Long-Term Effects of Dextranomer Endoscopic Injections for the Treatment of Urinary Incontinence: An Update of a Prospective Study of 61 Patients

H. B. Lottmann,* M. Margaryan, S. Lortat-Jacob, M. Bernuy and G. Läckgren†

From the Service de Chirurgie Viscérale Pédiatrique (Y. Révillon), Hôpital Necker Enfants-Malades (HBL, MM, SLJ), Paris and Fondation Ellen Poidatz (MB), Saint-Fargeau Ponthierry, France, and Section of Urology, University Children’s Hospital (GL), Uppsala, Sweden

Purpose: To treat sphincteric deficiency in children endoscopic bladder neck injections may avoid or salvage more complex procedures. A prospective study to assess the efficacy of bladder neck injections of dextranomer based implants (Deflux®) was done in a 7-year period in 61 patients.

Materials and Methods: From September 1997 to September 2004 we enrolled in the study 41 males and 20 females 5 to 18 years old with severe sphincteric incompetence, including exstrophy-epispadias in 26, neuropathic bladder in 27, bilateral ectopic ureters in 5, and miscellaneous in 3. Preoperative evaluation consisted of medical history, urine culture, urinary tract ultrasound and videourodynamic. This evaluation was repeated 6 months and 1 year after treatment, and yearly thereafter. Of the patients 17 underwent 2 and 4 underwent 3 treatment sessions to achieve a definitive result. At each evaluation the case was considered cured—a dryness interval of 4 hours between voids or CIC, significantly improved—minimal incontinence requiring no more than 1 pad daily and no further treatment required, and treatment failure—no significant, long lasting improvement. Videouro dynamics were mainly useful to study the evolution of bladder capacity, activity and compliance. Followup after the last injection was 6 to 84 months (mean 28).

Results: Mean injected volume per session was 3.9 cc (range 1.6 to 12). Postoperative complications were temporary dysuria in 2 patients nonfebrile urinary tract infection in 10, orchid-epididymitis in 1 and urinary retention with pyelonephritis in 1. The incidence of dryness or improvement during followup was 79% (48 of 61 patients) at 1 month, 56% (31 of 55) at 6 months, 52% (24 of 46) at 1 year, 51% (18 of 35) at 2 years, 52% (16 of 31) at 3 years, 48% (12 of 25) at 4 years, 43% (9 of 21) at 5 years, 36% (4 of 11) at 6 years and 40% (2 of 5) at 7 years. The success rate according to pathological condition was similar in cases of neuropathic bladder and the exstrophy-epispadias complex (48% and 53%, respectively). The success rate in re-treated cases was 38%. After treatment a contracted bladder developed in 6 patients. Also, of the 35 patients with at least 2 years of followup an increase in capacity of at least 50% was observed in 12 of 18 with an initially small bladder. No side effects related to the substance were observed.

Conclusions: Endoscopic treatment for pediatric severe sphincteric deficiency with dextranomer implant, a nontoxic, nonimmunogenic, nonmigratory synthetic substance, was effective up to 2 years in half of the patients. Subsequently at up to 7 years of followup a slow decrease in efficacy was observed and treatment remained beneficial in 40% of the patients.

Key Words: bladder, urinary incontinence, bladder exstrophy, dextran, epispadias

Treating major incontinence in children and adolescents remains a therapeutic challenge for the pediatric urologist. The 2 conditions for successful treatment are the achievement of sufficient outlet resistance and a compliant nonoveractive bladder with adequate capacity. Bladder outlet resistance can be increased by major surgical procedures, such as bladder neck plasty, slings, urethral lengthening or an artificial urinary sphincter. However, these procedures do not reliably achieve a satisfactory result in every patient.1–4 Also, in many instances the cost of dryness is the loss of the ability to void spontaneously and patients must perform CIC to empty the bladder. In extreme cases, particularly when previous procedures have failed, the bladder neck must be closed and a continent catheterizable reservoir created.5,6 In this context endoscopic injections of bulking agents appear to be an option before major surgical procedures or as an adjunct when these reconstructive techniques fail to achieve acceptable social continence. The results of efficacy, defined as cured (dry) or improved continence, remain variable with safety concern issues.

Dextranomer/hyaluronic acid copolymer (Deflux®) is nonmigratory, nonallergenic, nonmutagenic and nonimmunogenic. The synthetic substance is biodegradable as hyaluronic acid is degraded and it promotes ingrowth collagen and fibroblasts to maintain the implant in place. Long-term results of endoscopic treatment for vesicoureteral reflux in several hundred children were reported by Läckgren et al.7 In 2002 Caione and Capozza reported the use of dextranomer/hyaluronic acid copolymer for major incontinence in 16 children and young adults.8 They achieved acceptable short-
term success rate with improved incontinence in 50% of patients after 1 year of followup. We have similarly previously reported short-term efficacy with Deflux® when treating a group of 31 children with severe organic incontinence. Preliminary results showed that at 3 years 50% of patients were dry or significantly improved. These 31 patients were subsequently followed regularly until 7 years after the last treatment session. The study is still ongoing. We updated our results in the 61 patients who are now enrolled and undergoing regular followup.

MATERIALS AND METHODS

All 5 to 20-year-old patients treated at our institutions for severe incontinence were eligible for study inclusion. Exclusion criteria were vesicoureteral reflux, uncontrolled overactivity and poor bladder compliance. Informed consent was obtained from the patient or parents. Urine was sterile at the time of treatment. From September 1997 to September 2004, 41 males and 20 females 5 to 20 years old (mean age 10.3) were enrolled in the study. Of the patients 26 had exstrophy-epispadias, 27 had neuropathic bladder, 5 had bilateral ectopic ureters and 3 had a miscellaneous condition, including epispadias-type urethral duplication, traumatic urethral rupture and isolated bladder neck deficiency in 1 each. All except 4 patients wore diapers for major incontinence. The 4 patients who refused to wear diapers changed the underwear several time daily. CIC was done in 39 patients at the time of initial evaluation. Four patients with neuropathic bladder had undergone a previous bladder neck sling procedure to improve continence, whereas 16 with the exstrophy-epispadias complex had undergone previous Young-Dees bladder neck plasty with bladder augmentation in 3. Four of 5 patients with bilateral ectopic ureters had undergone various type of bladder neck plasty.

Of the 61 patients 1 to 3 injections were done in 40, 17 and 4, respectively, representing 86 treatment sessions. Repeat injection was proposed in patients who had some improvement after the first treatment session but not sufficient to be considered significant. Usually all treatments were performed in a 12-month period. When up to 3 treatment sessions failed to improve continence, other treatment options were considered. No re-treatment after later failure has been proposed to date to patients in this series.

Patients were placed under general anesthesia for endoscopic injection. Mean injected volume per session was 3.9 cc (range 1.6 to 12). Injections were placed in males at the bladder neck and below the verumontanum in the area of the external sphincter. In females injection placement was all along the urethra. Male patients who had undergone previous Young-Dees type bladder neck plasty were injected along the tube and below the verumontanum. All injections were performed transurethrally.

Except at the 5 first treatments a suprapubic catheter was systematically inserted and kept on continuous drainage for 5 days postoperatively to allow the puncture site to heal before the patient started to void or catheterize again. This was done to limit the risk of early postoperative urinary retention. Treatment was without complications in most patients, although 2 experienced temporary dysuria and 10 had a nonfebrile urinary tract infection, including 1 with encrusted cystitis that resolved after adequate treatment, 1 with orchiepididymitis, and 1 with urinary retention and pyelonephritis. Also, in 1 patient pneumonia developed postoperatively. None of the 22 patients who voided before treatment had to start CIC after treatment or had significant post-void residual urine. No adverse effects related to the dextranomer based implants were observed.

The result of treatment on continence and bladder capacity was evaluated at 1, 6 and 12, and each consecutive year using videourodynamics, renal ultrasound, urine culture and subjective feedback regarding continence from the patient and family. Videourodynamics were mainly useful for studying the evolution of bladder capacity, activity and compliance. Results were classified as cured—a dryness interval of 4 hours between voids or CIC, significantly improved—minimal incontinence requiring no more than 1 pad daily and no further treatment requested by the patient and treatment failure—no long lasting improvement observed due to persistent low outflow resistance. Results in term of continence are reported to the delayed followup after the last injection. They were subclassified according to the initial pathological condition, previous treatments and patient sex. Results are reported as trends only since the series was too heterogeneous and limited to allow statistical analysis.

RESULTS

In regard to continence, after 1 month 48 of 61 patients (79%) were dry or improved. At 6 months 31 of 55 patients (56%) were dry (33%) or improved (23%). At 1 year 24 of 46 patients (52%) were dry (28%) or improved (24%). At 2 years 18 of 35 patients (51%) were dry (25.5%) or improved (25.5%). At 3 years 16 of 31 patients (52%) had sustained dryness (26%) and/or improved continence (26%). In this group 31 patients had a longer followup of 36 to 84 months (mean 66). In this subgroup 3 years after receiving treatment were 16 of 31 patients (50%). At 4 years 12 of 25 patients (48%) were dry or improved. At 5 years 9 of 21 patients (43%), at 6 years 4 of 11 (36%) and at 7 years 2 of 5 (40%) were dry. Eight of the 21 patients (38%) who underwent 2 or 3 treatment sessions were dry (5 or 24%) or improved (3 or 14%). According to patient sex 54% of males (22 of 41) and 60% of females (12 of 20) were dry or improved. Also, 2 male patients who were improved became dry at puberty.

According to pathological condition the success rate was comparable in cases of neuropathic bladders (13 of 27 or 48%) and exstrophy-epispadias (14 of 26 or 53%) (figs. 2 and 3). Previous bladder neck reconstruction was associated with failures as well as with successful outcomes. Regarding CIC, all except 3 of the 27 patients with neuropathic bladder were on CIC at the time of treatment, of whom 1 achieved dryness and 2 experienced failure. In the subgroup of 17
patients with epispadias only 1 was on CIC and became dry after treatment. Only 2 of the 9 patients with bladder exstrophy were on CIC and they significantly improved after treatment. The 3 patients in the exstrophy-epispadias subgroup who were on CIC also underwent ileocystoplasty. All other patients voided, including 5 with ectopic ureter and 3 with miscellaneous conditions.

It is difficult to analyze the impact of CIC compared to spontaneous voiding on the result of treatment. In patients with incontinence of neuropathic origin no characteristics have been identified to date that could predict a greater chance of success with endoscopic treatment, considering that no patient with a noncompliant bladder or uncontrolled overactivity was included in the study. Although the number was too small to make any statistically significant conclusion, of patients in whom incontinence was related to the exstrophy-epispadias complex those with epispadias with or without previous bladder neck plasty achieved a higher success rate than those with classic bladder exstrophy (10 of 17 or 59% vs 4 of 9 or 44%) (fig. 3). In the other categories patient numbers were too small to draw any conclusion. As evaluated in the 31 patients with a followup of at least 3 years, bladder capacity increased in 12 of 18 initially small bladders and remained normal in 9, while 4 initially dry patients had recurrent leakage secondary to bladder deterioration. Another 2 patients with shorter followup also had bladder contraction.

All 6 patients with later bladder deterioration had incontinence of neuropathic origin. All were on CIC and anticholinergics. Compared to patients with incontinence of neuropathic origin no predictive factor of bladder deterioration could be identified from pretreatment data. Five of these 6 patients underwent augmentation, of whom 4 became dry again and 1 was significantly improved 3 months after surgery. In this boy continence is still progressing. The remaining patient is still incontinent with a spared upper urinary tract. Excluding these 6 cases of secondary bladder deterioration in this study no long-term side effects were observed that were related to the injection of bulking agent.

DISCUSSION
The use of bulking agents to manage major incontinence in children and adolescents is not a new concept. One of the first reports, that by Vorstman et al, was published more than 20 years ago.10 However, most bulking agents used in the early phase, such as polytetrafluoroethylene paste or bovine collagen, have been abandoned due to safety concerns and/or the lack of long-term sustained efficacy due to resorption of the injected material. Thus, only polymethylsiloxane (Macroplastique®) or dextranomer based implants (Deflux®) have recently been used for this indication in the pediatric population.

Regarding short-term results, Halachmi et al used Macroplastique® and noted 42% improved continence in 28 children in a 13-month study in 2004, although none achieved complete dryness.11 In 2003 in a 5-year followup study of Macroplastique® 3 of 15 children were reported to be cured.12 Caione et Capoza reported Deflux® results in a 1-year period in 16 children, of whom 75% daytime dryness and 50% achieved nighttime dryness.13 Results were measured in minutes of dryness. They observed a slight decrease in the percent in 2 years. Mathews et al used Deflux® in 20 children with the exstrophy-epispadias complex to increase outlet resistance to stimulate bladder growth in 18 and improve continence in 2.13 They noted no benefit for increasing bladder capacity but achieved a significant effect on continence in the 2 patients with persistent leakage after bladder neck plasty. They concluded that injection of a bulking agent may have a role in providing additional outlet resistance in children in whom bladder neck reconstruction is partially successful. Similarly Misseri et al reported on 6 males and 10 females who underwent Deflux® injections for incontinence.14 At a mean followup of 9.5 months 3 patients achieved dryness after injection, of whom all had a catheterizable channel and two-thirds had undergone bladder augmentation. Another 5 patients with an augmented bladder and a continent catheterizable channel had significant im-

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Dry</th>
<th>Improved</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epispadias Exstrophy</td>
<td>7</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Ectopic ureter</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

**Fig. 2. Results by etiology. BNR, bladder neck reconstruction**
proven to be less effective. As recommended by Duffy and Ransley, this makes it harder if bladder neck plasty is finally considered, thereby making it less likely if bladder neck plasty is considered, we agree with Guys et al that an expectations. We observed that after an initial high success rate, with up to 70% of patients dry or significantly improved during the first 6 months after treatment, there is a decrease in the positive effect down to 50% during the first 18 months. Therefore, the decrease in effect is much slower and it stabilizes at around 40% of patients, who are dry or significantly improved up to 7 years after the last treatment session. Interestingly, Guys et al reported the results of a similar prospective study in 46 children with major structural incontinence related to neuropathic bladder dysfunction that was treated with endoscopic polydimethylsiloxane injections. They observed achieved similar results, in that after the initial success rate of 68% acute deterioration in positive results occurred during the first 12 months. They attained a success rate of 47%, including continence in 33% of patients and significant improvement in 14% at a mean follow-up of 6 years with better results in girls with a stable bladder. No more than 3 injections were recommended if a satisfactory result was not achieved.

Regarding the initial pathological condition, although these conditions are totally different, we achieved similar results in the group of patients with neuropathic bladder and the group of patients with the exstrophy-epispadias complex. In the neuropathic bladder group only 4 of 27 patients underwent previous bladder neck surgery. Although we do not routinely determine leak point pressure, we agree with Chernoff et al that patients with the initial highest outlet resistances have the highest chance of success, provided that they have a low pressure bladder reservoir. Although our number of patients are still too limited to provide statistical analysis, in the exstrophy-epispadias group patients in whom incontinence was associated with penile posterior epispadias and good bladder capacity had a higher chance of success than patients with classic exstrophy and a small bladder.

We have not observed that previous bladder neck injections of bulking agents caused particular technical difficulties at subsequent procedures, such as a fascial sling or artificial urinary sphincter implantation. However, if bladder neck plasty is considered, we agree with Guys et al that an excessive number of re-injections can create scarred tissue, thereby making it harder if bladder neck plasty is finally needed. Moreover, re-injections after 2 injections are generally not effective. As recommended by Duffy and Ransley, in male patients with the exstrophy-epispadias complex and a nonexistent posterior urethra it is probably better to tubularize the bladder neck first and perform secondary bulking agent injection as necessary. In an initial report of our 33 first patients, including only 8 females, the success rate was higher in boys than in girls (65% vs 37.5%). By increasing the number of patients involved this trend was not confirmed and our current success rate was similar in males and females (54% and 60%, respectively).

Safety issues have been a concern. Macroplastique® has shown particle migration with Henly et al stating that migration is attributable to the particle size of the substance. They performed a study in dogs, in which particle migration of Macroplastique® was found in the lymph nodes, lung, kidneys and brain. Sternberg et al found no Deflux® migration in an experimental study in rabbits. To our knowledge no major adverse event has been reported with the use of bulking agents to date for managing major incontinence in the pediatric population.

Positive aspects in favor of bulking agents are lower costs, shorter hospitalization and less trauma in the patient than major continence surgical procedures. Another convenience is that endoscopic injections can be beneficial if the patient has already undergone failed surgical attempts.

CONCLUSIONS

Our updated data confirm that endoscopic treatment for severe organic urinary incontinence with dextranomer based implants (Deflux®, a nontoxic, nonimmunogenic, nonmigratory synthetic substance, was durable up to 7 years of follow-up in more than a third of the patients. These results in terms of efficacy, durability and safety match favorably with those achieved with other bulking agents. Even if the success rate is limited in the long term, due to its relative simplicity this treatment can be proposed to manage major incontinence in children as a primary procedure or as a salvage procedure when a bladder neck procedure was considered and failed. Information that is not over optimistic should be provided to the patient and parents regarding the expected success rate.

Abbreviations and Acronyms

CIC = clean intermittent catheterization

REFERENCES