

# Endoscopic treatment of vesicoureteric reflux with Deflux: a Canadian experience

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## Abstract

**Introduction:** Vesicoureteric reflux is a common problem encountered in urological practice. Traditionally, if medical management with low-dose antibiotic prophylaxis failed, the only alternative was ureteroneocystostomy. Recently, promising results with subureteric injection of dextranomer/hyaluronic acid copolymer (Deflux) have renewed interest in the endoscopic treatment of vesicoureteric reflux (VUR).

**Objective:** We reviewed the outcome of the subtrigonal injection (STING) procedure with Deflux at a single pediatric hospital and included the rate of VUR resolution and complications.

**Methods:** An Institutional Review Board approved the retrospective review of all cases of STING performed with Deflux at the Children's Hospital of Eastern Ontario, from April 2003 to October 2005. We used voiding cystourethrogram (VCUG) or radionuclide cystogram (RNC) for diagnosis of VUR. The most common indications for surgery were breakthrough infection, progression of renal scars and parental preference. A subureteral or intra-ureteral injection, at the 6 o'clock position, delivered the material to support the ureter and correct VUR.

**Results:** We reviewed the cases of 64 patients, 47 girls (73%) and 17 boys (27%), with a mean age of 6 years (range 1–17 yr) and a mean follow-up of 8 months (range 2–23 mo). A total of 26 patients (41%) had bilateral VUR and 38 (59%) had unilateral VUR (90 renal units were treated). Overall cure rate was 79.7% (51/64) per child and 74% (67/90) per renal unit. Among the 64 patients treated, 62.5% (40/64) were cured with a single injection, and a second and third injection raised the cure rate to 78% (50/64) and 79.7% (51/64), respectively. Contralateral low-grade *de novo* VUR was present in 7.9% (3/38) of the 38 unilateral cases. Postoperatively, *de novo* hydronephrosis developed in 3.3% (3/90) of the ureters, in 2 patients.

**Conclusions:** The endoscopic treatment of VUR with Deflux is a feasible outpatient procedure, requires minimal operating room time and is associated with low morbidity. In our study, it demonstrated a cure rate of 80% of patients and 74% of renal units. Dysfunctional voiding and neurogenic bladder (NB) do not seem to adversely affect results. STING should be considered for failed open reimplants, because it is much less morbid than redo reimplants. Further experience with the material and increased use of intraureteral injection may improve our cure rates.

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The concept of subureteric injection therapy for the treatment of vesicoureteric reflux (VUR) is not a new one. Since Matouschek's initial description of the technique in 1981,<sup>1</sup> and the first clinical series reported by O'Donnell and Puri in 1984,<sup>2</sup> it has evolved into a viable therapeutic alternative to ureteroneocystostomy. The main issue going forward has been the efficacy and safety of the material chosen to perform the procedure. Materials such as Teflon, bovine collagen and Macroplastique have all been used, but concerns about efficacy and safety have tempered their use.<sup>3-6</sup> Since the introduction of Deflux into clinical use by Stenberg and Läckgren in 1995,<sup>7</sup> this material has predominated in the endoscopic treatment of VUR. Deflux comprises dextranomer microspheres suspended in hyaluronic acid and has been shown to engender minimal local tissue reaction and to not migrate in an animal model.<sup>8</sup> This material was approved for use in Canada in June 2003, although our centre initially started using it under compassionate release from Health Canada in April 2003. Here we present the most recent Canadian series of endoscopic treatment using the subtrigonal injection of Deflux for VUR.

## Materials and Methods

We retrospectively reviewed all cases of subtrigonal injection (STING) performed with Deflux at the Children's Hospital of Eastern Ontario, with Institutional Review Board approval. The start date for data acquisition was April 2003, when our first experience with the use of this material occurred. All patients who entered into the study had vesicoureteric reflux, as determined by either voiding cys-

touretrogram (VCUG) or radionuclide cystogram (RNC). Indications for intervention were standard and included the following: breakthrough urinary tract infection, progressive renal scarring, noncompliance with medical therapy, nonresolution of VUR and parental preference. Patients with more complicated urinary anomalies, such as ectopic ureter and ureteroceles, were excluded from this therapeutic option. Patients with dysfunctional elimination syndrome were treated conservatively with timed-voiding, double-voiding, high-fibre diet and stool softener. Those who had not improved with this management and who had indication for treatment of the VUR were offered endoscopic treatment.

All procedures were carried out as day surgery, with the patients under general anaesthetic. All patients received parenteral antibiotic prophylaxis before STING. The procedures were performed by varied members of the urology team, including residents (PGY3–5), fellows and attending staff. The technique comprises a subureteric or intra-ureteric transurethral injection of Deflux with a pediatric cystoscope. A 20-gauge needle is inserted 2 to 3 mm proximal to the ureteral orifice and delivers the material underneath the ureter at the 6 o'clock position for the subureteric technique. Alternatively, for the intra-ureteric technique, the needle is inserted in the floor of the intravesical ureter, which is visualized by directing the cystoscope water flow at the orifice to be treated. This latter technique was usually used for high-grade reflux with wide-open gaping orifices.<sup>9</sup> The injection proceeded until we obtained a "bulge" with an elevated, inverted crescent shape of the orifice. Patients were maintained on their antibiotic prophylaxis until reflux was documented to be absent on postoperative cystogram. Patients were observed with a renal ultrasound at 6 weeks postoperative and an RNC at 6–12 weeks after STING. Patients who failed initial injection were offered continued observation, a second injection or ureteroneocystostomy. Except for 1 patient who had Von

Willebrand's disease, no patients were offered more than 3 injections.

Primary outcome comprised reflux status (resolution v. nonresolution), and secondary outcomes included occurrence of such adverse events as hydronephrosis, *de novo* contralateral VUR, flank pain, increase of serum creatinine, gross hematuria or UTI post-STING. The outcomes were analyzed overall, and a subgroup analysis was carried out for patients with duplex collecting systems, dysfunctional voiding and neurogenic bladder (NB).

## Results

Sixty-four patients, 47 girls (73%) and 17 boys (27%) with a mean age of 6 years (range 1–17 yr) underwent STING with Deflux from April 2003 to October 2005. Twenty-six children (41%) had bilateral and 38 (59%) had unilateral VUR, for a total of 90 renal units treated with a mean follow-up of 8 months (range 2–23 mo). The RNC follow-up showed that the overall cure rate per child was 79.7% (51/64), and the cure rate per renal unit treated was 74.4% (67/90). Among the 64 patients treated, 62.5% (40/64) were cured with a single injection, while a second and third injection raised the cure rate to 78.1% (50/64) and 79.7% (51/64), respectively. The only patient who had 3 injections was an NB case with Von Willebrand's disease, and he was cured.

There were 62 children with primary VUR and 2 children (3 renal units) with VUR secondary to NB. Cure was achieved in all 3 units with secondary VUR. Renal scarring was documented in 30% (27/90) of renal units on ultrasound. Thirteen additional patients had suspicion of renal scarring on US and dimercapto-succinic acid renal scan (DMSA) renal scan documented scarring in 6 of this group; therefore, 33 of 90 renal units (36.6%) had scarring. The mean operating room time was 26 minutes, and the mean amount of Deflux injected per renal unit was 0.9 mL (range 0.3–1.8 mL). Four patients had a total of 6 complete duplex units, and the cure rate

was 66.6% (4/6). Dysfunctional voiding syndrome was diagnosed in 23 children (mean age 7 yr), and the cure rate was 91.3% (21/23), with only 2 patients needing 2 injections among those who were cured. Four patients with a total of 5 renal units were injected after failure of an open re-implant, curing 4 renal units (80%). We injected 2 renal units associated with a Hutch diverticulum, and 1 was cured (50%). Two patients had NB, with a total of 3 refluxing renal units; 1 child had unilateral reflux and was cured after 1 injection; the other child with bilateral reflux needed 3 injections for cure.

Contralateral low-grade *de novo* VUR was seen in 7.9% (3/38) of the patients treated for unilateral VUR. They were observed clinically; 1 resolved spontaneously on follow-up cystogram, and the other 2 remain symptom-free. Postoperatively, *de novo* hydronephrosis developed in 3.3% (3/90) of renal units in 2 patients. One of these patients presented to the emergency department with lumbar pain. Lasix Technetium-99 m mercaptoacetyltriglycine (MAG-3) renal scan showed no obstruction in either patient, and no further intervention was necessary. The hydronephrosis in 2 renal units resolved, and 1 had improvement of the dilatation on follow-up US. One patient with a solitary kidney presented with a transient increase of serum creatinine that resolved in 24 hours with no intervention. The patient with Von Willebrand's disease presented with clot retention the night of surgery. He had been pretreated with 1-deamino-8-D-arginine vasopressin (DDAVP) and required platelet transfusion to stop bleeding.

## Discussion

Our series demonstrates an overall patient cure rate of 80%, with resolution of reflux in 51 of 64 children treated. The cure rate per ureter was 74.4% (67/90). These results are acceptable when we compare the cure rate obtained by open surgery, especially if we take into account the non-invasive nature of the STING technique. Only

21.6% (11/51) of the patients among those who were cured needed more than a single injection. As in our standard practice, most children have RNC for follow-up of their VUR during observational management; there were no sufficient data on the grade of reflux before the surgery in this series. In addition, some girls had only RNC performed. There are several reports suggesting that RNC has a higher sensitivity to detect reflux, when compared with VCUG.<sup>10-13</sup> However, several published series of endoscopic treatment of reflux have based their cure rate on VCUG,<sup>9,14-16</sup> which can lead to a higher false-negative result. All patients in our series were observed postoperatively with RNC. This may result in a more sensitive documentation of cure and may account for the fact that our cure rate is lower than some recently reported series. There is an ongoing discussion about whether a postoperative cystogram is necessary after an open ureteral re-implant, since the cure rate is close to 98% in the hands of pediatric urologists. Endoscopic treatment of VUR shows inconsistent cure rates, with results varying among different centres and different materials injected. Thus, it seems there is still a role for postoperative cystogram.

Dysfunctional elimination syndrome is commonly associated with VUR. Homayoon and colleagues reported 342 children with VUR diagnosed before 6 months of age and found that 20% developed dysfunctional voiding after the age of toilet training.<sup>17</sup> In our series, 35.9% (23/64) of the children had a concomitant diagnosis of dysfunctional elimination syndrome, an association that may be related to the often-present constipation. All children with constipation were encouraged to increase fluid and fibre in their diet and to use timed-voiding and double-voiding techniques to decrease residual urine. The patients with dysfunctional voiding who did not resolve the VUR with this management were candidates for endoscopic injection. In this series, patients with dysfunctional elimination syndrome did well, with a 91% (21/23) cure rate. This cure rate was

higher than that for our overall cohort and may be explained by the concomitant use of bowel and bladder management, which might have benefited our toilet-trained cohort. In our experience, dysfunctional elimination syndrome is not a contraindication for the STING procedure.

Renal scarring can be related to congenitally dysplastic kidneys, or it can be secondary to recurrent febrile urinary infections. In a prospective study, Goldraich and Goldraich found a 44% rate of renal scarring on DMSA renal scan in 314 refluxing kidneys in 202 children investigated after a urinary infection.<sup>18</sup> Our results showed 36.7% (33/90) of renal units had scars. Admittedly, this could be an underestimate, since not all patients in our series had DMSA scans.

In this series, only 2 patients had secondary VUR; this small number does not afford a subgroup analysis. Neurogenic bladder can impose a challenging situation for endoscopic injection when marked bladder wall trabeculation is present. We treated 3 renal units in 2 patients with NB, and all were cured, but it is difficult to draw conclusions because of the small sample size. Granata and others<sup>19</sup> compared STING with Teflon in 40 ureters to 41 open re-implants in children with NB bladder and showed 72.5% and 95.5% cure rates, respectively. They concluded that, although the cure rate is lower, STING is the initial treatment for VUR in NB because of its technical simplicity, outpatient nature and rapid recovery.<sup>19</sup>

A duplex system usually does not make the injection more difficult, but it requires higher skill and training of the surgeon to ensure an adequate posterior support for both ureters. We treated 4 patients, with a total of 6 complete duplex renal units; the cure rate was 66.7% (4/6). Our results with the duplex system were similar to those reported by Lackgren and colleagues.<sup>16</sup> The best technique for these cases seems to be the injection of the 2 ureters as a “whole,” with a single subureteric 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.

Endoscopic injection is an attractive alternative for the management of a failed open re-implant. Four patients with 5 renal units were injected postfailure of an open re-implant in this series, with a cure of 4 units (80%). The STING provides a good cure rate of the VUR and obviates the need for a second open operation, with all risks posed by dissection of tissues with fibrosis and scarring from previous open repair.

The complication rate in this series was low. Contralateral low-grade *de novo* VUR was present in 7.9% (3/38) of the patients treated for unilateral VUR—an incidence rate comparable to a previous report.<sup>20,21</sup> *De novo* contralateral reflux had a good outcome when patients were observed clinically, and it appears that no further intervention is necessary if patients are symptom-free. The low-grade nature of such reflux might explain the high rate of improvement with observation. As shown in our results, postoperative hydronephrosis occurs but rarely requires intervention. The “bulking effect” created by the subureteral injection may create a partial and temporary dilation of the ureter, especially in previously dilated compliant systems. Eighteen percent of the Deflux volume is absorbed after a few weeks of the injection, and an additional 1% volume reduction occurs within 3 months,<sup>20</sup> possibly alleviating this temporary obstruction. However, it can take weeks to months to a complete resolution of the hydronephrosis. If there is clinical suspicion of significant symptomatic obstruction, it would not be prudent to wait for resolution; placement of a double J stent or percutaneous nephrostomy tube would be required. Although ureteral obstruction has been described as a nonfrequent and temporary complication,<sup>22</sup> a postoperative ultrasound is recommended to assure the kidneys are not compromised. Hematuria was absent or mild in most children and was limited to

the first day postinjection. Patients with known bleeding diatheses should receive perioperative management, comparable with that for open surgery.

The limitations of our study include that the data collected in the charts may be biased. Our series encompassed a learning curve with the new material, and a further analysis excluding the initial 50 cases should be conducted. There is no VCUg in all patients preoperatively, owing to our preference for RNC in girls, which makes it difficult to assess the cure rate per grade.

## Conclusion

The endoscopic treatment of VUR with Deflux is a feasible outpatient procedure, requires minimal operating room time and causes low morbidity. It demonstrated a cure rate of approximately 80% of patients and 74% of renal units. The use of dextranomer/hyaluronic acid copolymer produces an adequate support of the posterior ureter and promotes resolution of VUR. Dysfunctional voiding and neurogenic bladder does not seem to adversely affect results. One should consider STING for failed open reimplant, because it is much less morbid than redo reimplant. Further experience with the material and increased use of intraureteral injection may improve our cure rates.

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## References

1. Matouschek E. Die Behandlung des vesikorenalen Refluxes durch transurethrale Einspritzung von Teflon paste. *Urologe A* 1981;20:263.
2. O'Donnell B., Puri P. Treatment of vesicoureteric reflux by endoscopic injection of Teflon. *BMJ* 1984;289:7-9.
3. Malizia AA, Reiman HM, Myers RP, et al. Migration and granulomatous reaction after periurethral injection of polytef (Teflon). *JAMA* 1984; 251:3277-81.
4. Hafekamp A, Mohring K, Staehler G, et al. Long-term efficacy of sub-

5. Leonard MP, Decter A, Mix LW, et al. Endoscopic treatment of vesicoureteral reflux with collagen: preliminary report and cost analysis. *J Urol* 1996;155:1716-20.
6. Dodat H, Aubert D, Chavrier Y, et al. Vesicoureteric reflux in children: long-term results of endoscopic treatment by Macroplastique injection. *Prog Urol* 2004;14:380-4.
7. Stenberg A, Läckgren G. A new bioimplant for the endoscopic treatment of vesicoureteral reflux: experimental and short-term clinical results. *J Urol* 1995;154:800-3.
8. Stenberg AM, Sundin A, Larsson BS, et al. Lack of distant migration after injection of a 125iodine labeled dextranomer based implant into the rabbit bladder. *J Urol* 1997;158:1937-41.
9. Kirsch AJ, Perez-Brayfield M, Smith EA, 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.
10. Conway JJ, King LR, Belman AB, et al. Detection of vesicoureteral reflux with radionuclide cystography: a comparison study with roentgenographic cystography. *Am J Roentgenol Radium Ther Nucl Med* 1972;115: 720-7.
11. McLaren C.J., Simpson E.T. Direct comparison of radiology and nuclear medicine cystograms in young infants with vesico-ureteric reflux. *BJU Int* 2001;87:93-7.
12. Merrick MV, Notghi A, Chalmers N, et al. Long-term follow up to determine the prognostic value of imaging after urinary tract infections. Part 1: reflux. *Arch Dis Child* 1995;72:388-92.
13. Nasrallah PF, Nara S, Crawford J. Clinical applications of nuclear cystography. *J Urol* 1982;128:550-3.
14. Lavelle MT, Conlin MJ, Skoog SJ. Subureteral injection of Deflux for correction of reflux: analysis of factors predicting success. *Urology* 2005; 65:564-7.
15. Capozza N, Lais A, Nappo S, et al. The role of endoscopic treatment of vesicoureteral reflux: a 17-year experience. *J Urol* 2004;172:1626-9.
16. Lackgren G, Wahlén 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.
17. Homayoon K, Chen JJ, Cummings JM, et al. Voiding dysfunction: outcome in infants with congenital vesicoureteral reflux. [discussion 1094]. *Urology* 2005;66:1091-4.
18. Goldraich NP, Goldraich IH. Followup of conservatively treated children with high and low grade vesicoureteral reflux: a prospective study. *J Urol* 1992;148:1688-92.
19. Granata C, Buffa P, Di Rovasenda E, et al. Treatment of vesico-ureteric reflux in children with neuropathic bladder: a comparison of surgical and endoscopic correction. *J Pediatr Surg* 1999;34:1836-8.
20. Kirsch AJ, Perez-Brayfield MR, Scherz MC. 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.
21. Elmore JM, Kirsch AJ, Lyles RH, et al. New contralateral vesicoureteral reflux following dextranomer/hyaluronic acid implantation: incidence and identification of a high risk group. *J Urol* 2006;175:1097-101.
22. Vandersteen DR, Routh JC, Kirsch AJ, et al. Postoperative ureteral obstruction after subureteral injection of dextranomer/hyaluronic acid copolymer. *J Urol* 2006;176:1593-5.

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