



Effectiveness of dextranomer/hyaluronic acid copolymer injection in pediatric population with vesicoureteric reflux having associated congenital anomalies: our experience and detailed review

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Abstract

Background Successful resolution of vesicoureteric reflux (VUR) via endoscopic methods has been achieved in the last two decades. After investigating multiple agents, Deflux is being used at most of the centers. We have studied the safety and efficacy of Deflux in our patients having VUR with complex urogenital anomalies and reviewed the literature.

Methods We have retrospectively collected the data of 28 children with the diagnosis of VUR, treated endoscopically over a period of 3 years. The data were collected from the hospital records and analyzed. The data included demographics, associated anomalies, grades of reflux, number of ureters affected, treatment given, number of sittings required, initial findings of micturating cystourethrograms, follow-up cystogram findings, and details of the procedure done. The data were evaluated for overall success rates in children with associated anomalies.

Results Among the 28 patients, 22 children with 33 affected ureter units having associated anomalies (secondary VUR) were included in the study, with 18 boys and 4 girls. Six children having primary VUR and not associated with other congenital anomalies were excluded. The reflux was unilateral in 10 (45.45%) children and bilateral in 12 (54.54%) children. Reflux was Grade II in 11 (33.33%), Grade III in 9 (27.27%), Grade IV in 2 (6.06%), and Grade V in 11 (33.33%) of the 33 ureters. After the first injection of Deflux, complete resolution was observed in 28 (84.84%) ureters and 5 (15.15%) had partial resolution of the VUR at 3-month follow-up. At 1 year of the first injection, complete resolution was achieved in 32 (96.96%) ureters and 1 (3.03%) ureter still had persistent Grade IV reflux, for which he had undergone ureteric reimplantation.

Conclusions We have observed that by endoscopic method reflux resolution was achieved in 84.84% after 1st and 96% children after 2nd injection. So based on our experience, we recommend the Deflux procedure as the primary treatment modality for VUR even in patients with associated complex urological anomalies and bladder dysfunction.

Keywords Vesicoureteric reflux · Endoscopic · Deflux · Ureter

Introduction

Reflux of the urine back into the kidneys, popularly termed as vesicoureteric reflux (VUR), is the common urological condition affecting a larger group of pediatric population. It has been seen that approximately 10–40% of children who present with urinary tract infection (UTI) and 0.4–1.8%

asymptomatic children are diagnosed as having VUR [1]. It is imperative to treat these children as prolonged reflux leads to recurrent pyelonephritis and renal scarring [2].

Among the many treatment options described in literature, the conservative treatment by antibiotic prophylaxis aims to minimize long-term renal scarring and long-term consequences [2]. Being non-invasive and cost-effective, this modality of management has its own limitations in the form of long duration of treatment, patient compliance, difficult monitoring as it requires regular cystourethrograms, risk of developing antibiotic resistance, and lost to follow-up [3].

Open surgical management, although not without complications, sets a high standard with the success rates reaching up to 98%. Endoscopic management of VUR with multiple substances has been evaluated previously with variable

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success rates [4]. Ever since its introduction, endoscopic management has been able to make its presence as an alternative to antibiotic prophylaxis and open ureteric reimplantation [5]. Apart from vesicoscopic and laparoscopic ureteric reimplantation, injection of a biomaterial in the subureteral space to correct reflux by elongating the intramural length of ureter is an effective endoscopic technique for all grades of reflux [3].

Many tissue-augmenting biomaterials have been used endoscopically for subureteral injection such as cross-linked bovine collagen, polytetrafluoroethylene (PTFE), polydimethylsiloxane (microplastic), and dextranomer/hyaluronic acid copolymer (Market name—Deflux) microspheres [5]. Many researchers have evaluated the effectiveness of dextranomer microsphere injection in their studies with the success rates of 65% to 90% [4]. We have reviewed the literature and evaluated the effectiveness of dextranomer copolymer injection in higher grades of reflux (II–V) in pediatric population with associated congenital anomalies and primary reflux.

Materials and methods

This was a retrospective observational study conducted in the Department of Pediatric Surgery at Sawai Man Singh (SMS) Medical College and Hospital, Jaipur, and included 28 children with the diagnosis of VUR, treated endoscopically over a period of 3 years (January 2015–December 2018). We have retrospectively collected data from the hospital records, tabulated, and analyzed. The data included demographic profile of the patients, associated anomalies, grades of reflux, side and number of ureters affected, treatment given, number of settings required for complete resolution, initial findings of micturating cystourethrograms (MCU), follow-up cystogram findings, and details of the procedure performed.

Procedure

The procedure was performed in patients having VUR ranging from Grades II–V. Children with Grade II and III reflux were given Deflux only when there was either recurrent urinary tract infection or cortical scar on renal dynamic scan in spite of optimal antibiotic prophylaxis. The patients were admitted 1 day prior to the procedure. These ureteral injections were performed by a single surgeon (PM) using the STING technique under general anesthesia. Cystoscopy was performed to visualize the urethra and bladder anatomy. Under direct vision, a 3.5F × 23G (Tip) × 350 mm needle was inserted 2–3 mm below the ureteric orifice at 6 o' clock position using a 9.5-Fr cystoscope. The injection started slowly after advancing the needle 4–5 mm in the lamina propria of the submucosa

of the ureter. After that, the needle was withdrawn slowly to form the appearance of a “volcanic bulge” of the injected material. A slit-like ureteric opening just above the nipple-like appearance of the mound confirms the correct placement of the needle and injected material. The mean volume of the injected copolymer was 0.5 ± 0.16 ml.

Post-operative

Post-procedure antibiotic prophylaxis was continued for 3 months. Follow-up ultrasonography and cystourethrograms were performed after 3 months of the procedure (Fig. 1). If no reflux was observed on the MCU, urethrograms were repeated after 1 year of the procedure and if there is persistent reflux, then the second sitting of the injection Deflux was given after 6 months of the 1st injection. Follow-up scans were done after 1 year and yearly thereafter for 3 years to look for renal size, pelvic diameters, ureteric dilatations, and the site and size of the injected Deflux. Successful reflux treatment was considered as either no reflux or Grade I reflux on MCU and without hydroureteronephrosis on follow-up renal ultrasonography. Antibiotics were stopped after successful treatment.

Results

Among the 28 children, 22 children with 33 affected ureter units having associated anomalies (secondary VUR) were included in the study, with 18 boys and 4 girls (Table 1). Six children with primary VUR were excluded. The reflux was unilateral in 10 (45.45%) children and bilateral in 12 (54.54%) children. The reflux was graded according to International Reflux Classification and was Grade II in 11 (33.33%), Grade III in 9 (27.27%), Grade IV in 2 (6.06%), and Grade V in 11 (33.33%) of the 33 ureters. The associated anomalies were anorectal malformation in 9, congenital pouch colon in 5, extrophy bladder in 3, neural tube defects in 2, posterior urethral valve in 2, and medical renal disease in 1 patient.

In these 22 children, 32 ureter units were underwent Deflux injection and follow-up cystogram were done after 3 months, 6 months, and 12 months after the procedure. After the first injection of Deflux, complete resolution was observed in 28 (84.84%) ureters and 5 (15.15%) had partial resolution of the VUR at 3-month follow-up. At 6 months, among the 5 ureters having partial resolution, 2 ureters with Grade V reflux had no improvement at all, so a second injection of Deflux was given in these patients. At 3 months of the second injection, one ureter unit achieved complete resolution and one had persistent reflux. At 1 year of the first injection, complete resolution was achieved in 32 (96.96%) ureters and 1 (3.03%) ureter still had persistent Grade IV

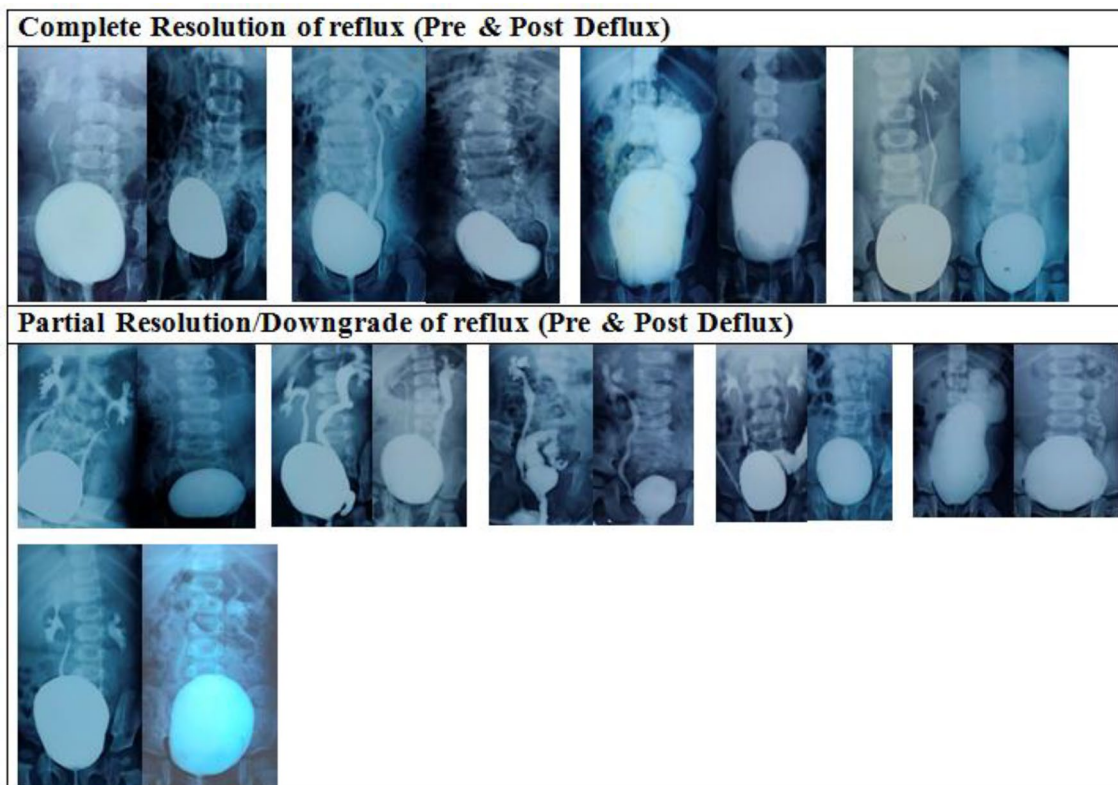


Fig. 1 Follow-Up MCU with complete and partial resolution of VUR after Deflux procedure

Table 1 Demographic details

Demographic details	N (%)
Total no of patients	22
Median age (years)	0.98
Gender ratio (M:F)	4.5:1
Unilateral	10 (45.45)
Bilateral	12 (54.54)
Total no of ureter units	32
Associated anomalies	[ARM 9, CPC 5, NTD 2, PUV 2, Extrophy 3, MRD 1] ^a
Grades of reflux	
II	11 (33.33)
III	9 (26.2)
IV	2 (11.9)
V	11 (33.33)

^aARM, anorectal malformation; CPC, congenital pouch colon; NTD, neural tube defects; PUV, posterior urethral valve; MRD, medical renal disease

reflux, for which the patient underwent ureteric reimplantation (Table 2).

Table 2 Results showing outcomes of Deflux injection in children with secondary VUR

Follow up	CR (%)	PR (%)	No of ureters
1st follow-up (3 month)	28(84.84)	5 (15.15)	33
Last follow-up	32 (96.96)	1 (3.03)	33

CR, complete resolution; PR, partial resolution

We have observed a significant (Grade III—100%, IV—100%, and V—50%) resolution of reflux in patients with primary reflux (Grade III—1, IV—1, and V—4) also but they were excluded as they were not the part of the study group.

Discussion

Reverse flow of urine from bladder to the ureters and kidneys is known as vesicoureteric reflux (VUR). It is graded according to the international grading system based on radiology as follows [6]:

- Grade I: Reflux of urine in ureter but not reaching up to the renal pelvis without any dilatation.

- Grade II: Reflux extending up to the renal pelvis without any ureteric dilatation.
- Grade III: Mild-to-moderate dilatation of ureter and renal pelvis with slight or no any blunting of fornices.
- Grade IV: Moderate dilatation of ureter, pelvis, and calyces with complete obliteration of sharp angle of fornices and maintained papillary impression in most calyces.
- Grade V: Grossly dilated and tortuous ureter along with pelvic and calyceal dilatation. Loss of papillary impression in most calyces is there.

Broadly, there are two types of reflux, primary—when it is due to congenital weakness of the vesicoureteric junction (VUJ) and secondary—when it is due to associated anomalies of the urogenital system or of neurogenic in origin [7].

These children present mainly with urinary tract infections (UTI). When children with VUR develop a UTI, it causes renal scarring which appears as a photopenic area on a nuclear scan. This condition of renal scarring with reflux is known as reflux nephropathy. The whole management guidelines are directed to prevent UTIs and reflux nephropathy. VUR can be easily diagnosed and graded by a voiding cystourethrogram (VCUG). Along with the reflux, a VCUG can also diagnose the causes of secondary reflux such as posterior urethral valve, ureterocele, and other bladder anomalies [8].

VUR resolves spontaneously in majority of children with lower grades of reflux, probably due to increased intramural length of the ureter as the child grows, while in Grade V, it is unlikely to resolve spontaneously. The rate of spontaneous resolution is more than 80% for Grades I and II, more than 50% for Grade III, and nearly 30% in Grade IV patients [9, 10]. These children are kept on long-term antibiotic prophylaxis till the complete resolution of VUR. For Grade III–IV VUR, surgery is required only in children who develop breakthrough UTIs, or renal scarring on nuclear scan. Many surgical options are available as per current literature and can be done via both open and endoscopic methods. Open surgeries are reserved for children having either failed endoscopic treatment or complex VUR. Endoscopic management has gained popularity as an established alternative to long-term antibiotic therapy and becoming the standard of care in the last two decades [8].

Endoscopic treatment involves cystoscopy-guided injection of a biomolecule in the subureteric region to decrease the ureteric diameter and prevent reflux. Initially, polytetrafluoroethylene (PTFE/Teflon) was used, but due to its migrating nature and embolic complications, it has been discontinued. Cross-linked bovine collagen has also been explored, but it gets disappeared with time. Polydimethylsiloxane is another molecule used for VUR

and incontinence, but it also has disadvantages of migration and recurrence of reflux. After the approval of Food and Drug Administration in 2001, Dextranomer/hyaluronic acid copolymer (Deflux) has been used and has shown excellent results [4]. Deflux is a biomolecule formed by a combination of dextranomer microspheres and hyaluronic acid which is biocompatible, gets stabilized at the place of injection by inducing mild inflammatory reaction around it, and is nonimmunogenic [8]. Its properties such as biodegradable, particle size larger than 80 micron, non-allergic, known to promote ingrowth of fibroblasts, and collagen formation make it an ideal implantable substance for tissue augmentation [5].

Since the introduction of endoscopic technique in 1981, the technique and the biomaterial have seen a lot of modifications and advancements. Clinically, the first biomolecule was Teflon and injected by STING (Subureteric Teflon Injection) technique. In 2004, this technique was further modified by doing a hydrodistention of ureter and injecting the biomaterial directly into the submucosa (intraureteral) of the ureter under vision, further augmenting the previous mound. This technique was recognized as HIT (Hydrodistention Implantation Technique) method which achieved more than 90% success rates after single injection [11]. The ureteral augmentation procedure is performed under general anesthesia and with cystoscopic guidance by a pediatric cystoscope having an offset lens. The bladder is kept half-filled to avoid tension in the submucosal layer and better visualization of the ureter. The biomaterial is injected via a specialized needle. Some authors have modified the needle length along with a few other features and named it like Puri's 4Fr disposable catheter [5]. The needle is passed in the ureteric orifice and at 6'o clock position the Deflux is injected sufficient enough to produce a cone/bulge which takes the shape of a "volcano." Sometimes, a second injection is needed to achieve good coaptation of ureter and this technique is known as double HIT method. If even after the double HIT the coaptation of ureter is not enough, then a classic STING is done or a supraureteric injection is required to achieve the desired results [11]. The volume of the injected biomolecule and the height of mound have been debated a lot in the literature. The average injected volume is 0.5–1 ml in various studies [3–5]. This is also correlating with our findings of 0.5 ml. Some of the authors have correlated the mound height and VUR resolution. Contrasting opinions are available in the literature for morphology and mound height as a predictor of success. In 2005, Lavelle et al. concluded that the volume of injected material and the successful outcome are not significantly correlated [3]. Hida'a et al. also reported that the mound morphology is not a reliable predictor of outcome [12]. However, in 2016, Zambaiti et al. measured the mound height ultrasonographically and concluded that at least 9.8 mm mound in post-operative scan

predicts reflux resolution [13]. The success rates range from 60% to more than 90% in different studies. Increasing VUR grade has a negative effect on the success rate of Deflux procedure. In a systemic review by Routh et al., the overall success rate of Deflux injection was found to be 77% per ureter [14]. Puri et al. reported successful resolution of reflux in 89% of children after first injection and more than 95% after 2nd and 3rd injections of Deflux [5]. Associated voiding dysfunction also decreases the success rate as it can displace the implant and results in recurrence of reflux [15]. We have achieved a success rate of 96.96% at 1 year of follow-up and 1 (3.03%) child with Grade IV reflux required open ureteric reimplantation. The reason for nonresolution of reflux with endoscopic method in this child could be the abnormal VUJ with Grade V reflux due to associated anomalies (congenital pouch colon). Reflux is invariably associated in a good number of patients with congenital pouch colon and similar observations have been published by the senior author (PM) in his previous reports also [16]. We have observed an overall success rate of more than 96% in our patients with secondary VUR having associated anomalies and four out of six patients with primary VUR. This is higher than 77.4% observed by Zambaiti et al. [13]. Kirsch and colleagues reported 89% success rates with the endoscopic techniques [17]. Perez-Brayfield et al. treated 93 ureters having VUR with various congenital anomalies (neurogenic bladder, diverticula, duplication, ureterocele, ectopic ureter, posterior urethral valve, epispadias, etc.) and failed open surgery with overall 69% success rates [18]. We have achieved a success rate of 84.84% after first injection and 96.96% after second injection in children with congenital anomalies. This is slightly higher than that of the previous reports. On reviewing the published literature and their sample size, we accept small sample size as the limitation of our study and will consider these data as preliminary results for a pilot study and will continue the study further in future to publish with a bigger sample size. Inclusion of only the children with secondary reflux and associated complex urogenital anomalies further restricted the sample size. We have found Deflux procedure as safe and highly efficacious in patients with complex VUR. Open surgical repair being the gold standard can be avoided in many children by giving a chance of Deflux procedure.

Conclusion

Endoscopic treatment of reflux has been used since the last two decades and gives impressive results. Even in patients with bladder dysfunction and complex VUR, this procedure is still beneficial and a cure can be achieved in a good number of patients. Based on our experience, we

recommend the Deflux procedure as the primary treatment modality even in patients with associated complex urological anomalies and bladder dysfunction.

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Data availability The data that support the findings of this study are available on request from the corresponding author, [Praveen Mathur]. The data are not publicly available due to institutional protocol and government restrictions.

Declarations

Conflict of interest None.

Financial disclosure None.

Ethical approval Ethical approval was waived in view of the retrospective nature of the study. All patients were managed and treated as per standard institutional protocol.

Informed consent Written and informed consent has been obtained from the parents of all the subjects.

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