Prospective Study of Polydimethylsiloxane vs Dextranomer/Hyaluronic Acid Injection for Treatment of Vesicoureteral Reflux

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Abbreviations and Acronyms

Dx/HA = dextranomer/hyaluronic acid copolymer
FDA = United States Food and Drug Administration
PDMS = polydimethylsiloxane
SUI = stress urinary incontinence
US = ultrasound
UTI = urinary tract infection
VCUG = voiding cystourethrogram
VUR = vesicoureteral reflux

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Purpose: Endoscopic injection of a bulking agent is becoming a first-line treatment for low grade vesicoureteral reflux. We prospectively compared the efficacy of 2 such products commercially available in Canada.

Materials and Methods: A total of 275 patients with documented grade I to V vesicoureteral reflux were prospectively enrolled in a comparative study between April 2005 and February 2011 to be randomly treated endoscopically with either polydimethylsiloxane (Macroplastique®) or dextranomer/hyaluronic acid copolymer (Deflux®). Of the ureters 202 were treated with polydimethylsiloxane and 197 with dextranomer/hyaluronic acid copolymer. Patients were followed with voiding cystourethrography at 3 months and renal ultrasonography at 3 months and at 1 year. Median followup was 4.3 years. The primary outcome was surgical success (resolution vs nonresolution), and secondary outcomes included occurrence of adverse events.

Results: Vesicoureteral reflux was fully corrected in 182 of 202 ureters (90%) treated with polydimethylsiloxane, compared to 159 of 197 (81%) treated with dextranomer/hyaluronic acid copolymer ($p < 0.05$). Obstruction was found in 5 ureters. Univariate and multivariate analyses did not allow identification of any characteristics that could explain the significant difference in the success rates except for the type of product used.

Conclusions: We present the largest known prospective evaluation comparing 2 bulking agents for the treatment of vesicoureteral reflux. Endoscopic injection of polydimethylsiloxane resulted in a better success rate than dextranomer/hyaluronic acid copolymer. The rate of resolution obtained with the latter is lower than those previously published due to the inclusion of high grade reflux.

Key Words: endoscopy, hyaluronic acid, injections, urinary tract infections, vesico-ureteral reflux

VESICOURETERAL reflux results from a short ureteral tunnel combined with the absence of adequate detrusor support behind the intravesical ureter. The primary goal of treatment is to avoid pyelonephritis and renal scarring, and to preserve renal function. Management strategies include active surveillance, antibiotic prophylaxis, endoscopic injection and ureteral reimplantation.

Endoscopic subureteral injection has gained popularity and has evolved as a prime therapeutic alternative to antibiotic prophylaxis and ureteroneocystostomy since its initial

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description by Matouschek in 1981,[1] and its first clinical use reported by O'Donnell and Puri in 1984.[2] However, the perfect bulking agent has yet to be found. The ideal substance should be biocompatible, nontoxic, nonmigratory and nonantigenic, as well as causing minimal inflammation and maintaining its shape and volume. Several injectables have been investigated for the treatment of VUR and SUI, each associated with different safety issues and success rates, including polytetrafluoroethylene, bovine collagen, autologous material (fat, chondrocytes, blood), polydimethylsiloxane (Macroplastique), dextranomer/hyaluronic acid copolymer (Deflux), polyacrylate/polyalcohol copolymer (Vantris®) and, more recently, polyacrylamide hydrogel (Bulkamid®).[2–10]

Polydimethylsiloxane is composed of soft, pliant, textured, solid polydimethylsiloxane elastomer (40%) resuspended in a bioexcretable polyvinylpyrrolidone carrier hydrogel (60%) with microparticles of a median minimal diameter of 140 μm. Polydimethylsiloxane was first commercialized in Europe in 1991 and received approval from Health Canada in 1998. In 2006 the FDA approved polydimethylsiloxane for the treatment of SUI. Dx/HA is a dextranomer hyaluronic acid copolymer in sodium hyaluronan solution. Stenberg and Läckgren introduced Dx/HA in 1995,[8] and in 2001 it received FDA approval for the endoscopic treatment of pediatric VUR. In 2003 the FDA and Health Canada approved clinical trials of nonanimal stabilized hyaluronic acid (Zuidex™) for the treatment of female SUI.

In our prospective study, which used a single injection of PDMS or Dx/HA by a single surgeon, we aimed to compare the effectiveness and complications of these 2 agents for endoscopic treatment of VUR. The primary objective was to compare the success rate of Dx/HA and PDMS, and the secondary end point was to enumerate adverse events.

PATIENTS AND METHODS

Patients

After institutional research ethics board approval, we offered all of our patients (adults and children) with symptomatic VUR entry into a prospective protocol between April 2005 and June 2011. A total of 275 patients with documented VUR were assigned to subureteral injection of polydimethylsiloxane or Dx/HA by simple randomization, with 1 material being injected in every other patient. Inclusion criteria were VUR based on recent (less than 3 months prior) VCUG, decision for surgical treatment, and participation in planned followup including VCUG at 3 months and US at 3 months and at 1 year. Exclusion criteria consisted of previous endoscopic treatment of VUR, active infection at injection, untreated elimination dysfunction defined by a 3-day diary and validated questionnaires (Dysfunctional Voiding Symptom Score,[11] Rome III[12]), and absence of followup imaging. Dimercapto-succinic acid scans were performed in clinically indicated cases, ie grade IV or V reflux, multiple pyelonephritis, delayed management of febrile UTI and abnormal US. After exclusion of 20 patients (25 ureters, 12 treated with PDMS and 13 with Dx/HA) without postoperative VCUG, 52 males and 203 females with documented VUR remained for analysis (see figure).

We systematically captured patient characteristics (age, gender, presentation, voiding pattern and medical/surgical history), preoperative imaging study findings (VUR grade, laterality, hydronephrosis, scarring and renal function), surgical notes (orifice appearance, material type, injection volume), events occurring during surgery, postoperative imaging results, any postoperative symptoms and duration of followup (table 1). Reflux was graded according to the International Classification of Vesicoureteral Reflux.[13]

Technique

One experienced surgeon performed each procedure using a pediatric cystoscope (8.5Fr) with the patient under general anesthesia. The hydrodistention implantation technique (double HIT) was preferred and performed on an outpatient basis.[14] A flexible 5Fr pediatric endoscopic needle was used with the PDMS administration gun, and a 3.5Fr polytetrafluoroethylene coated needle was used to inject Dx/HA. The median injected volume for the 2 groups (1.0 ml) did not differ significantly (PDMS 0.5 to 2.6 ml, Dx/HA 0.5 to 2.8 ml). Patients were followed with US and VCUG at 3 months, with VCUG repeated as needed depending on clinical evolution. All patients were followed at 1 year with US. Success was described as the absence of VUR on postoperative VCUG. All patients were followed yearly until February 2013, for a median of 4.3 years (range 2 to 7.8).

Statistics

The primary outcome was surgical success (resolution vs nonresolution), and secondary outcomes included the occurrence of adverse events and the evaluation of factors contributing to treatment failure. We planned to recruit for 200 ureters per injected material arm, expecting 5% to 10% loss to followup. Statistical analyses were conducted using SPSS®, version 15. Continuous variables were compared using the t-test. Categorical variables were compared by chi-square or Fisher exact test, and $p < 0.05$ was deemed statistically significant.

RESULTS

Median age at surgery was 50 months (range 6 to 780). VUR was bilateral for 72 patients (28%). Thus, a total of 399 refluxing units were injected and analyzed. Of the 255 patients 122 (202 ureters) underwent endoscopic treatment with polydimethylsiloxane and 133 (197) were injected with Dx/HA. VUR was graded as I in 35 ureters, II in 133, III in 160, IV in 62 and V in 9. All patients except 2 in the PDMS group (with pain during