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Endoscopic injection therapy

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Since the U.S. Food and Drug Administration approved dextranomer/hyaluronic acid copolymer (Deflux) for the treatment of vesicoureteral reflux, endoscopic injection therapy using Deflux has become a popular alternative to open surgery and continuous antibiotic prophylaxis. Endoscopic correction with Deflux is minimally invasive, well tolerated, and provides cure rates approaching those of open surgery (i.e., approximately 80% in several studies). However, in recent years a less stringent approach to evaluating urinary tract infections (UTIs) and concerns about long-term efficacy and complications associated with endoscopic injection have limited the use of this therapy. In addition, there is little evidence supporting the efficacy of endoscopic injection therapy in preventing UTIs and vesicoureteral reflux-related renal scarring. In this report, we reviewed the current literature regarding endoscopic injection therapy and provided an updated overview of this topic.

Keywords: Endoscopy; Injections; Vesicoureteral reflux

INTRODUCTION

Vesicoureteral reflux (VUR), a common urologic diagnosis that affects approximately 1% of all children, may increase the risk of pyelonephritis and renal scarring. Before the introduction of endoscopic injection therapy, the mainstay of surgical treatment for VUR was open ureteral reimplantation. The cure rate, depending on the procedure and the severity of reflux, was 98.1% (95% confidence interval [CI], 95.1–99.1) [1]. Drawbacks of open surgery are the abdominal incision, required hospitalization, temporary indwelling of a urinary catheter, and possible damage to the trigone. Minimally invasive surgical techniques have overcome some of these limitations; however, postoperative complications such ureteral obstruction still occasionally occur.

Since Matouschek first used polytetrafluoroethylene (PFTE, Teflon) injection at the ureteral orifice to treat VUR [2], endoscopic injection treatment has been widely used by urologists. This approach corrects VUR by injecting a bulking agent to elevate and coapt the ureteral orifice and detrusor tunnel. Endoscopic injection treatment is minimally invasive, performed on an outpatient basis, and technically straightforward, with a relatively short learning curve and low complication rate. These advantages have led to its widespread use in last 2 decades.

Considerable progress has been made regarding the injection technique and materials used. Dextranomer/hyaluronic acid (Dx/HA, Deflux, Salix Pharmaceuticals, NJ, USA) is currently the most widely used bulking agent approved by the U.S. Food and Drug Administration (FDA) and has shown an overall mean success rate of 83% [1]. However, the reporting of long-term success rates and delayed complications has resulted in a controversy over

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the use of endoscopic injection treatment. In this review, we reviewed the injection materials, techniques, success rates, and recent issues for endoscopic injection treatment.

MATERIALS FOR ENDOSCOPIC INJECTION

1. PTFE (Teflon)

PTFE is a widely used biomaterial for medical applications such as vascular grafts and tissue replacement patches and was the first material investigated for endoscopic treatment of VUR [2,3]. Since the experience with PTFE exceeds 20 years, long-term results and durability of PTFE have been assessed [4-6]. A study evaluating PFTE in patients with a mean follow-up of 13.5 years reported the absence of reflux in 95% of injected ureters on routine voiding cystourethrogram (VCUG) [4]. These data demonstrated long-term durability and efficacy, even in high-grade reflux (III–V), with a success rate of 68.4%. However, there is a concern that PFTE particles could migrate to other organs such as the brain and lungs [7,8]. Despite of the convincing long-term outcome with PTFE, the concerning information regarding the possibility of particle migration limited the use of PTFE and it has been nearly abandoned.

2. Polydimethylsiloxane (Macroplastique)

To reduce migration of implant particles while maintaining a durable implant, polydimethylsiloxane was developed as a soft tissue bulking agent. This solid, elastomeric silicone was incorporated into a patented device called Macroplastique (Congentix Medical, Orangeburg, NY, USA). Polydimethylsiloxane has a mean maximum particle diameter of 209 μm and is highly viscous, requiring an administration device that can withstand high pressure [9]. In comparison with other bulking agents, the higher viscosity and its nonresorbable nature preventing shrinkage of the product increase its reliability. This bulking agent has been used in Europe and Canada with success rates similar to those of other bulking agents [10]. Although a recent prospective study reported that polydimethylsiloxane resulted in a better success rate than Dx/HA (90% vs. 81%, $p<0.05$), most of previous studies did not reveal major differences in success rates between polydimethylsiloxane and other materials. Most polydimethylsiloxane particles have diameters greater than 100 μm; however, the presence of particles with diameters less than 80 μm raises the possibility of long-distance migration [11,12]. These concerns about migration have prevented polydimethylsiloxane from gaining popularity in the United States and it has been displaced by Dx/HA.

3. Dx/HA (Deflux)

After the FDA approved Dx/HA for the treatment of VUR in 2001, even urologists who had considerable experience with PTFE switched to using Dx/HA. There was a rapid increase in the use of endoscopic injection therapy, and some researchers recommended Dx/HA injection as the first-line treatment for VUR [13,14]. Dx/HA is a highly viscous gel consisting of Dx microspheres (80–250 μm in diameter) in non–animal-stabilized HA, which acts primarily as a carrier to deliver the biocompatible Dx to the implantation site.

Success rates for Dx/HA injection vary widely depending mainly on the VUR grade, and the overall success rate reported is 77% [15]. Although sufficient data have been accumulated to understand short-term success, the long-term durability of Deflux is still a subject of concern. Several groups have published long-term results after endoscopic injection [16-21]. The time of last follow-up VCUG varied from 1 to 12 years, and overall recurrence rate ranged from 12% to 54%. However, regular follow-up VCUG is required prospectively to evaluate the long-term durability of Deflux, even after postoperative images confirm the success of the procedure; therefore, there has been a lack of comprehensive long-term data until now.

4. Polyacrylate Polyalcohol copolymer (Vantris)

Polyacrylate Polyalcohol copolymer (PPC) (Vantris, Promedon, Córdoba, Argentina), a new nonbiodegradable substance of synthetic origin belonging to the acrylic family, was first introduced in 2010 to treat VUR [22]. The average diameter of particles is 320 nm which can reduce the risk of migration and nonbiodegradable nature leads to the formation of a fibrotic capsule that can result in better stability and long-term durability in treating VUR. Several studies reported successful short-term outcomes (88.6%–93.8% of resolution rate) with PPC, which are similar or even superior to Dx/HA [23-25]. However, ureteral obstruction was more commonly seen in PPC group within several months or even years after injection [24-26] and a recent animal study also revealed that PPC leaded severe fibrosis on injection site [27]. These results have raised a caution for ureteral obstruction after PPC injection and a long-term data should be followed.

ENDOSCOPIC INJECTION TECHNIQUES

Subureteric Teflon injection (STING) was introduced

by O'Donnell and Puri [3] in 1984 and has been used as a representative technique for endoscopic injection. The STING technique involves inserting the needle 2–3 mm below the ureteric orifice at the 6 o'clock position, advancing it for 4–5 mm into the submucosal plane, and creating a mound that elongates the intramural ureter. The STING technique was still used widely after the introduction of Dx/HA for injection therapy. The initial study on this procedure with Dx/HA reported a success rate of 69% 12 months after the procedure [28]. Drawbacks of this technique were the relatively low success rate and concern regarding the caudal migration of material.

A study published in 2004 reported that the success rate of the hydrodistention implantation technique (HIT), which is a modification of STING, was higher than that of the original STING procedure (92% HIT vs. 79% STING, $p<0.05$) [29]. The HIT procedure therefore became the representative injection technique. Advantages of HIT include better visualization of the distal ureteral lumen, which enables more accurate placement of the injector needle at the distal ureter and better visualization of the lumen configuration during the procedure. In addition, the HIT procedure results in better coaptation of the distal ureter, whereas the STING procedure involves only the ureteral orifice. A recent meta-analysis showed that the overall resolution of VUR was significantly higher for patients who underwent HIT (82.5%) compared to those who underwent STING (71.4%) (pooled odds ratio [OR], 0.54; 95% CI, 0.42–0.69; $p<0.0001$) [30].

In recent years, the HIT procedure has been modified to include 2 tandem intraluminal ureteric tunnel injections (double HIT). With hydrodistention, injection of the bulking agent creates a bulge, which initially coapts the detrusor tunnel, and a second implant within the most distal intramural tunnel leads to coaptation of the ureteric orifice [31]. Double HIT requires a higher injection volume and has a reported success rate of up to 93% [32,33]. Results of a recent survey showed that double HIT was the most commonly used technique for endoscopic correction of VUR by pediatric urologists in the United States [34]. In our experience, multiple punctures of the mucosa can sometimes cause leakage of the injected material. Therefore, an additional distal ureter injection could be beneficial in the event of insufficient coaptation of the ureteric orifice after the first HIT injection.

FACTORS RELATED TO THE SUCCESS OF ENDOSCOPIC INJECTION

The single most important factor affecting the success rate of endoscopic injection is the preoperative grade of VUR. Although the success rate varied depending on the authors' conflicts of interest, overall success rates with Dx/HA reported in a systematic review were 89% (grade I), 83% (grade II), 71% (grade III), 59% (grade IV), and 62% (grade V) [15]. As previously mentioned, many studies reported an increased success rate by using the HIT modification (89% HIT vs. 71% STING) [29] with some exceptional studies reporting no significant difference in success rates between the 2 approaches [35].

Surgeon experience is another important factor for successful results [18,36]. Kirsch et al. [18] demonstrated that their success rate increased after first 20 cases with further improvement after the first 100 cases (success rate of 60% for first 20 cases vs. 80% for last 20 cases). Our data with 382 injections between January 2008 and December 2013 are consistent with these findings. Results of cumulative sum analysis revealed that this improvement tended to flatten and then decline after the initial 110 cases. The success rate improved gradually with high-grade VUR, whereas relatively few cases were required to reach a stable success rate for grade II VUR. The key technical points gained through experience appear to be the ability to clearly visualize the ureteral floor, which facilitates needle placement to the proper depth. In addition, acclimatization to the pressure and volume of injection material required to create the mound may improve outcomes.

Results of multivariate logistic regression analysis indicate that creation of a mound that elevates and coapts the orifice is the most important factor determining the success of endoscopic injection [37,38]. However, the mound morphology and lack of hydrodistention in the ureter are somewhat subjective. An online survey asking pediatric urologists to predict whether the procedure was successful based on the appearance of the mound just after the injection showed that the mound morphology was not a reliable predictor of outcome [39]. Nevertheless, the surgeon's impression of needle placement, the injected volume, development of the mound, and tactile sensation of tissue distention still provide important information about the success of the procedure.

Although there is increased awareness of bladder and bowel dysfunction (BBD) in patients with VUR, the role of BBD in the success of injection therapy is unclear [37,38,40,41]. According to articles cited in the 2010 American Urological Association guideline on the management of primary VUR and its meta-analysis, in children with VUR treated with subureteral injection therapy, resolution rates at 3–12 months were 50% for those with BBD and 89% for

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those without BBD [1]. More recent studies report higher success rates, suggesting that injection therapy should be considered for patients with BBD [42-44]. However, the effect of BBD on the outcome of injection therapy is difficult to determine because of the complex manifestations of BBD, which include overactive bladder, urge incontinence, voiding postponement, underactive bladder, dysfunctional voiding, and constipation.

APPLICATION FOR COMPLEX CASES

1. Paraureteral diverticulum

For a paraureteral diverticulum (PUD), ureteral reimplantation is generally performed because of the presumed underlying structural defect of the ureteral hiatus. However, Perez-Brayfield et al. [45] reported a success rate of 67% for endoscopic injection therapy in patients with PUD. In a subsequent study, they reported a success rate of 81% after a single injection. Their results suggested that a diverticulum diameter greater than 2.6 times that of the ureteral diameter was a risk factor for treatment failure; however, their study was limited by the small number of cases [46]. A more recent study reported a 79% success rate for endoscopic injection in 28 renal units in patients with PUD and identified the following predictors of success: low PUD index, late onset of reflux on VCUG, and position of the ureteral orifice [47]. Based on these evidences, injection therapy could be considered as a treatment option in selected cases of PUD.

2. Ureteral duplication

Results of a meta-analysis of endoscopic injection therapy showed that the success rate for VUR in patients with ureteral duplication (50%) was lower than that of patients with single systems (73%) regardless of VUR grade [48]. However, several studies evaluating potential predictors of success with injection therapy reported that ureteral duplication was not associated with treatment failure [37,49]. More recent studies have reported better success rates (68.4%–73%) after a single injection [50-52], with the possibility of additional injections if needed.

PREVENTION OF URINARY TRACT INFECTIONS AND RENAL DAMAGE

It remains unclear whether surgical correction of VUR using an endoscopic approach will prevent further renal damage or urinary tract infections (UTIs). The incidence of febrile UTIs after injection therapy has been reported as 0.75% to 27% after successful treatment [41,48,53] (Table

Table 1. Summary of the key studies for the outcomes of endoscopic injection therapy

Study	Study design	Year	No. of patients	Follow-up (yr)	Result
Febrile UTIs					
Läckgren et al. [16]	Retrospective	2001	221	Mean, 5	Febrile UTIs: 3.5% of patients
Chi et al. [53]	Retrospective	2008	167	Median, 2.6	Febrile UTIs: 12% of patients
Hunziker et al. [70]	Retrospective	2012	1,271	Mean, 7.6	Febrile UTIs: 5.7% of patients, more frequently developed in female and bladder bowel dysfunction
Elder et al. [54]	Retrospective matched cohort	2007	152	1	Average number UTIs per patient: 0.28 on prophylaxis vs. 0.08 with endoscopic injection (p=0.029) 383% higher average number of UTIs on prophylaxis
Brandström et al. [55]	RCT	2010	203	2	Febrile UTIs: 57% on surveillance vs 23% with endoscopic injection vs 19% on prophylaxis (p=0.0002) in girls No differences in boy (p=0.28)
Renal damage					
Chertin et al. [17]	Retrospective	2009	507	Median, 13	No newly developed renal scar Deterioration of renal function: 7.5% of renal units UTIs incidence : overall 2.2%
Brandström et al. [56]	RCT	2010	203	2	New damage: 18% on surveillance vs. 12% with endoscopic injection vs 6% on prophylaxis (p=0.11)

UTIs, urinary tract infections; RCT, randomized controlled trial.

1). In a retrospective matched cohort study, Elder et al. [54] reported that the average number of UTIs in patients receiving antibiotic prophylaxis (0.28) was significantly higher than that of patients receiving injection therapy (0.08), and results of the regression analysis revealed a 383% higher incidence of UTIs in the antibiotic prophylaxis group. However, results of a randomized trial in Sweden (Swedish reflux trial) demonstrated that the rate of febrile UTIs was lower with endoscopic treatment (23%) compared with surveillance (57%) in girls, but did not differ significantly between endoscopic treatment and antibiotic prophylaxis [55]. No benefit from treatment was observed in boys older than 1 year with dilating VUR regarding prevention of febrile UTI.

The ability of injection therapy to protect against renal damage is still unknown. Few studies have evaluated the development of new renal damage, which includes both renal deterioration and scarring, following treatment of reflux with endoscopic injection [17,56]. One study reported that postoperative deterioration of renal function was developed in 7.5% of renal units and 9.1% of patients, respectively without newly developed renal scar after successful endoscopic injection [17]. The Swedish reflux trial compared the development of renal damage in children with dilating VUR who were randomized to different treatments [56]. The results showed that girls who received antimicrobial prophylaxis had the lowest incidence of renal scarring after 2 years, but the development of new renal damage in the injection therapy group did not differ significantly from that of the antibiotic prophylaxis or surveillance groups.

CURRENT TREND AND DEBATES ON ENDOSCOPIC INJECTION

After the FDA approved the use of Dx/HA to treat VUR in 2001, Dx/HA use dramatically increased between 2002 and 2006 [13,57], with some authors even recommending Dx/HA injection as the optimal first-line treatment for VUR [58]. However, according to a recent analysis of Pediatric Health Information System data, the trend of increased Dx/HA use was not sustained through 2011 [59]. This may be attributed in part to a change in the algorithm for evaluating UTIs to a less stringent "top-down approach," which resulted in a lower incidence of low-grade VUR. In addition, a shift toward decreasing interventions for low-grade VUR could reduce the usage of Dx/HA while the number of reimplantations for high-grade VUR remains unchanged. Evidence supporting a non-interventional approach may be the reason for fewer patients receiving injection therapy, with aggressive therapy reserved for select patients [60,61].

With the emergence of this trend toward less-invasive therapy, concerns regarding the long-term durability and complications of injection therapy have also emerged. The concerns of opponents to injection therapy are the decreased success rate during long-term follow-up and delayed-onset ureteral obstruction. For example, Lee et al. [21] reported 26% recurrence of VUR after 1 year, even in patients who showed immediate resolution of VUR (overall recurrence was 46%). Similarly, the Swedish reflux trial reported a 20% recurrence rate after 2 years with grade III VUR or higher. Although the reason for VUR recurrence is unclear, migration of the deposited material, which is accelerated by BBD, may play a role.

In addition to late recurrence of VUR, an increasing number of early and delayed ureteral obstructions have been reported, although the incidence was still lower than the rate associated with open surgery [62-65]. Most cases of ureteral obstruction were resolved after temporary double-J stenting [65], but some required open ureteral reimplantation because of inflammatory foreign body reaction [62,66]. Because delayed ureteral obstruction may occur as long as 5 years after injection therapy, it can be missed, resulting in silent loss of renal function. In addition, the calcification of injection material may be misdiagnosed as ureteral stones, because the density of Dx/HA implants on CT scans increases over time, appearing as progressive histopathologic changes [67,68].

Despite these limitations, injection therapy still has a role in treating VUR. Many families grow tired of the seemingly endless series of VCUGs while waiting for VUR resolution and fear the long-term effects of antibiotic therapy, even at low doses. In our institution, we usually consider injection therapy for patients with late detected VUR causing febrile UTI, older than 1 year, who have a lower chance of spontaneous resolution. Children with megaureter or large PUD are excluded from injection therapy. In light of recent studies reporting the low effectiveness of antibiotic prophylaxis and concerns about antibiotic-resistant strains [69], we believe injection therapy still has an important role in VUR treatment. Future research regarding the long-term efficacy in preventing UTIs and renal damage is required to determine the role of endoscopic injection therapy in the treatment of VUR.

CONCLUSIONS

Although open surgery remains the gold standard for treating VUR, the use of endoscopic injection therapy has

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grown considerably for the last decade with the advent of Dx/HA copolymer. Despite the excellent short-term success rate following injection therapy, increasing reports of complications such as delayed ureteral obstruction and concerns about durability limit the use of injection therapy. In addition, a less stringent approach for evaluating UTIs that resulted in lower detection of low-grade VUR may have contributed to the decrease in endoscopic injection treatments. Nevertheless, endoscopic injection treatment is a convenient method that can cure the condition through a single procedure without the need for major surgery. Considering recent disappointing reports regarding the efficacy of antibiotic prophylaxis, a revised approach to the management of VUR may be needed, with patients classified according to several factors in addition to reflux grade. A future randomized, prospective, long-term follow-up study is required to determine the optimal use of injection therapy for VUR.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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