Efficacy of dextranomer hyaluronic acid and polyacrylamide hydrogel in endoscopic treatment of vesicoureteral reflux: A comparative study

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Abstract

Introduction: Various bulking agents are available for vesicoureteral reflux (VUR) endoscopic treatment, but their inconsistent success rates and costs are concerns for urologists. Recently, polyacrylamide hydrogel (PAHG) has been shown to have a good overall success rate, which seems comparable to dextranomer hyaluronic acid (Dx/HA), currently the most popular bulking agent. Our objective was to compare the short-term success rate of PAHG and Dx/HA for VUR endoscopic treatment in children.

Methods: We performed a prospective non-randomized study using PAHG and Dx/HA to treat VUR grades I to IV in pediatric patients. All patients underwent endoscopic sub-ureteric injection of PAHG or Dx/HA, using the double-HIT technique, followed by a 3-month postoperative renal ultrasound and voiding cystourethrogram. Treatment success was defined as the absence of de novo or worsening hydronephrosis and absence of VUR.

Results: A total of 90 pediatric patients underwent an endoscopic injection: 45 patients (78 ureters) with PAHG and 45 patients (71 ureters) with Dx/HA. The mean injected volume of PAHG and Dx/HA was 1.1 mL and 1.0 mL, respectively. The overall success rate 3 months after a single treatment was 73.1% for PAHG and 77.5% for Dx/HA. Postoperatively, 1 patient in each group presented with acute pyelonephritis and 2 patients in the Dx/HA group developed symptomatic ureteral obstruction.

Conclusion: Success rates of PAGH and Dx/HA in endoscopic injections for VUR treatment were comparable. The rate of resolution obtained with Dx/HA was equivalent to those previously published. The lower cost of PAHG makes it an interesting option.

Introduction

Vesicoureteral reflux (VUR) affects 1% to 3% of children.[1] VUR and urinary tract infections (UTI) can lead to renal scarring and subsequent loss of renal function.[2] Treatment options for VUR include close observation, long-term antimicrobial prophylaxis, ureteral reimplantation, and endoscopic injection. Despite the high success rate of ureteral reimplantation, the endoscopic technique is considered by many to be the gold standard, especially for low-grade VUR, because of its less invasive character and high success rate similar to the open surgical technique.[3] Multiple injection techniques have been tried, but the double-HIT as described by Kirsch and colleagues optimizes ureteral coaptation and facilitates performance, with no significant short-term complications.[4]

Over the last decades, dextranomer hyaluronic acid (Dx/HA, Deflux, Oceana Therapeutics Ltd, Dublin, Ireland) has become the most commonly used bulking agent worldwide. It is the most studied material, offering good success rates, with available long-term data of at least 3 years.[5,6] However, Dx/HA is not the perfect bulking agent; its success rate varies widely,[7] as it has a significant recurrence rate and shows 25% shrinkage in the following weeks following the injection.[8] Moreover, Dx/HA is expensive and the cost of endoscopic treatment has increased over the years mainly because of the increase in the amount of product needed to be injected.[9] A search for a better bulking agent is therefore pertinent.

Polyacrylamide hydrogel (PAHG, Bulkamid, Contura, Copenhagen, Denmark) has been used to treat stress urinary incontinence (SUI) and has been shown to be safe.[10,11] It has had the European conformity mark since 2003 for female SUI. Cloutier and colleagues recently studied PAHG in VUR and demonstrated a success rate comparable to Dx/HA, at lower cost and without significant complications.[12] Our primary objective was to compare the short-term efficacy of PAHG and Dx/HA in VUR treatment; our secondary objective was to document any adverse events.

Methods

We performed a single centre, single surgeon, prospective non-randomized study comparing PAHG and Dx/HA in the endoscopic treatment of VUR from March 2011 to December 2013. The research ethics board at our centre approved the study protocol. All patients had a preoperative voiding cystourethrogram (VCUG) and renal ultrasound. A dimercapto-succinic acid scan (DMSA) was obtained to document renal function and scars, if judged necessary. We included pediatric patients (under 18 years olg) with VUR grades I to IV confirmed at the most recent VCUG (less than 3 months), according to the International Classification System.[13] The follow-up included VCUG at 3 months and ultrasound at 3 months and 1 year. We excluded patients with previous endoscopic treatment of VUR, active infection at the time of injection, untreated dysfunctional elimination syndrome defined by 3-day diary and validated questionnaires (DVSS,[14] Rome III[15]), and absence of follow-up imaging studies. We also excluded patients with neurogenic bladder, VUR grade V, and history of bladder exstrophy, due to the complexity of these cases and their variability of success with endoscopic injection.

Injections were performed with the patient under general anesthesia, using a pediatric cystoscope. A 3.5-Fr polytetrafluoroethelene-coated needle was used to inject each product. The choice of the bulking agent was based on product availability at the time of surgery and alternative use of both agents for consecutive patients was encouraged. Sterile urine was a prerequisite to proceed with the injection. All injections were performed using the double-HIT technique.[16] The definition of success was the absence of de novo or worsening hydronephrosis and VUR grade 0 at VCUG 3 months after the injection. Possible adverse events after injection were investigated at the 3-month follow-up and compiled for each patient.

We planned to recruit 70 ureters per injected material arm, expecting 5% to 10% lost to follow-up. Statistical analyses were computed using SAS software (SAS v.9.3, SAS Institute, Cary, NC). A comparison between the two cohorts of the study was done with Fisher's exact test or Chi-square test for nominal data. Wilcoxon signed-rank test was used for continuous data. Significance was set at <0.05.

Results

A total of 90 pediatric patients underwent an endoscopic injection of either PAHG or Dx/HA and met all required criteria for analysis. In total, 45 patients were listed in each treatment group, for a total of 78 and 71 refluxing renal units (RRU) injected with PAHG and Dx/HA, respectively. The median age at surgery was 52 months for PAHG and 49 months for Dx/HA (p = 0.20). Baseline patient characteristics from each group were comparable (Table 1). The reasons for the VUR diagnosis are presented in Table 2. For most patients, the indication for surgery was breakthrough febrile UTI (Table 3).

The median follow-up was 1.8 years. The mean injected volume of bulking agent per ureter was 1.1 mL for PAHG and 1.0 for Dx/HA (p = 0.56). Overall, for the first endoscopic injection, the success rate per RRU for grades I to IV VUR was 73.1% with PAGH, compared to 77.5% with Dx/HA (Table 4) (p = 0.54). We could not identify a statistically significant difference for this primary objective between the two groups.

Few postoperative complications were reported. One patient suffered from a febrile UTI 3 weeks after endoscopic injection with PAGH and a persistent VUR was confirmed by VCUG. In the Dx/HA group, 1 patient also suffered from a pyelonephritis. Moreover, 2 patients suffered from symptomatic ureteral obstruction a few days after the surgery. One of these 2 patients needed a temporary ureteral stent to relieve the obstruction. De novo contralateral low-grade VUR was seen in 2 ureters in each group on postoperative imaging. No further procedure was necessary as the VUR usually self-resolve.

Failures were documented for 36 ureteral units (22 patients). In the PAHG group, a single endoscopic injection was unsuccessful for 21 ureters (14 patients). For secondary procedures, patients either underwent observation without antibiotic prophylaxis (9 RRU) mainly when circumcision was performed simultaneously at the initial procedure, re-injection (11 RRU), or ureteral reimplantation (1 ureter, VUR grade IV). Of these 11 re-injected ureters, 9 (82%) were successfully treated with the second injection and 2 had persistent failure on VCUG at 3 months.

In the Dx/HA group, the initial endoscopic injection was unsuccessful for 16 ureters (14 patients), 8 were observed and injection was repeated in 7 ureteral units and success at 3 months was seen in 5 ureters (71%). Ureteral reimplantation was performed for 1 ureter (VUR grade IV).

Table 1. Baseline characteristics of patients

Characteristics	PAHG	Dx/HA	*p* value
No. patients	45	45	—
Male:Female	11:34	7:38	0.29
Refluxing ureters	78	71	—
Bilateral reflux	28	27	—
Duplicated system*	14	9	0.23
Patients with corrected voiding dysfunction	21	28	0.14
Renal scars (DMSA scan)	19	23	0.40

*Some patients presented reflux in both moieties and were injected for both ureters. PAHG: polyacrylamide hydrogel; Dx/HA: dextranomer/hyaluronic acid copolymer.

Table 2. Reasons of VUR diagnosis

Reasons	PAHG	Dx/HA
Pyelonephritis	43	41
Prenatal hydronephrosis	2	4

PAHG: polyacrylamide hydrogel; Dx/HA: dextranomer/hyaluronic acid copolymer.

Table 3. Indications for endoscopic treatment of VUR

Indications	PAHG	Dx/HA
Febrile UTI	35	26
New scars	7	6
Reflux persistence	1	5
Parental desire	2	8

VUR: vesicoureteral reflux; PAHG: polyacrylamide hydrogel; Dx/HA: dextranomer/hyaluronic acid copolymer.

Discussion

Since its first description in 1984, endoscopic injection of VUR has been the subject of many studies with multiple bulking agents.[16] However, Dx/HA is the only bulking agent that has been FDA approved for treatment of pediatric vesicoureteral reflux. Dx/HA is a combination of equal parts dextranomer microspheres and sodium hyaluronate.[17] It is a biocompatible material without immunogenic properties, no potential to cause malignant transformation, and a lack of distant migration.[18,19] Its success rate varies widely in the literature notably because of different injection techniques used, variable definitions of success and variability in surgeon experience. The overall success rate ranges between 68% and 92%.[5] A systematic review showed a 77% success rate at 3 months and a negative influence of high VUR grade on outcomes.[7] Long-term studies are less prevalent. However, Lee and colleagues demonstrated a significant failure rate with success rates of 46% at 1 year and 73% at 6 to 12 weeks.[8] Moreover, Kamdem and colleagues showed a 4-year incidence of recurrent febrile UTI of 18.9% after Dx/HA injection[20] and Yankovic and colleagues reported a 4-year incidence of calcification at the site of injection with Dx/HA.[21]

PAHG is a polymer gel consisting of 2.5% cross-linked polyacrylamide and 97.5% water. It is a biocompatible agent, micro-particle-free, non-resorbable and migration-resistant.[22] Its safety and efficacy in female SUI has been documented.[10,11] Its efficacy in the treatment of VUR has been recently studied for the first time, showing a 1-year success rate of 81.2%.[12] So far, there are no published studies comparing PAGH with Dx/HA for the subureteral endoscopic injection of VUR. The success rate obtained in the present study at 3 months with PAHG (73.1%) and Dx/HA (77.5%) were comparable to previous studies, with no significant statistical difference between the two products.

The surgeon found both agents easy to manipulate and inject. A slightly greater amount of PAHG (1.1 mL) was used per ureter compared to Dx/HA (1.0 mL). PAGH is actually more liquid than Dx/HA, and this property may increase the volume of agent needed to obtain a "mountain-range" appearance of the orifice as described by Molitierno and colleagues.[23] Both products are delivered in 1-mL syringe, and once a syringe is used, its content cannot be preserved until the next intervention. Because the cost of a 1-mL syringe of PAGH is significantly lower than Dx/HA in Canada (about 50%), it is interesting to compare the number of syringes used during a procedure, considering that the same syringe could be used during the same intervention on both ureters in cases of bilateral VUR. The number of syringes used per intervention for PAGH and Dx/HA were 1.73 and 1.65 syringes, respectively. This corresponds to an equivalent number of syringes by surgery, 2 for each product, whereas PAGH is almost half the price of Dx/HA.

Due to the lack of long-term studies with PAGH, the long-term preservation of the bulking agent remains unknown. In 2011, Toozs-Hobson and colleagues reported a statistically non-significant reduction of efficacy from 67% at 12 months to 64% at 24 months in the treatment for SUI with injection of PAGH.[11] Those conclusions were consistent with previous results from Ghoniem and colleagues.[24]

Few complications were noted with both bulking agents and they were similar in both groups. However, one patient needed a ureteral stent postoperatively in the Dx/HA cohort. Many case series have described ureteral obstruction after injection of Dx/HA. The rate of obstruction was variable between different studies.[25-27] There are many potential causes of obstruction, such as anatomical variants and surgeon technique, which should be considered beyond the bulking agent itself.

Follow-up of patients is still ongoing. During this study and in our daily practice, VCUG is not routinely performed 1 year following the procedure as we make efforts to apply the ALARA principle and to reduce urethral manipulations on our patients. We believe that VCUG should only be performed in cases of recurrent UTIs post-injection or recurrent symptoms. We would not consider re-injecting an asymptomatic patient despite a newly positive VCUG (documented as resolved VUR at 3 months) after a year of follow-up without prophylaxis.

We acknowledge that the actual study presents limitations. The lack of external randomization may lead to some

Table 4. Radiological success rate (VCUG) after endoscopic injection

VUR grade	PAHG		Dx/HA		*p* value
	No. RRU	Success (%)	No. RRU	Success (%)	
I	7	7 (100)	8	6 (75)	0.47
II	20	13 (65)	19	16 (84.2)	0.27
III	30	22 (73.3)	33	27 (81.8)	0.55
IV	21	15 (71.4)	11	6 (54.5)	0.44

VUR: vesicoureteral reflux; PAHG: polyacrylamide hydrogel; Dx/HA: dextranomer/hyaluronic acid copolymer; RRU: refluxing renal units.

bias. We also had a relatively small group of patients with a short-term cystographic follow-up of 3 months. Our study could not show significant statistically difference between the success rates of PAGH and Dx/HA. Because both bulking agents have similar cure rates, a larger sample size would have been needed to detect a statistically significant difference. However, the size of our cohort was comparable to previous studies that compared VUR treatment with bulking agents. Our results are consistent with those reported by the authors who did not see a significant difference in cure rates when comparing Dx/HA and Macroplastique.[28-30] Even if no statistical difference was shown between both products, the price difference is an important consideration in choosing a bulking agent.

Conclusion

We present the first prospective evaluation comparing PAHG and Dx/HA for the treatment of pediatric VUR. Despite differences in material properties, both bulking agents are safe for the treatment of patients with VUR with few complications. The rate of resolution obtained with Dx/HA was equivalent to those previously published (68%–92%). Endoscopic injection of Dx/HA resulted in a slightly better success rate (77.5%) when compared to PAHG (73.1%), but was not significantly different ($p = 0.54$). The number of syringes used per intervention was similar for both products and the unit cost of Dx/HA was nearly twice that of PAHG. The lower cost of PAHG makes it an interesting option and a multicentre prospective study should be considered.

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