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Ureteral Obstruction After Endoscopic Treatment of Vesicoureteral Reflux: Does the Type of Injected Bulking Agent Matter?

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Abstract

Purpose of Review Endoscopic injection of bulking agents for the treatment of vesicoureteral reflux (VUR) has become a therapeutic alternative to antibiotic prophylaxis and ureteral reimplantation. Although considered as a safe and efficient procedure, several studies have reported cases of ureteral obstruction (UO) after endoscopic correction of VUR. This review article evaluates the present VUR literature to estimate the incidence of UO following endoscopic injection of different substances, while also discussing the impact of injection technique and implant volume.

Recent Findings Twenty-five publications were identified that provided detailed information on 64 females and 32 males (age range, 7 months–48 years) that developed UO after endoscopic treatment of VUR using dextranomer/hyaluronic acid (Dx/HA), polyacrylate polyalcohol (PP), polydimethylsiloxane (PDMS), calcium hydroxyapatite (CaHA), polytetrafluoroethylene (PTFE), or collagen. There was some variation in the reported incidence of UO among these materials: Dx/HA (0.5–6.1%), PP (1.1–1.6%), PDMS (2.5–10.0%), CaHA (1.0%), and PTFE (0.3%). Postoperative UO was described following subureteric transurethral injection (STING), intraureteric hydrodistension implantation technique (HIT), combined HIT/STING and double HIT. The injected volume ranged widely, also depending on the type of bulking agent: Dx/HA (0.3–3.0 mL), PP (0.3–1.2 mL), PDMS (1.0–2.2 mL), CaHA (0.4–0.6 mL), and PTFE (1.5–2.0 mL). The timing of UO varied from immediately after the procedure to 63 months. Over half of patients showed asymptomatic hydroureteronephrosis on follow-up imaging, whereas the remaining presented with symptoms of acute UO or fever.

Summary UO remains a rare complication after endoscopic correction of VUR, generally reported in less than 1% of treated cases, which appears to be independent of the injected substance, volume, and technique. However, long-term follow-up is recommended as asymptomatic or delayed UO can occur, potentially leading to deterioration of renal function.

Keywords Vesicoureteral reflux · Ureter · Endoscopy · Ureteral obstruction · Deflux · Vantris

Introduction

Vesicoureteral reflux (VUR), the retrograde flow of urine from the bladder into the ureter and collecting system of the kidney, is one of the most frequently detected urinary tract abnormalities, affecting approximately 1 to 2% of the pediatric population and 25 to 40% of children presenting with urinary tract infection (UTI) [1, 2]. Contemporary treatment options for VUR comprise conservative medical management with observation or continuous antibiotic prophylaxis (CAP), ureteral reimplantation, and endoscopic injection of bulking agents into the submucosa of the refluxing ureteric orifice [3, 4]. It has been shown that the success of antibacterial therapy for VUR is largely dependent on patient compliance and involves the risk of antibiotic-resistant uropathogens accompanied by potential breakthrough UTIs [5]. Furthermore, a meta-analysis of clinical trials including 17,972 children with primary VUR has demonstrated a lack of efficacy for CAP in terms of decreasing the incidence of UTIs and renal parenchymal damage [6]. In contrast, anti-reflux surgery (i.e., open, laparoscopic, or robotic-assisted operations) has success rates of 88 to 98% [6, 7], but these remain invasive procedures

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that usually require inpatient hospitalization and temporary urinary catheter drainage. Consequently, endoscopic correction of VUR, which can easily be performed on an outpatient basis with minimal postoperative pain and no need for catheterization, has become an accepted therapeutic alternative with resolution rates ranging from 77 to 83% [6, 8]. In addition to these relatively high cure rates, it is a safe procedure and the number of reported adverse events following endoscopic treatment of VUR seems to be very low [9–11]. One potential complication after endoscopic injection of tissue augmenting substances is the development of ureteral obstruction (UO). Although this is a rare complication and most of the large studies have not reported any relevant cases of postoperative UO [9], a growing body of evidence has arisen over recent years to suggest that it can occur in some instances [12–17]. The first case series from the 1990s described symptomatic patients with UO that presented within several hours of subureteral polytetrafluoroethylene (PTFE or Teflon) injection, associated with signs of acute obstruction [18]. More recently, Snodgrass [19] has reported a case of delayed, asymptomatic UO 16 weeks following injection of dextranomer/hyaluronic acid (Dx/HA) copolymer (or Deflux®), which has since been corroborated in other series, as far on as 63 months postoperatively [20••, 21, 22]. Postoperative UO has also been identified after injection of various other bulking agents including polyacrylate polyalcohol (PP or Vantris®) [12], collagen [14], calcium hydroxyapatite (CaHA or Coaptite®) [15], and polydimethylsiloxane (PDMS or Macroplastique®) [16]. This review article evaluates the present literature to estimate the incidence, timing, and manifestation of UO following endoscopic injection of various tissue augmenting substances for the treatment of VUR, while also discussing the potential impact of injection technique and implant volume.

Material and Method

Information Sources and Literature-Based Search

In order to identify as many scientific articles as possible that reported cases of UO after endoscopic injection therapy for VUR, a systematic literature-based search was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [23] using MEDLINE®, EMBASE®, Scopus®, Web of Science™, CINAHL®, Centre for Reviews and Dissemination (CRE), and Cochrane Central Register of Controlled Trials (CENTRAL). These electronic databases were last accessed on 20 April, 2019, using a combination of the following linked Medical Subject Headings (MeSH) and search terms: "*vesicoureter* reflux**" AND "*endoscop**" OR "*cystoscop**" OR "*deflux**" OR "*vantris**" OR "*teflon**" OR "*collagen**" OR "*hydroxyapatite**" OR "*polydimethylsiloxane**" AND "*ureter* obstruction**". No language restrictions were imposed and reference lists of identified publications were manually searched for additional studies. All duplicate listed items were deleted.

Selection Process and Data Extraction

All identified publications were reviewed by title, keywords, and abstract by one of the authors (F.F.), and an unblinded, systematic full-text assessment of selected studies was independently performed by both authors (F.F. and P.P.). Only articles that reported in detail on the type of bulking agent used, injection technique, and/or implant volume were considered for this review. Additionally, timing (i.e., acute or delayed), manifestation (i.e., symptomatic or asymptomatic), and results from histopathological analysis of excised UO were recorded. Relevant data was then extracted into an electronic database in a standardized manner. Any discrepancies between the authors during this selection process were resolved by mutual consensus.

Results

Summary of the Systematic Review on Cases of Postoperative UO

Overall, 25 publications (published between 1991 and 2018) were identified that provided detailed information on the occurrence of UO after endoscopic correction of VUR: 10 retrospective single−/multicenter studies [13, 24–28, 29••, 30•, 31••], 9 case reports [14, 19, 22, 32–37] and 6 case series [18, 20••, 21, 38–40]. Only three authors [29••, 31••, 41] used two different bulking agents in their cohorts. Data from these articles was critically evaluated for this review and is summarized in Table 1. In total, 95 pediatric cases (age range, 7 months–13 years) and one adult case (a 48-year-old woman with renal transplant) of UO following endoscopic treatment of primary or secondary VUR were reported. UO occurred in these patients after endoscopic injection of various tissue augmenting substances: Dx/HA ($n = 55$), PP ($n = 23$), PDMS ($n = 13$), CaHA ($n = 2$), PTFE ($n = 2$), and collagen ($n = 1$). There was some variation in the reported incidence rates of postoperative UO among these injectable materials: Dx/HA (0.5–6.1%), PP (1.1–1.6%), PDMS (2.5–10.0%), CaHA (1.0%), and PTFE (0.3%). Cases of UO were described following subureteric transurethral injection (STING), intraureteric hydrodistension implantation technique (HIT), combined HIT/STING, and double HIT. Ten (10.4%) of the identified 96 patients that eventually developed UO after endoscopic correction of VUR received repeated injections of Dx/HA, PP, or CaHA using either STING, HIT, combined

Table 1 Summary of relevant literature on UO after endoscopic treatment of VUR

Author	Year	Patients (*n*=)	Injection technique	Implant material	Volume (mL)	Repeated injections	Timing of UO	Clinical symptoms	Renal function deterioration	Histology reported
Perovic S, et al. [18]	1991	2	STING	PTFE	1.5–2.0	No	Acute	Yes	No	No
Snodgrass WT [19]	2004	1	STING	Dx/HA	0.8	No	Delayed	No	No	Yes
Seifert HH, et al. [32]	2006	1	STING	Dx/HA	3.0	Yes	Delayed	No	Yes	Yes
Serrano Durba A, et al. [24]	2006	5	STING	PDMS	–	No	–	No	No	No
Kirlum HJ, et al. [14]	2006	1	STING	Collagen	–	No	Delayed	No	No	Yes
Önol FF, et al. [33]	2006	1	STING	CaHA	0.65	Yes	Delayed	No	Yes	Yes
Vandersteen DR, et al. [13]	2006	5	STING	Dx/HA	0.3–1.0	No	Acute, delayed	Yes ($n = 4$)	No	No
Zaccara A, et al. [34]	2007	1	STING	CaHA	0.4–0.6	No	Delayed	No	No	Yes
Aaronson DS, et al. [38]	2008	2	STING	Dx/HA	0.8–1.0	No	Delayed	Yes ($n = 1$)	Yes ($n = 1$)	Yes
Kempf C, et al. [39]	2010	2	STING	PDMS	–	No	Acute	Yes	Yes ($n = 2$)	No
Mazzone L, et al. [40]	2011	5	STING, HIT/STING	Dx/HA	0.7–1.2	Yes ($n = 1$)	Acute, delayed	Yes ($n = 2$)	Yes ($n = 1$)	No
Arlen AM, et al. [35]	2012	1	HIT	Dx/HA	0.7	No	Delayed	No	Yes	Yes
Zemple RP, et al. [22]	2012	1	STING	Dx/HA	1.0	No	Delayed	No	Yes	No
Abbo U, et al. [36]	2012	1	STING	Dx/HA	–	No	Delayed	Yes	No	No
Nseyo U, et al. [37]	2013	1	STING	Dx/HA	1.4–1.6	No	Delayed	Yes	No	Yes
Rubenwolf PC, et al. [21]	2013	4	STING, HIT/STING	Dx/HA	1.0–1.9	No	Delayed	Yes ($n = 1$)	No	Yes
Alizadeh F, et al. [25]	2013	7	STING, HIT, HIT/STING	PP	0.5–1.2	No	Acute, delayed	Yes ($n = 5$)	No	No
García-Aparicio L, et al. [26]	2013	5	STING, HIT, double-HIT	Dx/HA	0.6–1.1	Yes ($n = 3$)	Acute, delayed	Yes ($n = 3$)	Yes ($n = 1$)	No
Alenezi H, et al. [27]	2013	2	HIT	Dx/HA	0.4–0.7	No	Acute	Yes	No	No
Şencan A, et al. [28]	2014	3	STING	PP	0.4–0.6	Yes ($n = 1$)	Delayed	Yes	Yes ($n = 1$)	Yes
Chung JM, et al. [41]	2015	7	STING, HIT	Dx/HA, PDMS	1.6 ± 0.6	No	Acute, delayed	Yes ($n = 4$)	No	No
Ben-Meir D, et al. [29••]	2016	9	HIT	Dx/HA, PP	1.0–2.0	No	Delayed	No	No	No
Papagiannopoulos D, et al. [20••]	2016	3	Double-HIT	Dx/HA	1.0–2.0	No	Delayed	Yes ($n = 2$)	Yes ($n = 3$)	No
Okawada M, et al. [30•]	2018	8	STING	Dx/HA	–	No	Acute, delayed	Yes ($n = 1$)	No	No
Chertin B, et al. [31••]	2018	18	STING, HIT	Dx/HA, PP	1.4 ± 0.6, 0.9 ± 0.6	Yes ($n = 3$)	Delayed	Yes ($n = 10$)	No	Yes

HIT/STING, or double HIT. The reported volume of injected bulking agent in cases of postoperative UO ranged widely, which was also depending on the type of implant: Dx/HA (0.3–3.0 mL), PP (0.3–1.2 mL), PDMS (1.0–2.2 mL), CaHA (0.4–0.6 mL), and PTFE (1.5–2.0 mL). The reported timing of UO following endoscopic treatment of VUR ranged from immediately after the procedure (i.e., within hours) to 63 months. Fifty-two (54.2%) cases of UO after endoscopic correction of VUR showed asymptomatic hydroureteronephrosis on follow-up imaging studies, whereas 44 (45.8%) presented with flank/unspecific abdominal pain ($n = 27$), febrile UTI/unspecific fever ($n = 9$), anuria ($n = 5$), or nausea/vomiting ($n = 3$). In 13 (13.5%) patients, a deterioration or loss of renal function was detected at time of UO diagnosis. Histopathological analysis of obstructed ureters that subsequently required resection and ureteral reimplantation was performed in eleven studies, all reporting analogous patterns of granulomatous foreign body reaction with fibrotic pseudoincapsulation of the injected implant and infiltration of giant cells, which appeared to be similar among the used tissue augmenting substance.

Potential Risk Factors for Postoperative UO

Due to the infrequency of cases, the exact cause of UO following endoscopic injection therapy for primary or secondary VUR remains relatively unclear and may be multifactorial [20••].

Type of Bulking Agent Since the first description of endoscopic treatment of VUR in the early 1980s, various tissue augmenting substances have been introduced and UO was observed following injection of most materials including Dx/HA, PP, PDMS, CaHA, PTFE, and collagen. The overall incidence of postoperative UO ranges from 0 to 10.0% in published large series [9, 41], with some variation depending on the type of bulking agent used: Dx/HA (0.5–6.1%) [13, 25, 26, 30•, 40, 41], PP (1.1–1.6%) [12, 28, 31••], PDMS (2.5–10.0%) [16, 41], CaHA (1.0%) [15], and PTFE (0.3%) [17]. However, the variance in the rate of UO in these studies is most likely related to the number of associated anatomical variants (e.g., refluxing megaureter with distal aperistaltic segment) [26, 31••, 38] or functional risk factors (e.g., bladder and bowel dysfunction or neurogenic bladder) [13, 20••, 25, 28, 41] rather than the type of implant. In fact, a recent multicenter study found no statistical difference in the incidence of UO after endoscopic correction of VUR using Dx/HA or PP in a homogenous pediatric population [31••].

Injection Technique Over the years, various endoscopic injection techniques have been described for the treatment of VUR: STING [42], HIT [43], and double-HIT [44]. Although approximately two-thirds of the identified patients in this review that subsequently developed UO were treated with the STING procedure, this finding most likely represents a selection bias given the worldwide popularity of this injection technique. Indeed, several authors have observed cases of UO with all techniques [25, 26]. In contrast, a large series from Russia including 4,898 ureters, which was presented at the 26th Congress of the European Society for Pediatric Urology, reported a significantly higher incidence of postoperative UO when comparing HIT (1.6%) to STING (0.5%) [45].

Injected Volume

In 2002, a case of symptomatic UO post injection of PDMS was reported, which the authors attributed to excess amount of injected material in the wrong tissue plane [16]. Interestingly, Kirsch et al. [46] have shown that 18% of Dx/HA is absorbed after a few weeks of injection and an additional 1% reduction occurs within 3 months, which may explain transient cases of UO that resolve spontaneously and do not require any intervention. More recently, Vandersteen et al. [13] have demonstrated that the injected volume of Dx/HA does not correlate with the incidence of postoperative UO. Our review of the literature showed that the volume, which eventually led to UO ranged from 0.3 to 3.0 mL, depending on the type of bulking agent used. Additionally, Sorensen et al. [47] observed an obvious trend towards larger injection volumes in the endoscopic treatment of VUR. Arlen et al. [35] noted that the volume of foreign material excised at the time of ureteral reimplantation appeared significantly greater than the initially injected volume, which may be secondary to calcification and exaggerated local tissue reaction. Given the fact that there is a large variation in molecular mass and particle size among the available tissue augmenting substances, it is probable that a volume that might not cause UO with one implant may lead to obstruction with a different material. In general, it is advised not to exceed the recommended injection volume that is stated in the instruction leaflet of each bulking agent.

Repeated Injection A few years ago, a case series from Switzerland [40] indicated that repeated injections may be a potential risk factor for the development of UO, possible due to decreased tissue compliance. It has been shown that endoscopic correction of VUR can lead to edema of the distal ureter, fibrotic encapsulation with granulomatous foreign body reaction and chronic inflammation [26, 28, 31••, 32, 33], thus predisposing to UO. Routh et al. [48] and Stenberg et al. [49] have studied these associated histopathological changes in detail. Calcifications at the injection site have also been reported [50, 51]. In the present study, only 10% of identified patients that eventually developed postoperative UO received repeated injections [26, 28, 31••, 32, 33, 40]. Furthermore, no case of UO occurred in a series of 851 children with high-grade VUR (1,287 refluxing units) following

259 re-injections and 133 third injections [52•], suggesting that this factor actually may not be relevant.

Timing and Manifestation of Postoperative UO

The reported timing of UO after endoscopic treatment of VUR appears to be highly variable, ranging from immediately after the procedure to 63 months postoperatively. In general, patients with early-onset UO seem to present acutely within several days of injection, associated with pain, nausea, vomiting, or anuria [13, 18, 25–27, 30•, 39–41]. Acute cases of UO may occur due to increased resistance at the ureterovesical junction caused by the tissue augmenting substance itself or injection in the wrong tissue plane [29••, 53]. However, there is also a concerning trend of delayed UO, which may either lead to obstructive symptoms [20, 28, 31••, 36–38] or more frequently to asymptomatic hydroureteronephrosis found on routine follow-up imaging [14, 19, 21, 22, 25, 26, 29••, 32–35, 38, 40]. Ben-Meir et al. [29••] have recently suggested several mechanisms, which could explain the occurrence of late-onset or progressive UO: gradual increase of resistance at the ureterovesical junction, ineffective ureteral peristalsis, and coaptation or chronic inflammation. Moreover, cases of postoperative UO may be discovered incidentally during the diagnostic work-up of unspecific fever or febrile UTI [20••, 21, 28].

Conclusions

UO is a well-known but rarely reported complication after endoscopic correction of VUR. Reported incidence rates of postoperative UO are generally less than 1% of treated cases, which appears to be independent of the injected bulking agent, volume, and technique. It has been indicated that UO can be caused by perioperative edema alone. In such cases, a more conservative approach to await resolution without need for intervention is feasible. However, in the presence of obvious clinical or radiological signs and deterioration of renal function, further management options must be considered. In general, long-term follow-up after endoscopic correction of VUR is recommended as asymptomatic or delayed UO can occur in some instances, potentially leading to deterioration of renal function.

Compliance with Ethical Standards

Conflict of Interest Florian Friedmacher and Prem Puri each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This review article does not contain any studies with human participants or animals performed by the author.

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