Histology Proved Malpositioning of Dextranomer/Hyaluronic Acid in Submucosal Ureter in Patients After Failed Endoscopic Treatment of Vesicoureteral Reflux

David Ben-Meir,* Sara Morgenstern, Bezalel Sivan, Rachel Efrat and Pinhas M. Livne

From the Departments of Pediatric Urology (DB-M, BS, PML) and Pediatric Anesthesia (RE), Schneider Children's Medical Center of Israel and Department of Pathology, Rabin Medical Center (SM), Petach Tikva and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Abbreviations and Acronyms

DHA = dextranomer/hyaluronic acid

HIT = hydrodistention implantation technique

STING = subureteral injection

VUR = vesicoureteral reflux

Submitted for publication November 13, 2011.

Study protocol received institutional review board approval.

* Correspondence: Department of Pediatric Urology, Schneider Children's Medical Center of Israel, Petach Tikva 49 202, Israel (telephone: 972-3-925-3347; FAX: 972-3-925-3282; e-mail: davidbm@clalit.org.il).

See Editorial on page 16.

Purpose: We histologically investigated the cause of failed endoscopic treatment of vesicoureteral reflux with dextranomer/hyaluronic acid injections in children.

Materials and Methods: A total of 192 children underwent dextranomer/hyaluronic acid injection at our institution between January 2008 and September 2010. The study population consisted of 13 children (22 ureters) with vesicoureteral reflux who underwent ureteroneocystostomy following failed endoscopic injections (1 to 2) of dextranomer/hyaluronic acid. In all cases the dextranomer/hyaluronic acid was implanted in the mucosa of the mid to distal ureteral tunnel following hydrodistention of the ureter. The medical records were reviewed, and specimens of the archived distal ureters removed during surgery were examined histologically.

Results: Mean patient age was 4.1 years. Mean dose of dextranomer/hyaluronic acid was 0.9 ml (both treatments) and mean lag between treatments was 13.4 months. Indications for open surgery were recurrent urinary tract infections and/or residual or aggravated reflux grade IV or higher. Histological study revealed that the dextranomer/hyaluronic acid was malpositioned in 21 of 22 ureters, residing in the muscle fibers in 2, adventitia in 14 and periureteral space in 5.

Conclusions: This is the first known study to provide a histologically proved cause of failure of endoscopic treatment of vesicoureteral reflux with dextranomer/hyaluronic acid injections in children. Malpositioning of the material outside the submucosal ureter was identified in a high percentage of cases. Larger studies are needed to corroborate these findings.

Key Words: dextranomer-hyaluronic acid copolymer, ureter, vesico-ureteral reflux

DEXTRANOMER/HYALURONIC acid injection, approved by the Food and Drug Administration in 2001, is currently considered the first-line treatment for surgical correction of grades II to IV vesicoureteral reflux in children. Initially dextranomer/hyaluronic acid was injected into the submucosal space of the ureteral orifice at the 6 o'clock position.[1] In a 2004 modification Kirsch et al implanted dextranomer/hyaluronic acid in the mucosa of the mid to distal ureteral tunnel following hydrodistention of the ureter.[2] A recent multivariate model comparing these 2 methods revealed a better 3-month outcome for the latter procedure (cure rate 52% vs 48%), although the difference reached only trend level statistical significance.[3] Several reasons

0022-5347/12/1881-0258/0
THE JOURNAL OF UROLOGY®

Vol. 188, 258-261, July 2012
Printed in U.S.A.
DOI:10.1016/j.juro.2012.03.019

have been suggested for the high failure rate of endoscopic dextranomer/hyaluronic acid injection relative to open surgery, although none has been histologically proved.[4–6] We sought to elucidate the cause of failure of endoscopic dextranomer/hyaluronic acid injection by histological assessment of the distal ureters removed during ureteroneocystostomy.

METHODS

The study was conducted at a tertiary pediatric medical center, and the protocol was approved by the institutional review board. A total of 192 children underwent dextranomer/hyaluronic acid injection between January 2008 and September 2010. Overall success rate (defined as no reflux on voiding cystourethrogram at 6 months) was 75%. The sample included 13 children with VUR who underwent ureteroneocystostomy following failed endoscopic injection of 1 to 2 courses of DHA injection. Children with a double collecting system or dysfunctional voiding were excluded. All patients were treated by 1 of 2 experienced senior pediatric urologists who used an identical DHA injection technique (HIT). The bladder was emptied before the procedure. In all cases the surgeons reported a good response, defined as the appearance of a ureteral mound following the injection, and the procedure and postoperative period were unremarkable.

Background, disease related and treatment related data were collected by review of the medical files. The archived distal ureters removed during surgery were examined for tissue pathology and position of the DHA material.

RESULTS

The study group included 7 girls and 6 boys. Mean patient age was 4.7 years (range 2 to 11.1). A total of 22 ureters were examined. Data on VUR grading and laterality and amount of DHA injected are presented in the table. Mean DHA dose was 0.9 ml (range 0.5 to 1.5) in the first course of treatment and 0.9 ml (0.4 to 2) in the second. Mean lag time between treatments was 13.4 months (range 8 to 20). All patients underwent cystography 6 to 8 months after DHA treatment. Indications for ureteroneocystostomy were persistence/progression of reflux grade IV or higher and recurrent urinary infections. Injected ureters that did not exhibit reflux following endoscopic therapy were not removed.

Surgery consisted of intravesical cross-trigonal ureteral reimplantation. A wide resection to remove the dextranomer/hyaluronic acid mound intact was performed, and a naive ureter was reimplanted. The excised distal ureters were sent for histological assessment.

The formalin fixed, paraffin embedded specimens were stained with hematoxylin and eosin and reviewed by a senior pediatric pathologist. The DHA appeared as an amorphous, round, light yellowish, paste-like material surrounded by a giant cell, foreign body reaction. In 21 of the ureters examined the DHA was malpositioned, residing in the muscle fibers in 2, the adventitia in 14 and the periureteral space in 5 (see figure). In only 1 ureter was the DHA located in the correct submucosal plane. In all specimens there was a main bulk of material starting 1 to 2 cm from the distal end of the ureters, with no continuous smear of DHA that could imply a dislodgment process.

DISCUSSION

During endoscopic surgery for vesicoureteral reflux DHA is injected in the form of dextranomer microspheres suspended in a carrier gel of hyaluronic acid. The hyaluronic acid is absorbed within 1 to 2 weeks and the dextranomer microspheres are encapsulated by fibroblasts. The collagen ingrowth that follows this process accounts for the low (23%) total volume loss.[1]

Researchers have suggested different mechanisms to explain DHA injection failures, including misplacement of the implant, loss of graft volume by phagocy-

Patient characteristics

	Initial VUR Grade		DHA Course 1 (ml)		Post-DHA VUR Grade		DHA Course 2 (ml)		Interval Between Treatments (mos)	Post-DHA VUR Grade	
Pt No.—Gender	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt		Rt	Lt
1—F	4	3	1.0	0.5	3	1	1.4	0.6	17	3	2
2—M	4		1.0		4		1.0		9	4	0
3—M		4	1.0			4					
4—F	4		1.0		3						
5—F	2	3	Not evaluated		0	3	0.8	1.2	18	0	3
6—F	4	4	Not evaluated		4	4					
7—M	5		1.0		5		1.0		8	5	0
8—F	4	4	1.0	1.0	3	3	0.8	1.2	20	0	3
9—F	2	4	0.5	1.5	3	2	2	1.0		3	2
10—F	4		0.7		3			1.0		3	
11—M	5	5	1.0	1.0	4	3	1.6	0.4		5	3
12—M	5	3	1.0	1.0	3	3	0.8	1.2		4	2
13—M		4	1.0			3					