Endoscopic treatment of vesicoureteral reflux in children with subureteral dextranomer/hyaluronic acid injection: a single-centre, 7-year experience

Mihovil Biočić, MD, PhD*
Jakov Todorić, MD*
Dražen Budimir, MD*
Andrea Cvitković Roić, MD, PhD†
Zenon Pogorelić, MD, PhD*
Ivo Jurić, MD, PhD*
Tomislav Šušnjar, MD*

From the *Department of Pediatric Surgery, University Hospital Split and Split University School of Medicine, Split, and the †Polyclinic Helena, Svetice 36, Zagreb, Croatia

Accepted for publication
Sept. 6, 2011

Correspondence to:
Z. Pogorelić
Department of Pediatric Surgery
University Hospital Split
Spinčićeva 1, 21 000 Split
Croatia
zenon@vip.hr

DOI: 10.1503/cjs.003411

Background: The goals of medical intervention in patients with vesicoureteral reflux are to allow normal renal growth, prevent infections and pyelonephritis, and prevent renal failure. We present our experience with endoscopic treatment of vesicoureteral reflux in children by subureteral dextranomer/hyaluronic acid copolymer injection.

Methods: Under cystoscopic guidance, dextranomer/hyaluronic acid copolymer underneath the intravesical portion of the ureter in a subureteral or submucosal location was injected in patients undergoing endoscopic correction of vesicoureteral reflux.

Results: A total of 282 patients (120 boys and 162 girls) underwent the procedure. There were 396 refluxed ureters altogether. The mean age of patients was 4.9 years. The mean overall follow-up period was 44 months. Among the 396 ureters treated, 76% were cured with a single injection. A second and third injection raised the cure rate to 93% and 94%, respectively. Twenty-two (6%) ureters failed all 3 injections, and were converted to open surgery.

Conclusion: Endoscopic treatment of vesicoureteral reflux can be recommended as a first-line therapy for most cases of vesicoureteral reflux, because of the short hospital stay, absence of complications and the high success rate.

Contexte : Chez des patients qui présentent un reflux vésico-urétéral, les objectifs de l'intervention médicale sont de permettre une croissance rénale normale, de prévenir les infections, la pyélonéphrite et l'insuffisance rénale. Nous présentons notre expérience du traitement endoscopique du reflux vésico-urétéral par injection infra-urétérale du copolymère dextranomère-acide hyaluronique chez des enfants.

Méthodes : Sous cystoscopie, le copolymère dextranomère-acide hyaluronique a été injecté sous la portion intravésicale de l'uretère dans la région infra-urétérale ou sous-muqueuse chez des patients qui devaient subir une correction endoscopique pour reflux vésico-urétéral.

Résultats : En tout, 282 patients (120 garçons et 162 filles) ont subi l'intervention, pour un total de 396 uretères touchés par le reflux. L'âge moyen des patients était de 4,9 ans. Le suivi global moyen a été de 44 mois. Parmi les 396 uretères traités, 76 % ont été corrigés au moyen d'une simple injection. Une seconde, puis une troisième injection ont porté le taux de guérison à 93 % et à 94 %, respectivement. Vingt-deux uretères (6 %) n'ont pas répondu aux 3 injections et pour ces cas, on a utilisé la chirurgie ouverte.

Conclusion : Le traitement endoscopique du reflux vésico-urétéral peut être recommandé en traitement de première intention dans la plupart des cas de reflux vésico-urétéral en raison de la brièveté du séjour hospitalier, de l'absence de complications et du taux de réussite élevé.

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 (UTI) or acute pyelonephritis. The International Reflux Grading system classifies VUR into 5 grades depending on the degree of retrograde filling and dilatation of the renal collecting system.[1] Vesicoureteral reflux is estimated to occur in 1%–3% of children.[1] Younger children are more prone to VUR because of the relative shortness of the submucosal ureters. In children with UTIs, the incidence of VUR is 29% in boys and 14% in girls.[2] Although

VUR is more common in boys antenatally, in later life there is a definite female preponderance with 85% of patients being female.[1,2] Traditionally, if medical management with low-dose antibiotic prophylaxis failed, the only alternative was open surgery.[3] In recent years, endoscopic subureteral transurethral injection (STING) has become a first-line therapy for children with VUR because of its high success rates and a very low incidence of complications.[1,3–5] Since Matouschek's initial description of the subureteral injection technique in 1981[6] and the first clinical series reported by O'Donnell and Puri in 1984,[7] it has evolved into a therapeutic alternative to open surgery. Injectable agents, such as Teflon, bovine collagen and Macroplastique, have all been used; however, concerns about efficacy and safety have limited their use.[1,3,8] Since the approval of dextranomer/hyaluronic acid copolymer (Deflux), endoscopic management of VUR has become an established alternative treatment in children.[1,9] Both dextranomer and hyaluronic acid are biocompatible, which means that they do not cause clinically important reactions within the body. In fact, hyaluronic acid is produced and found naturally within the body.[1,9] We present our results of endoscopic treatment using the subureteral Deflux injection (SDIN) for VUR in children at our institution.

Methods

Patients

We reviewed the case records of children who underwent endoscopic correction of VUR with dextranomer/hyaluronic acid copolymer injection at the Department of Pediatric Surgery, University Hospital Split from November 2002 through November 2009. All patients enrolled in the study had VUR, as determined by either voiding cystourethrogram (VCUG), dynamic radionuclide cystogram (DRNC) or ultrasound cystography. Indications for intervention were standard and included the following: breakthrough UTI, progressive renal scarring, noncompliance with medical therapy, nonresolution of VUR and parental preference. Lower grade reflux (grade 1) was treated only if the radionuclide scans showed renal scarring or if patients had recurrent UTIs while on antibiotic prophylaxis. Patients with associated urinary anomalies, such as double canal system, small kidney syndrome and neurogenic bladder, were also included in this study.

Materials

Hyaluronic acid and dextran copolymer (Deflux; Q-Med AB) was used. 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 was 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. In most patients, only 1 puncture at 6 o'clock was needed. Only in a few patients, when an adequate subureteral mound was not attained, was another puncture performed at a different location, depending on local findings. In cases of duplication and complete separation of the ureters, injection was done under the refluxing ureter, and a second injection was usually given laterally under the distal ureter to ensure that the both ureters were elevated. This technique was first described by O'Donnell and Puri.[7] In 2005, we began using the Kirch modification.[10] The mean amount of each substance injected into the ureter was 0.9 (range 0.5–1.4) mL, and the amount was determined according to reflux grade or shape of the ureteral orifice. The average duration of the procedure was 12.5 (range 7–23) minutes. The mean overall follow-up period was 44 (range 12–84) months. All procedures were performed by 2 experienced surgeons (M.B. and D.B.).

Follow-up

All patients in this study underwent endoscopic correction as a day procedure. 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. Follow-up VCUG was performed in children with recurrent UTIs. Successful reflux correction was defined as absent or converted high grade to grade 1 reflux on follow-up. Patients were maintained on their antibiotic prophylaxis until reflux was documented to be absent. Patients for whom the initial injection failed were offered continued observation and/or a second injection, and those for whom a second injection failed received a third injection. Surgery was performed only in case of unsuccessful reflux correction after 3 injections. We considered VUR to be recurrent if after 3 months of initial successful SDIN the condition returned 12 months or earlier.

Results

During the study period, 282 children, 162 girls (57%) and 120 boys (43%) with a mean age of 4.9 (range 5 mo to 15 yr) years underwent subureteral injection with dextranomer/hyaluronic acid copolymer because of VUR. Of these, 102 patients (36%) had bilateral and 180 (64%) had unilateral VUR. Of 396 treated ureters, 180 (45%) were right-sided and 216 (55%) were left-sided. According to the International Reflux Grading system, reflux was grade 1 in 34 (9%) ureters, grade 2 in 131 (33%), grade 3 in 150 (38%), grade 4 in 51 (13%) and grade 5 in 30 (7%; Table 1).

The results of treatment in children with simplex reflux

ureters are shown in Table 2. Among the 349 ureters, 271 (78%) were cured with a single Deflux injection. A second and third injection raised the cure rate to 324 (93%) and 328 (94%), respectively. In this group, 21 (6%) ureters failed all 3 Deflux injections and were converted to open surgery.

Results of treatment of VUR with neurogenic bladder are shown in Table 2. Among the 4 ureters, 2 (50%) were cured with a single Deflux injection. A second injection raised the cure rate to 100%.

Results of treatment of VUR in children with a double canal system are shown in Table 2. Among the 22 ureters, 16 (73%) were cured with a single Deflux injection. A second and third injection raised the cure rate to 21 (95%) and 22 (100%), respectively.

Results of treatment of VUR in children with small kidney syndrome are shown in Table 2. Among the 14 ureters, 7 (50%) were cured with a single Deflux injection. A second injection raised the cure rate to 13 (93%), and the rate remained the same with a third injection. One (7%) ureter in this group failed all 3 Deflux injections and we converted to open ureteral reinplantation.

Results of treatment of recidivous VUR in children after open surgery are shown in Table 2. Among the 7 ureters, 4 (57%) were cured with a single Deflux injection. The rate increased to 100% with a second or third injection.

Treatment results for all children are shown in Table 3. Among the 396 ureters treated, 300 (76%) were cured with a single injection. A second and third injection raised the cure rate to 369 (93%) and 374 (94%), respectively. Twenty-two (6%) ureters failed all 3 injections and were converted to open ureteral reinplantation. The overall success rate was 94%.

Discussion

Since VUR is a common disorder seen in children, much effort has been placed on its treatment. The association between VUR, UTI and renal damage is well known. Reflux nephropathy is the cause of end-stage renal failure in 3%–25% of children and in 10%–15% of adults.[11] Previously, long-term administration of antibiotics as prophylaxis for UTI has been advocated as the preferred management option for VUR treatment in children.[12] However, prolonged use of antibiotics is also associated with bacterial resistance, and breakthrough UTI is not uncommon. Many studies have shown a low spontaneous resolution rate for high-grade reflux. Schwab and colleagues[13] determined the resolution rate of patients with VUR on observation therapy. They found that reflux grades 1–3 resolved at a rate of 13% yearly during the initial 5 years of follow-up and then at a rate of 3.5% yearly during subsequent follow-up. Reflux grades 4 and 5 resolved at a rate of 5% yearly. Bilateral reflux resolved more slowly than unilateral reflux, and it resolved more rapidly in boys than in girls. McLorie and colleagues[14] showed that 93% of patients with grade 4 and 83% of those with grade 3 VUR had persistent reflux after 2 years of observation therapy, and 70% with grade 4 and 50% with grade 3 VUR had persistent reflux after 5 years of this therapy. Tamminen-Möbius and colleagues[15] also showed that 84% of children with grades 3 and 4 VUR still had reflux after 5 years of observation therapy. The only alternative to management with low-dose antibiotic prophylaxis was open surgery. With the advance in surgical endoscopy, cystoscopic injection of bulking agents has gained popularity, and endoscopic correction of VUR has become an established alternative to long-term antibiotic prophylaxis and surgical intervention for the treatment of VUR.[5,9,12] Since the first experiment of endoscopic injection in a pig model in 1984, many substances have been studied with variable results. Polytetrafluoroethylene (Teflon, Polytef) is efficacious but is associated with possible particle migration and granuloma formation.[16,17] Polydimethysiloxan (Silicon, Macroplastique) also shares the same problem, with marked local inflammatory response and migration.[18] There is a real concern because of possible malignant alteration as a result of the influence of silicon on the tissue.[19] Cross-linked bovine collagen (Zyderm, Zypast, GAX-35, GAX-65) has been used as the main alternative to polytetrafluoroethylene. It causes minimal tissue reaction locally when injected, but long-term studies have shown that collagen is not an ideal tissue augmentation substance because of its tendency to disappear with time, resulting in recurrence of VUR. There is also a risk because of allergic reactions to the bovine protein and prion disease transmission.[11,20] Dextranomer/hyaluronic acid copolymer (Deflux) is biocompatible material that consists of microspheres of dextranomer mixed with a stabilized 1% nonanimal hyaluronic acid. Dextranomer microspheres are formed by cross-linking dextran polymers into porous beads 80–250 μm in diameter.[5,9,11,12] Deflux fulfills all of the criteria required for the ideal implantable material and has advantages over other tissue-augmenting substances. Deflux is nonimmunogenic, noncarcinogenic and biodegradable. When compared with other bulking agents, it has a bigger size, therefore migration is less likely a problem.[5,12] Deflux is the only tissue-augmenting substance that has been approved by the

Table 1. Reflux ureters of all treated groups

Vesicouretal reflux	Simplex reflux ureters	Neurogenic bladder	Double canal system	Small kidney syndrome	Recidive after surgery
Grade					
1	28	0	4	1	1
2	116	2	10	3	0
3	135	1	6	7	1
4	45	1	2	2	1
5	25	0	0	1	4
No. of ureters (n = 396)	349	4	22	14	7
No. of children (n = 282)	241	4	16	14	7

U.S. Food and Drug Administration. We call the endoscopic procedure with Deflux SDIN because it really corresponds to injection of Deflux into a ureteral orifice; STING is not an adequate term, because the letters "T" (Teflon) and "G" (gun) in this procedure (with Deflux), do not mean anything.

Table 2. Results of treatment of vesicouretal reflux in all children

		1st injection				2nd injection				3rd injection			
			Success				Success				Success		
Defect; VUR grade	No. reflux ureters	SDIN	Yes (%)	No	Recur.	SDIN	Yes (%)	No	Recur.	SDIN	Yes (%)	No	Surgery
Simplex reflux ureters													
1	28	28	26 (93)	2	0	10	10 (100)	0	0	—	— —	—	—
2	116	116	108 (93)	5	3	27	18 (67)	9	0	10	1 (10)	9	9
3	135	135	99 (73)	36	0	25	18 (72)	7	0	5	2 (40)	3	3
4	45	45	26 (58)	19	0	7	4 (57)	3	0	6	0 (0)	6	6
5	25	25	12 (48)	13	0	9	3 (33)	6	0	4	1 (25)	3	3
Total	349	349	271 (78)	75	3	78	53 (68)	25	0	25	4 (16)	21	21
Neurogenic bladder													
1	0	0	— —	—	—	0	— —	—	—	—	— —	—	—
2	2	2	2 (100)	0	0	1	1 (100)	0	0	—	— —	—	—
3	1	1	0 (0)	1	0	1	1 (100)	0	0	—	— —	—	—
4	1	1	0 (0)	1	0	0	— —	—	—	—	— —	—	—
5	0	0	— —	—	—	0	— —	—	—	—	— —	—	—
Total	4	4	2 (50)	2	0	2	2 (100)	0	0	—	— —	—	—
Double canal system													
1	4	4	4 (100)	0	0	—	— —	—	—	—	— —	—	—
2	8	8	4 (50)	4	0	2	2 (100)	0	0	—	— —	—	—
3	6	6	6 (100)	0	0	2	2 (100)	0	0	1	1 (100)	0	0
4	4	4	2 (50)	2	0	2	1 (50)	1	0	—	— —	—	—
5	—	—	— —	—	—	—	— —	—	—	—	— —	—	—
Total	22	22	16 (73)	6	0	6	5 (83)	1	0	1	1 (100)	0	0
Small kidney syndrome													
1	1	1	1 (100)	0	0	1	1 (100)	0	0	—	— —	—	—
2	3	3	2 (67)	1	0	1	1 (100)	0	0	—	— —	—	—
3	7	7	4 (57)	3	0	3	2 (67)	1	0	1	0 (0)	1	1
4	2	2	0 (0)	2	0	2	2 (100)	0	0	—	— —	—	—
5	1	1	0 (0)	1	0	—	— —	—	—	—	— —	—	—
Total	14	14	7 (50)	7	0	7	6 (93)	1	0	1	0 (0)	1	1
VUR in children after open surgery													
1	1	1	1 (100)	0	0	0	— —	—	—	0	— —	—	—
2	0	0	— —	—	—	0	— —	—	—	0	— —	—	—
3	1	1	0 (0)	1	0	1	1 (100)	0	0	0	— —	—	—
4	1	1	1 (100)	0	0	0	— —	—	—	0	— —	—	—
5	4	4	2 (50)	2	0	2	2 (100)	0	0	0	— —	—	—
Total	7	7	4 (57)	3	0	3	3 (100)	0	0	0	— —	—	—

Recur. = recurrence; SDIN = subureteric Deflux injection; VUR = vesicouretal reflux.

Table 3. Overall results of treatment of vesicouretal reflux in all children

					Success, no. (%)	
Defect	Ureters	1st SDIN, no. (%)	2nd SDIN, no. (%)	3rd SDIN, no. (%)	Yes	No
Simplex reflux ureters	349	271/349 (78)	53/78 (68)	4/25 (16)	328/349 (94)	21/349 (6)
Neurogenic bladder	4	2/4 (50)	2/2 (100)	— —	4/4 (100)	0 (0)
Double canal system	22	16/22 (73)	5/6 (83)	1/1 (100)	22/22 (100)	0 (0)
Small kidney syndrome	14	7/14 (50)	6/7 (86)	0/1 (0)	13/14 (93)	1/14 (7)
VUR after open surgery	7	4/7 (57)	3/3 (100)	— —	7/7 (100)	0 (0)
Total	396	300/396 (76)	69/96 (72)	5/27 (18)	374/396 (94)	22/396 (6)

SDIN = subureteric Deflux injection; VUR = vesicouretal reflux.

Our series demonstrates an overall cure rate of 374 of 396 (94%) ureters, of which 300 (76%) were cured with a single injection. Our results are excellent compared with those obtained in other series (Table 4), especially if we take into account the noninvasive nature of the technique. Although in our series 96 (24%) ureters required more than 1 injection, only 27 (7%) needed 3 injections. Although a third injection had relatively limited success (only 18% in our study) for these children it means a lot, because they are spared from surgery. We believe that surgeons should always try a third injection despite additional cost. Twenty-two (6%) ureters failed all 3 injections and were converted to open surgery. The result from our series was comparable to most of the published data in the literature.[9,10,12,21–25] We attributed the slightly lower success rate after a single injection to the less advanced technique used in our centre during the early phase of our study. Nevertheless, most patients were able to be cured after 2 or 3 injections at most. Recently, in other centres, there has been an increase in the number of vials of Deflux being used per patient.[1] All of our patients were followed up with DRNC and ultrasound at various time intervals after injection to ensure an objective assessment of the outcome. Similar to other published reports, we did not notice any major complications associated with the use of Deflux in our series.[1,3,5,9–12,21–25] In 4 patients, local migration of material caudal to the ureteral orifice was observed. In these patients, the edge of the bolus touched the ureteral orifice, but it was incompetent. A similar result was reported by Kirch an colleagues[10,27] and Capozza and Caione.[28] Results of endoscopic treatment in grade 4 and 5 VUR are substantially weaker than in grades 1–3; As such, some authors are hesitant about the feasibility of endoscopic treatments for higher-grade VUR.[29] We do not agree with that attitude. In our series involving patients with primary VUR, there were 25 ureters with grade-5 VUR, and 88% of them were cured with 1, 2 or 3 injections. Menezes and Puri[30] reviewed 166 ureters with grade-5 VUR and reported success in 160 of them (96%). They concluded, and we agree, that endoscopic treatment should be the first-line treatment in the management of high-grade VUR. Capozza and colleagues[31] recommended endoscopic treatment of VUR after a failed ureteral reimplantation. They reported success in 78% of their patients. In our series, we reported success in all 7 patients treated endoscopically after a failed ureteral reimplantation. A double canal system usually does not make the injection more difficult, but it requires greater skill and training to ensure an adequate posterior support for both ureters. The best technique in these cases seems to be the injection of the 2 ureters as a "whole," with a single subureteral injection elevating the common ureteral sheath. Whenever this approach is not anatomically feasible owing to an ectopic location of one of the orifices, we usually inject the proximal orifice and then the distal ureter that comes from the superior unit. We noticed great success in groups of children with dubious indications, such as a double canal system, neurogenic bladder or small kidney syndrome. The cure rate in our patients with a double canal system was 100%, whereas for small kidney syndrome, success after 3 injections was 93%. Läckgreen and colleagues[32] reported a success rate of 63% in 68 children with a double canal system and a success rate of 70% in 40 children with small kidney syndrome. We had a success rate of 100% after a second injection in 4 children with VUR and a neurogenic bladder. Success in groups of children with a double canal system, neurogenic bladder or small kidney syndrome may be incidental, and owing to a small sample it is not possible to reach credible conclusions.

Table 4. Endoscopic treatment with Deflux for primary vesicouretal reflux in different series

Study	Year	No. ureters	Injected volume, mL	Follow-up, mo.	Success rate, %
Läckgren et al.[21]	2001	334	?	24–90	96
Kirsh et al.[10]	2003	139	0.8–2.0	3–18	93
Puri et al.[9]	2006	1101	0.2–1.5	3–46	96
Yu and Roth[22]	2006	162	1.0	2–26	93
Pinto et al.[23]	2006	86	?	3	84
Guerra et al.[24]	2007	64	0.3–1.8	2–23	80
Chung et al.[12]	2009	64	0.5–1.0	12–60	86
Chen et al.[25]	2010	239	0.1–2.3	3–68	88
Holmdahl et al.[26]	2010	66	0.2–2.0	24	86
Present series	2011	396	0.5–1.4	12–84	94

Until recently, there were no randomized controlled trials on this topic in the literature. Recently, a Swedish reflux trial in children by Holmdahl and colleagues[26] was the first major prospective, randomized controlled trial studying the use of endoscopic therapy in children. Patients with grade 3–5 reflux were randomly assigned to 1 of 3 treatment groups: low-dose antibiotic prophylaxis, endoscopic therapy and a surveillance group on antibiotic therapy only for febrile UTIs. The authors found that the endoscopic group had the greatest improvement in reflux status. After 2 years, endoscopic treatment results were significantly better than the spontaneous rate of resolution or downgrading in the prophylaxis and surveillance groups. They also noted that the rate of recurrent febrile UTIs was comparable to the prophylactic antibiotic group (23% with endoscopy and 19% with prophylactic antibiotics).

Most parents prefer the endoscopic treatment to the other treatment modalities.[4,33]

Chertin and Kocherov[34] reviewed the current literature regarding the outcome of endoscopic treatment of VUR using different tissue-augmenting substances, with special emphasis on long-term efficacy. They found that the short-term results in most series were similar to those reported for open surgery, but they also found a significant shortage of evidence-based literature on long-term follow-up after endoscopic correction of VUR using Deflux. Based on the high recurrence rate that has been reported after Deflux

injection, they highlighted a need for close observation beyond routine protocols, for appropriate parental counselling upon endoscopic correction and for further search for alternative tissue-augmenting substances.

Conclusion

Based on our retrospective review, endoscopic injection of Deflux 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 product for the endoscopic treatment of VUR. Parents should be offered this management option during discussion. However, they should be warned that a single injection is less likely to offer a cure in cases of grade-5 disease, although repeated injections can still result in high success rates.

Competing interests: None declared.

Contributors: M. Biočić, A. Cvitković Roić, Z. Pogorelić and I. Jurić designed the study. J. Todorić, D. Budimir and T. Šušnjar acquired the data, which M. Biočić and Z. Pogorelić analyzed. M. Biočić, J. Todorić, Z. Pogorelic and T. Šušnjar wrote the article, which M. Biočić, D. Budimir, A. Cvitković Roić, Z. Pogorelić and I. Jurić reviewed. All authors approved its publication.

References

1. Sorensen MD, Koyle MA, Cowan CA, et al. Injection volumes of dextranomer/hyaluronic acid are increasing in the endoscopic management of vesicoureteral reflux. *Pediatr Surg Int* 2010;26:509-13.
2. Puri P, Cascio S, Lakshmandass G, et al. Urinary tract infection and renal damage in sibling vesicoureteral reflux. *J Urol* 1998;160:1028-30.
3. Bae YD, Park MG, Oh MM, et al. Endoscopic subureteral injection for the treatment of vesicoureteral reflux in children: polydimethylsiloxane (Macroplastique) versus dextranomer/hyaluronic acid copolymer (Deflux). *Korean J Urol* 2010;51:128-31.
4. Capozza N, Lais A, Matarazzo E, et al. Treatment of vesico-ureteric reflux: a new algorithm based on parental preference. *BJU Int* 2003; 92:285-8.
5. Puri P, Chertin B, Velayudham M, et al. Treatment of vesicoureteral reflux by endoscopic injection of dextranomer/hyaluronic acid copolymer: preliminary results. *J Urol* 2003;170:1541-4.
6. Matouschek E. [Treatment of vesicorenal reflux by transurethral teflon-injection (author's transl)]. [Article in German] *Urologe A* 1981;20:263-4.
7. O'Donnell B, Puri P. Treatment of vesicoureteric reflux by endoscopic injection of Teflon. *Br Med J (Clin Res Ed)* 1984;289:7-9.
8. Cerwinka WH, Qian J, Easley KA, et al. Appearance of dextranomer/hyaluronic acid copolymer implants on computerized tomography after endoscopic treatment of vesicoureteral reflux in children. *J Urol* 2009;181:1324-8.
9. Puri P, Pirker M, Mohanan N, et al. Subureteral dextranomer/hyaluronic acid injection as first line treatment in the management of high grade vesicoureteral reflux. *J Urol* 2006;176:1856-9.
10. Kirsch AJ, Perez-Brayfield MR, Scherz HC. Minimally invasive treatment of vesicoureteral reflux with endoscopic injection of dextranomer/hyaluronic acid copolymer: the Children's Hospitals of Atlanta experience. *J Urol* 2003;170:211-5.
11. Puri P. Endoscopic correction of vesicoureteral reflux. *Curr Opin Urol* 2000;10:593-7.
12. Chung PH, Lan LC, Wong KK, et al. Deflux injection for the treatment of vesicoureteric reflux in children-a single centre's experience. *Asian J Surg* 2009;32:163-6.
13. Schwab CW Jr, Wu HY, Selman H, et al. Spontaneous resolution of vesicoureteral reflux: a 15-year perspective. *J Urol* 2002;168:2594-9.
14. McLorie GA, McKenna PH, Jumper BM, et al. High grade vesicoureteric reflux: analysis of observational therapy. *J Urol* 1990;144: 537-40.
15. Tamminen-Möbius T, Brunier E, Ebel KD, et al. Cessation of vesicoureteral reflux for 5 years in infants and children allocated to medical treatment. The International Reflux Study in Children. *J Urol* 1992;148:1662-6.
16. Reunanen MS, Toikkanenen S, Viljanto J. Long-term follow-up of tissue reactions caused by Teflon paste and cross-linked collagen in rats. *Pediatr Surg Int* 1991;6:241-4.
17. Miyakita H, Puri P. Particles found in lung and brain following subureteral injection of polytetrafluouroethylene paste are not Teflon particles. *J Urol* 1994;152:636-40.
18. Henly DR, Barrett DM, Weiland TL, et al. Particulate silicone for use in periurethral injections: local tissue effects and search for migration. *J Urol* 1995;153:2039-43.
19. Hatanaka S, Oneda S, Okazi K, et al. Induction of malignant fibrous histiocytoma in female. Fisher rats by implantation of cyanoacrylate, zirconia, polyvinylchloride or silicone. *In Vivo* 1993;7:111-5.
20. Haferkamp A, Mohring K, Staehler G, et al. Longterm efficacy of subureteral collagen injection for endoscopic treatment of vesicoureteral reflux in neurogenic bladder cases. *J Urol* 2000;163:274-7.
21. Läckgren G, Wåhlin N, Sköldenberg E, et al. Long-term followup of children treated with dextranomer/hyaluronic acid copolymer for vesicoureteral reflux. *J Urol* 2001;166:1887-92.
22. Yu RN, Roth DR. Treatment of vesicoureteral reflux using endoscopic injection of nonanimal stabilized hyaluronic acid/dextranomer gel: initial experience in pediatric patients by a single surgeon. *Pediatrics* 2006;118:698-703.
23. Pinto KJ, Pugach J, Saalfield J. Lack of usefulness of positioned instillation of contrast cystogram after injection of dextranomer/hyaluronic acid. *J Urol* 2006;176:2654-6.
24. Guerra LA, Khanna P, Levasseur M, et al. Endoscopic treatment of vesicoureteric reflux with Deflux: a Canadian experience. *Can Urol Assoc J* 2007;1:41-5.
25. Chen HC, Yeh CM, Chou CM. Endoscopic treatment of vesicoureteral reflux in children with dextranomer/hyaluronic acid — A single surgeon's 6-year experience. *Diagn Ther Endosc* 2010;2010. pii: 278012.
26. Holmdahl G, Brandström P, Läckgren G, et al. The Swedish reflux trial in children: II. Vesicoureteral reflux outcome. *J Urol* 2010;184:280-5.
27. Kirsch AJ, Perez-Brayfield M, Smith FA, et al. The Modified sting procedure to correct vesicoureteral reflux: improved results with submucosal implantation within the intramural ureter. *J Urol* 2004;171: 2413-6.
28. Capozza N, Caione P. [Role of the endoscopic treat ment of vesicoureteal reflux. A 16-years' experience]. [Article in Italian] *Minerva Pediatr* 2003;55:607-14.
29. Capozza N, Patricolo M, Lais A, et al. Endoscopic treatment of vesicoureteral reflux: twelve years' experience. *Urol Int* 2001;67:228-31.
30. Menezes MN, Puri P. The role of endoscopic treatment in the management of grade V primary vesicoureteral reflux. *Eur Urol* 2007;52:1505-9.
31. Capozza N, Nappo S, Caione P. Endoscopic treatment of vesicoureteral reflux in the previously reimplanted ureter: technical aspects and results. *Arch Esp Urol* 2008;61:249-53.
32. Läckgren G, Wahlin N, Skoldenberg E, et al. Endoscopic treatment of vesicoureteral reflux with dextranomer/hyaluronic acid copolymer is effective in either double ureters or a small kidney. *J Urol* 2003; 170:1551-5.
33. Ogan K, Pohl HG, Carlson D. Parental preferences in the management of vesicoureteral reflux. *J Urol* 2001;166:240-3.
34. Chertin B, Kocherov S. Long-term results of endoscopic treatment of vesicoureteric reflux with different tissue-augmenting substances. *J Pediatr Urol* 2010;6:251-6.