatment of VUR.[8] In recent years Vurdex was introduced for endoscopic treatment for VUR, it is consisted of the same biochemical composition as Deflux but significantly cheaper. It consists of cross-linked hyaluronic acid and positively charged dextranomer-based micro-particles that stimulate collagen growth and tissue regeneration at the injection site.[9]

The objective of this study was to compare the clinical efficacy of two similar tissue bulking agents, Deflux and Vurdex, used for a treatment of VUR in our institution.

Materials and methods

Patients

The case records of 104 children (24 boys and 80 girls; 164 ureters), who were treated endoscopically for primary VUR from January 2010 to January 2015 at the Department of Pediatric Surgery, University Hospital Split, were retrospectively reviewed. All patients enrolled in the study had VUR, as determined by either voiding cystourethrogram (VCUG). Dynamic radionuclide cystogram (DRNC) was used for follow up. Indications for intervention included the following: noncompliance with medical therapy, persistent reflux, recurring urinary tract infections, progressive renal scarring and parental preference. Exclusion criteria were patients with secondary reflux due to neurogenic bladder, duplicated refluxing ureters, primarily operated patients and patients operated after first or second injection. Informed consent was obtained from parents or legal guardians of all the patients and an *Institutional Review Board* of Split University Hospital approved the study protocol.

Material

Two similar tissue bulking agents, Deflux (Q-Med AB) and Vurdex (BioPolymer GmbH & Co. KG) were used for a treatment of VUR. Most of the patients were treated with Deflux until 2012, when using of Vurdex was started. Since then, Vurdex was in primary use in the treatment of VUR. Endoscopic treatment of VUR using Deflux (group 1) was performed in 65 children (106 ureters; grade I: 14; grade II: 30; grade III: 40; grade IV: 19; grade V: 3). Male to female ratio was 15:50. There were 24 patients with unilateral and 41 patients with bilateral VUR. The same procedure using Vurdex (group 2) was performed in 39 children (58 ureters; grade I: 12; grade II: 17; grade III: 20; grade IV: 7; grade V: 2). Male to female ratio was 9:30. There were 20 patients with unilateral and 19 patients with bilateral reflux. All procedures were performed with the children in the lithotomy position under general anesthesia. A 9.5-Fr pediatric cystoscope (Richard Wolf GmbH) was used to visualize ureteral orifices. Through a 3.7-Fr metallic needle, Deflux and Vurdex were injected submucosally in or below the ureteral orifice at the 6 o'clock position to create a prominent bulge and raise the distal ureter and ureteral orifice. The mean amount of each substance injected into the ureter was 1 mL (range 0.7 mL-1.2 mL) in both groups of patients. The mean amount of injected substance in Deflux group was 0.9 mL (range 0.7 mL-1.1 mL), while it was 1.0 mL (range 0.8 mL-1.2 mL) in Vurdex group. The amount of each substance injected into the ureter was determined according to reflux grade or shape of the ureteral orifice.

The costs of the single injection in Croatia (1 mL) are significantly lower when the Vurdex is used (€ 481.77) compared to the Deflux (€ 708.08).

Follow up

All patients in this study underwent endoscopic correction as a 1 day procedure; mean hospital stay was 1 day. Renal ultrasonography for detection of urinary obstruction and urine culture were performed 1 day after injection. All patients underwent ultrasonography and DRNC 3 months after discharge and urine culture every month. Thereafter, basic laboratory studies and renal ultrasonography occurred annually. Successful reflux correction was defined only as absent reflux on

TABLE 1. **Demographic data and the details of the reflux ureters of both treated groups**

VUR grade	Group 1 (Deflux)	Group 2 (Vurdex)	Total
I	14	12	26
II	30	17	47
III	40	20	60
IV	19	7	26
V	3	2	5
Number of ureters	106	58	164
Number of children	65	39	104
Sex			
Male	15 (23%)	9 (23%)	24 (23%)
Female	50 (77%)	30 (77%)	80 (77%)
Age (years)	4.7 (1-13)	5.1 (0-13)	4.8 (0-13)
Side			
Left	16	10	26
Right	8	10	18
Bilateral	41	19	60
Follow up	2-4 years	1-2.5years	1-4 years

VUR = vesicoureteral reflux

follow up. Mean overall follow up was 2 years (range 1-4 years). Surgery was performed only in case of unsuccessful reflux correction after three injections. All demographic data and details of the reflux ureters can also be seen in Table 1.

Statistical analysis

The data were analyzed using Z test, Excel for Windows 11.0 (Microsoft, Redmond, WA, USA) and Statistica for Windows 12.0 (Statsoft, Tulsa, OK, USA). All p values < 0.05 were considered statistically significant.

Results

During the study period, 104 children, 80 girls (77%) and 24 boys (23%) with a mean age of 4.8 years (range 0 to 13 years) underwent subureteral injections of dextranomer/hyaluronic acid based bulking agents because of VUR.

No significant difference in baseline characteristics (mean age, gender, reflux grade) were observed between group 1 and group 2. Results of treatment of VUR regarding grades in all children are shown in Table 2. After first injection of Deflux (group 1), success was achieved in 74 ureters (69.8%), after second injection in 91 ureters (85.8%) and after third injection in 99 ureters (93.3%). The overall success rate after Deflux injections (group 1) was 93.3% (99 of 106), Figure 1. VUR disappeared in 100.0% (14/14) for grade I, 96.6% (29/30) for grade II, 95.0% (38/40) for grade III, 84.2% (16/19) for grade IV and 66.6% (2/3) for grade V, Table 3.

After first injection of Vurdex (group 2), success was achieved in 43 ureters (74.1%), after second injection in 52 ureters (89.6%) and after third injection in 55 ureters (94.8%). The overall success rate after Vurdex injections (group 2) was 94.8% (55/58), Figure 1. VUR disappeared in 100.0% (12/12) for grade I, 100.0% (17/17) for grade II, 100.0% (20/20) for grade III, 71.4%

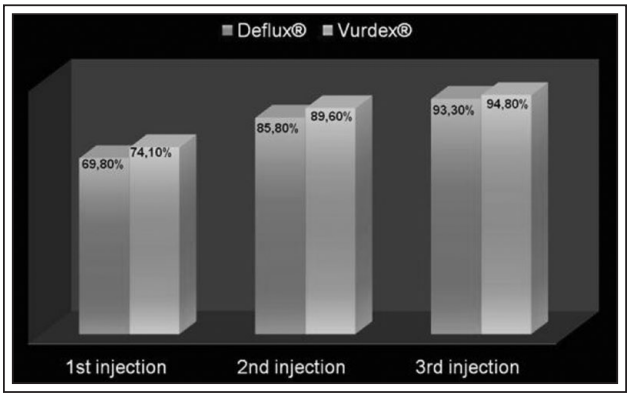

Figure 1. Overall results of treatment of VUR in both groups after first, second and third injection.

TABLE 2. **Results of treatment of VUR regarding grades in all children**

VUR grade	Reflux ureters	1st injection n	Success	%	2nd injection n	Success	%	3rd injection n	Success	%	Surgery
Deflux											
I	14	14	12	86	2	1	50	1	1	100	-
II	30	30	26	87	4	2	50	2	1	50	1
III	40	40	28	70	12	7	58	5	3	60	2
IV	19	19	7	37	12	6	50	6	3	50	3
V	3	3	1	33	2	1	50	1	0	0	1
Total	106	106	74	69.8	32	20	62.5	15	8	53.3	7
Vurdex											
I	12	12	9	75	3	3	100	-	-	-	-
II	17	17	13	76	4	4	100	-	-	-	-
III	20	20	16	80	4	2	50	2	2	100	-
IV	7	7	4	57	3	0	0	3	1	43	2
V	2	2	1	50	1	0	0	1	0	0	1
Total	58	58	43	74.1	15	9	60	6	3	50	3

VUR = vesicoureteral reflux

TABLE 3. **Comparison of treatment of VUR regarding grades in both groups**

VUR grade	Deflux n	Success	%	Vurdex n	Success	%	p*
I	14	14	100	12	12	100	1.000
II	30	29	96.6	17	17	100	0.446
III	40	38	95	20	20	100	0.309
IV	19	16	84.2	7	5	71.4	0.463
V	3	2	66.6	2	1	50	0.700
Total	106	99	93.3	58	55	94.8	0.714

*z-test
VUR = vesicoureteral reflux

TABLE 4. **Summarized results of treatment of VUR in both groups**

	Urethers	Success after 1st injection	%	Success after 2nd injection	%	Success after 3rd injection	%	Unsuccessful	%
Deflux	106	74/106	69.8	91/106	85.8	99/106	93.3	7/106	6.7
Vurdex	58	43/58	74.1	52/58	89.6	55/58	94.8	3/58	5.2
p*		0.557		0.485		0.714		0.714	

*z-test
VUR = vesicoureteral reflux

(5/7) for grade IV and 50.0% (1/2) for grade V, Table 3. There was no significant difference in cure rates between the two groups (p = 0.714), Table 4.

Higher rates of success in treating lower grades of VUR with Vurdex than Deflux were observed, while Deflux showed higher rates of success than Vurdex for higher grades of VUR but these differences were not statistically significant, Table 3.

Discussion

Endoscopic treatment for VUR has become an established alternative to long term antibiotic prophylaxis and ureteral reimplantation. Endoscopic subureteral injection of bulking agents has been in use for three decades now and has become a first-line therapy for children with VUR because of its advantages (no incision, no overnight hospital stay, short operative/anesthesia time, very low incidence of complications) and high success rates. It is less invasive and associated with less morbidity compared with open surgery. Ideal substance for subureteral injection should be biocompatible, biodegradable, biostable, easy to use and with no migrations after implantation. Multiple injectable substances have been developed and studied in order to provide the ideal treatment for VUR. Polytetrafluoroethylene (Teflon, Polytef) was initially used but fell into disfavor due to reports of distant particle migration and granuloma formation.[10,11] Polydimethysiloxan (Silicon, Macroplastique) shares the same problem, with migration, marked local inflammatory response and granuloma formation.[12,13] There is a real concern of possible malignant alteration because of the silicon influence on the tissue.[14] Cross-linked bovine collagen (Zyderm, Zypast) has also been used. Studies have shown that collagen is not an ideal substance for treatment of VUR, because of tendency to disappear with time, resulting in recurrence of VUR. There is also a risk of allergic reactions due to the bovine protein and prion disease transmission.[15] Autologous chondrocytes has also been used for treatment of VUR. The potential advantages include a sustained antireflux effect from viable chondrocytes, as well as an avoidance of biocompatibility risks because of their autologous nature but were abandoned because of frequent pain, occurrence of calcification and hematuria.[9] With the introduction of Deflux, endoscopic correction of VUR became very popular. Today it is the first-line treatment for VUR in most centers.[16] Deflux is a viscous gel consisting of dextranomer microspheres and stabilized nonanimal hyaluronic acid. Dextranomer microspheres are formed by cross-linking dextran polymers into porous beads 80-250 µm in diameter.[6-9,17,18] Deflux is nonimmunogenic, noncarcinogenic and biodegradable. It has a bigger size and therefore particle migration is less likely, compared to the other bulking agents.[6-9,18] Deflux is the only tissue-augmenting substance approved by the U.S. Food and Drug Administration. Since some authors have pointed to biodegradability of Deflux, polyacrylate polyalcohol bulking copolymer (Vantris), a non-biodegradable tissue-augmenting substance, has been developed. Published studies showed excellent results in treatment of all degrees VUR in children.[20] Recently a new product, Vurdex, appeared on the market for endoscopic treatment of VUR. Vurdex is also dextranomer/hyaluronic acid copolymer and has a biochemical composition similar to Deflux, but it contains positive charged particles, which stimulate collagen ingrowths into implantation place and regeneration of the tissue. It may be clinically significant because the positive charge plays a role in the implant through intercellular interactions leading to fibroblasts and collagen fibers surrounding the implant as well that microparticles size used ensures no migration. The most important advantage of Vurdex is significantly lower price than Deflux. In Croatia the price of single injection (1 mL) of Deflux is € 708.08 and the price of single injection of Vurdex is € 481.77. Overall success rate after Deflux injections was confirmed in numerous studies and is about 80%-96%.[6,8,9,16-19] Success rates of endoscopic therapy are comparable to open surgery with added benefits of being an outpatient procedure and minimal invasivity.[6,8,9] The most important predictors of success include preoperative reflux grade and the absence of functional/anatomic bladder abnormalities including voiding dysfunction, neuropathic bladder, duplicated systems, and ureterocele. Compared to open repair, endoscopic therapy is associated with decreased patient morbidity and possibly lower costs. Studies evaluating the cost-effectiveness of endoscopic treatment suggest that it may be superior to open ureteral reimplantation in some settings; however, it is unclear if this advantage remains in cases of high-grade, bilateral, and recurrent reflux. In our institution overall success of open surgery compared with endoscopic treatment was 97% and 94%, respectively.[8,9]

Until now there are no clinical studies confirming the success of Vurdex. Its actual efficiency in clinical application will be proven after a few years of monitoring. In the available literature we found only one study on a small sample of patients that compared the use of Deflux in relation to Vurdex. Bahtijarević et al in that study found similar overall success rate for

both bulking agents. In patients treated with Deflux overall success was 93.4% and in patients treated with Vurdex overall success was 90.5%. There was no statistical significance between the two groups. They also reported better results in treating lower grades of VUR with Vurdex than Deflux. The lack of this study was short follow up period.[20] The purpose of our study was to compare the clinical efficacy of Deflux and Vurdex in treatment of VUR. In our study, after first injection of Deflux success was 69.8%, after second injection 85.8% and after third injection in 93.3%. After first injection of Vurdex success 74.1%, after second injection 89.6% and after third injection 94.8%. There was no significant difference in cure rates between the two groups. In our study higher rates of success in treating lower grades of VUR with Vurdex were observed, while Deflux showed higher rates of success for higher grades of VUR but no statistically significant differences was found. Limitations of our study were relatively small sample of the patients and shorter follow up for Vurdex group. Slightly better results in patients treated with Vurdex can be interpreted with shorter follow up.

Conclusion

Based on our study, we can conclude that Deflux and Vurdex are equally good and effective bulking agents in the treatment of VUR, but the cost-effective is in favor to Vurdex because of the significantly lower price. The difference in price in our country is € 226.31 per injection. However, long term follow up on larger series of patients is required to properly assess superiority of either bulking agent. □

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