Journal of Pediatric Surgery 52 (2017) 2066–2069

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Urology

Endoscopic injection for primary vesicoureteric reflux: Predictors of resolution and long term efficacy☆,☆☆

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ARTICLE INFO

Article history:
Received 2 August 2017
Accepted 28 August 2017

Key words:
Vesicoureteral reflux
Endoscopy
Dextranomer/hyaluronic acid copolymer
Urinary tract infections
Ureter

ABSTRACT

Aim: We investigated the efficacy of endoscopic-Deflux-injection in treating primary-vesicoureteric-reflux (VUR) and identified factors to predict resolution.
Materials and methods: Records of children treated with Deflux for primary-VUR from 1995 to 2016 were reviewed, and outcomes were investigated.
Results: Eighty-eight ureters (35 bilateral, 18 unilateral) in 53 children underwent 124 injections. Thirty-five (66%) patients had single injection (13 unilateral, 22 bilateral). Fifteen (28%), two (37%), and one (2%) patients had two, three, and four injections, respectively. Overall success rate by ureters was 57% after single injection. Complete resolution occurred in 65% of ureters with VUR below grade III, 63% of grade III, 40% of grade IV, and 70% of grade V VUR. Four patients had reimplantation. The median follow up duration was 60 months (range 20–216 months). Univariate analysis showed that lower VUR grade ($p = 0.03$) and absent renal scars ($p = 0.04$) were statistically significant predictors of resolution. In multivariate analysis, absent renal scars were statistically significant ($p = 0.01$).
Conclusion: We demonstrated efficacy of endoscopic-Deflux-injection as the first line treatment for primary-VUR. Absent renal scar and lower VUR grade were statistically significant predictors of resolution after single injection.
Type of study: Case–Control / Retrospective Comparative Study.
Level of evidence: Level III.

Endoscopic injection has been recognized as a first line treatment of vesicoureteric reflux (VUR) in pediatric patients since it was introduced by O'Donnell and Puri in 1984 [1]. This procedure was further popularized in 2001, when dextranomer/hyaluronic acid (Dx/HA) copolymer (Deflux [Q-Med, Uppsala, Sweden]) was approved by the United States Food and Drug Administration as an injectable bulking agent in pediatric VUR. Previous studies have demonstrated that endoscopic injection is an effective and less invasive alternative to ureteral reimplantation [2–9]. Meta-analysis and systemic review reported an overall success rate of 77%–85% [10–12]. The AUA Guideline in 2010 has included endoscopic treatment in the management options for VUR [12]. There was a strong parental preference for endoscopic treatment rather than antibiotic prophylaxis or open reimplantation in a survey [13]. Although ureteral reimplantation has a higher success rate of 98%, a ureteric obstruction rate of up to 9% was reported [12,14]. In addition, ureteral reimplantation is a more technically demanding procedure, especially in infants.

Various factors that predict outcome after endoscopic injection such as age [9], gender [9], preoperative VUR grade [11,15–18], renal scarring [18], surgeon experience [11,15], injected volume [16], mound appearance [16,19] and dysfunctional voiding [2] had been suggested. Few studies had reported the incidence of urinary tract infection post procedure [10]. Our unit has previously published our intermediate outcome of endoscopic injection of Deflux as first line treatment [6]. In this study, we investigate the efficacy and long term clinical outcome of endoscopic Deflux injection in treating primary vesicoureteric reflux (VUR) in pediatric patients. Univariate and multivariate statistical analyses were performed to identify factors that can predict resolution after single endoscopic injection.

1. Materials and methods

Medical records of 71 children endoscopically injected with Deflux in our unit from 1995 to 2016 were reviewed. Approval for the study by institutional ethics committee was obtained. VUR was diagnosed in

☆ No work resembling the enclosed article has been published or is being submitted for publication elsewhere. We certify that we have each made a substantial contribution so as to qualify for authorship and that we have approved the contents.
☆☆ Conflicts of interest and source of funding: No conflicts of interests or source of funding to be disclosed.

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http://dx.doi.org/10.1016/j.jpedsurg.2017.08.033
0022-3468/

all children by micturating cystourethrogram and graded according to the International Classification System [20]. All urinary tract infections were confirmed by quantitative urine culture results in addition to evidence of pyuria and/or bacteriuria according to clinical guidelines from The American Academy of Pediatrics [21]. Preoperative investigations included renal and bladder ultrasonography to look for structural anomalies, micturating cystourethrogram (MCUG) to assess laterality and grading of the VUR, and Technetium 99 m labeled dimercaptosuccinic acid (99mTc-DMSA) scintigraphy to evaluate differential function and the presence of renal scarring. Patients with duplex kidneys with ectopic ureters, bladder exstrophy, secondary vesicoureteric reflux such as neurogenic bladder and posterior urethral valve were excluded. The presence of lower urinary tract symptoms (frequency, urgency, incontinence, weak stream, hesitancy) and constipation was screened. Those identified with bowel bladder dysfunction were evaluated and managed accordingly.

Indications for injection included breakthrough febrile urinary tract infection (UTI), persistent reflux, renal scarring and/or parental preference for injection over reimplantation or antibiotic prophylaxis. All injection procedures were done under general anesthesia with the patient in cystolithotomy position. A single dose of intravenous antibiotics was given immediately before the operation according to bacterial sensitivity result. A pediatric rigid cystoscope was used for the transurethral injection. The injection technique used initially was the classic STING (subureteral injection technique for the implantation of Teflon) technique, as suggested by O'Donnell and Puri [1]. The needle was inserted subureterically (2 to 3 mm below the orifice) and the tip was advanced under the distal ureter. From 2005 onwards, we also adopted the HIT or double HIT technique (intraureteric injection in combination with ureteral hydrodistention), by placing the needle directly into the patulous orifice and advancing into the subureteral space [22]. A subureteral or intraureteral injection site was used according to ureteral orifice anatomy. Deflux was injected to create a volcano morphology, a cone-shaped mound with a coapted ureteral orifice at its apex [1]. Post injection, the orifice was irrigated to confirm satisfactory coaptation.

All the patients were followed up with micturating cystourethrogram at 3 months after the procedure. Antibiotics prophylaxis was continued until resolution of reflux was demonstrated in follow up imaging. Those with persistent reflux were offered treatment options of second injection or reimplantation or to continue antibiotics prophylaxis. Micturating cystourethrogram was again performed at 12 weeks after repeated injections. Antibiotic prophylaxis was discontinued if resolution of VUR is confirmed.

Outcome measures included resolution of VUR confirmed by micturating cystourethrogram, urinary tract infections, complications, renal function and requirement of reimplantation of ureters. Success was strictly defined as complete reflux resolution on postoperative micturating cystourethrogram. Continuous variables were compared using the t test. Categorical variables were compared by Chi-square or Fisher's exact test. Univariate and multivariate logistic regression analysis was performed to identify predictors of reflux resolution post injection. Statistical significance was considered $p < 0.05$. The SPSS 17.0 software program was used to perform statistical analysis.

2. Results

From 1995 to 2016, 71 patients were identified to have vesicoureteric reflux and underwent endoscopic Deflux injections. Patients with neurogenic bladder (5), posterior urethral valve (7), and duplex kidney with ureterocele (3), and those who defaulted immediately after the injections (3) were excluded. Our study group included a total of 88 ureters (35 bilateral, 18 unilateral) in 53 children (33 males, 20 females) with primary VUR. A total of 124 endoscopic Deflux injections had been performed. The median age at endoscopic Deflux injection was 17 months. Twenty seven (51%) had renal scar. Patient demographics were displayed in Table 1.

Thirty five (66%) patients had single endoscopic injection (13 unilateral, 22 bilateral). Fifteen (28%), two (37%) and one (2%) patients had two, three and four Deflux injections, respectively. Fifty five (44%) injections were performed using the classic STING technique; a combined HIT and STING technique was used in 69 (56%) injections to tailor the configuration of ureteric orifices. The mean Deflux volume injected was 0.78 ml ± 0.30 ml. Twenty one (63%) male patients had circumcision performed in the same operation.

The overall success rate by ureters was 57% after a single endoscopic injection. Complete resolution after a single injection occurred in 50% of ureters with VUR grade I, 77% of grade II, 63% of grade III, 40% of grade IV and 70% of grade V VUR, respectively (Fig. 1). No intraoperative or perioperative complication occurred. Success rate after second injections in 27 refluxing ureters was 52%. Half of the patients who had 3 injections refused postoperative MCUG. One patient had persistent unilateral grade III VUR, which resolved after fourth injection.

Three (6%) female patients developed urinary tract infections postoperatively. One had persistent bilateral grade IV VUR and underwent pneumovesical Cohen reimplantation at 72 months of age (9 months after initial injection). The second patient had a second injection 4 months later for unilateral grade IV VUR and complete resolution was achieved. The third patient had no residual VUR on MCUG; she was found to have constipation and was managed with laxative and toilet training. None of the patients had worsening of renal function.

Four patients (8%), one boy and three girls, had reimplantation of ureters. Three patients had grade 4 VUR after one injection and bilateral renal scarring; they underwent pneumovesical Cohen reimplantation of ureters. One patient had two injections and robotic extravesical reimplantation of ureters performed. All achieved resolution of VUR postoperatively. In one patient with primarily negative MCUG on that side, contralateral grade I VUR was detected in post injection MCUG; he was on expectant management as that was a multicystic dysplastic kidney. The median follow up duration was 60 months (range 20–216 months).

2.1. Predictors of resolution

Univariate statistical evaluation showed that lower VUR grade ($p = 0.03$) and absent renal scars ($p = 0.04$) were statistically significant predictors of resolution of VUR (Table 2). In multivariate analysis, only absent renal scars were demonstrated to be statistically significant ($p = 0.01$) (Table 3). The volume of Deflux injected, injection technique, surgical experience, laterality, sex, age of patients, number of UTI, breakthrough UTI, and bowel bladder dysfunction did not attain statistical significance in univariate evaluation.

Table 1
Patient demographics.

	Resolved VUR N = 27 (%)	Non resolved VUR N = 26 (%)	p value
Sex			
Male	17 (63%)	16 (62%)	0.835
Female	10 (37%)	10 (38%)	
Breakthrough urinary tract infection	10 (37%)	13 (50%)	0.185
Renal scarring	11 (41%)	16 (62%)	0.741
VUR laterality			
Unilateral	11 (41%)	7 (23%)	0.001
Bilateral	16 (59%)	19 (77%)	
VUR grade			
I	2 (4%)	2 (4%)	0.927
II	7 (16%)	6 (13%)	0.442
III	14 (33%)	10 (22%)	0.034
IV	15 (35%)	15 (33%)	0.763
V	5 (12%)	12 (27%)	0.001
Bowel bladder dysfunction	2 (7%)	3 (12%)	0.313
Median follow up duration (months)	69	47	0.651