Endoscopic Injection Treatment of Vesicoureteral Reflux in Children: Meeting with the Factors Involved in the Success Rate

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ABSTRACT
The challenges and controversies in vesicoureteral reflux intervention guidelines resulted in a more individualized treatment planning. Endoscopic injection therapy is now widely used and is considered preferable, but still remains less successful than ureteral reimplantation. The endoscopic vesicoureteral reflux approach should be risk-adapted to current knowledge, so more experience and longer-term follow-up are needed. The precise of preoperative, intraoperative, and postoperative factors that affecting endoscopic injection therapy success rates and outcome have not yet been clearly determined.
The aim of this study was to investigate these associated factors. Although the reflux grade is the most well-known factor that can affect the success of the procedure, there is no agreement on which factors are the most influential for the efficacy of endoscopic reflux treatment. So, we carried out a broad review of published papers on this topic, and we presented all the potential predictive variables of endoscopic reflux resolution in children.

KEYWORDS
vesicoureteral reflux; children; endoscopic; injection; outcome; risk factors

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INTRODUCTION

Vesicoureteral reflux (VUR), as the most common and controversial urological abnormality in children, with a prevalence of 1% to 2%, is the most frequent predisposing risk factor for acute pyelonephritis, nephropathy with renal scarring, and decreased renal function (1). Renal damage may be congenital or acquired after infection, and the aim of the VUR-facilitating factor management is to prevent recurrent or breakthrough urinary tract infections, new renal scarring formation, and relative renal function deterioration (2). We can no longer view VUR as a homogeneous entity affecting all individuals equally. In contrary, we should take into consideration individual parameters and specific factors for a case by case and risk to benefit based deciding VUR management (1, 3).

Endoscopic injection treatment (EIT) became initially a popular alternative to open surgical ureteral reimplantation and long-term antibiotic prophylaxis in pediatric VUR management, as a minimally invasive and well tolerated method with a relatively short learning curve and low complication rate (4). Endoscopic treatment of a bulking agent was pioneered by Matouschek in 1981 (5) and was further developed and popularized by O'Donnell and Puri, who reported their experimental and clinical endoscopic Teflon injection results in 1984 (6). Since then, a lot of different substances have been used until the introduction of Deflux (7). EIT is nowadays recommended in selected centers as the first line therapy when intervention is needed (8, 9). It is considered preferable to ureteral reimplantation, which may be reserved for exclusive use in children not responding to EIT (9). In addition, parents of children with VUR are very likely to express a preference for EIT among all alternative options proposed (10). While open ureteral reimplantation has a maximum reported success rate of 98%, the most recently reported maximum radiographic EIT short-term cure rate is about 94% (11). Although EIT provides approximately a medium 80% cure rate, concerns about its long-term efficacy and delayed complications have resulted in a controversy over its real usefulness in recent years (4). Delayed post-injection ureteral obstruction is rare but may occur years postoperatively (11). EIT needs further evaluation of long-term outcomes (1).

Researchers have reported a variable success rate 50–94% of EIT, indicating differences in study design and methodology (12). There is significant disagreement on what a successful EIT constitutes, between the absence and the downgrading (presence of grade I-II or ≥2 grades improvement) of VUR, in combination or not with a recurrent febrile urinary tract infection (UTI) after injection (11, 12). One more or multiple reinjection procedures are frequently necessary in about 10–30% of cases with failed EIT (13, 14). Persistent VUR, is defined as that which is present three months after EIT, detected by follow-up cystography (15). In addition, reflux can recur in about 5–25% of children after a successful EIT (16, 17). Recurrent VUR, is defined as a proven VUR by repeated voiding cystourethrography (VCUG) in children with febrile UTI, any time after the first negative post-EIT cystography follow-up (15).

EIT success is evaluated in a short period of time, as in most studies it is determined after three months from the injection. If follow-up periods were longer, the recurrence rate might be higher (18, 19). There are reports of recurrence VUR rates as high as 26% after one year and 54% after two years from EIT (18). Fresh development of contralateral reflux after EIT for unilateral VUR is reported in the literature as well (9, 20). Persistent or recurrent VUR puts the children at risk for further UTIs and possible kidney damage. The precise pre/peri/post-operative factors affecting EIT success rates and outcome have not yet been clearly determined (21, 22). There is no agreement on which factors are the most influential for the endoscopic resolution of VUR, even with the use of artificial neural networks (23). We report the studies with positive correlation of factors with EIT cure rate, although there are many with opposite results.

EIT TECHNIQUE

EIT involves submucosal injection of a bulking agent to provide tissue augmentation and to improve the ureteral orifice valve mechanism (9, 24) (Figure 1). In the traditional STING (Subureteral Transurethral Injection) procedure, the needle is introduced under the bladder mucosa 2–3 mm below the refluxing orifice (9, 24). In the intraluminal HIT (hydrodistension implantation technique) technique, which has increased the success rate significantly (from 80% to 90%) (9, 16, 25–27), the needle is introduced into the mucosa inside the ureteral tunnel (9, 24). The advantages of HIT over STING include better visualization of the distal ureteral lumen with the aid of hydrodistension, more accurate placement of the injector needle at the desired position, better coaptation of ureteral orifice (27). In addition, the HIT technique has statistically significant success rate against STING technique for high grade reflux cases (28). Unlikely, other multivariate analyses have failed to demonstrate a significant difference in outcomes between the two techniques (22, 29, 30). The double HIT technique, currently achieving the highest success rates, involves one proximal and a second distal intraluminal ureteral injection site (9, 15). A combination of HIT and STING techniques can be performed in cases of HIT failure to coapt the ureter (31).

BULKING AGENTS

Over the years, many injectable agents have been investigated but only few of them are widely used. Thousands of children have been treated with different agents. Only four – Teflon, Deflux, Collagen, Silicone/Macroplastique – have been used in humans in large enough numbers to enable assessment of effectiveness (16, 32). The risk of new renal scarring is greatest among infants and young children aged under 5 years and therefore, the bolus created, using an injectable substance should persist for at least a period of 3 to 5 years (9). Deflux is now the most widely used and the most extensively studied bulking agent, which completely substituted the Teflon (16). Silicone/

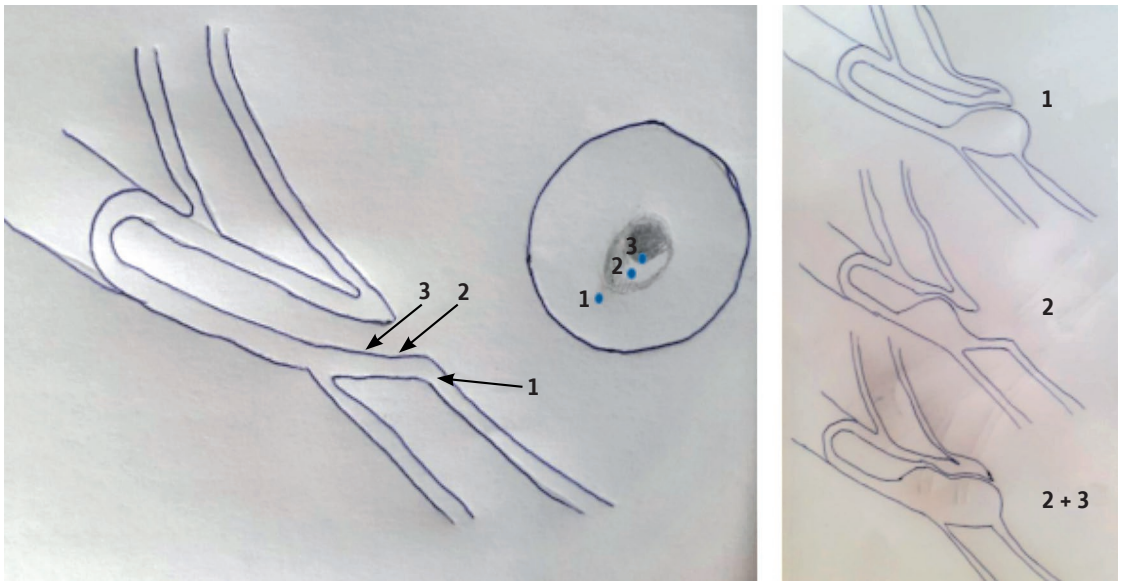

Fig. 1 Algorithm of endoscopic technique injection sites (1 = STING, 2 = HIT, 2 + 3 = Double HIT).

Macroplastique has been used with effectiveness that approaches that of Deflux (16). Biocompatibility of the substance, lack of potential for migration from the injection site, and absence of fibrosis or aggressive granulomatous reaction spreading to adjacent tissue are the ideal properties for the dominant or preferable injectable agent (4, 9, 12). The use of new polymer agents, like polydimethylsiloxane and polytetrafluoroethylene, is related with less recurrence rate in comparison with Deflux (33).

Studies have reported an increased success rate with the injected Vantris polymer agent and approved it as a more effective and promising material (with better stability and long-term durability) regardless of other confounding variables and the EIT technique (4, 34–39). In addition, Vantris presents more efficacy against Deflux in high grade VUR cure (40). However, ureteral obstruction and severe fibrosis on injection site are more commonly seen with Vantris use, and long-term data should be followed (4, 39–42). In a recent study, Vantris is presented as a completely effective agent for treating all high grade (IV–V) of primary (100% success rate after the second injection) and complex (100% success rate after the third injection) VUR in children, with the significant disadvantage of late (occurred within 3 years of EIT) severe ureteral obstruction in 8% of patients, that required surgical reimplantation (43).

PERIOPERATIVE FACTORS

There is a significant correlation between the endoscopically showed shapes of the ureteral orifice and their hydro-distension grade before the injection with the VUR grades and the EIT outcome (26, 44, 45). The cure rate in children with golf-hole type orifices is significantly lower than that of other types (46). The creation of a mound that elevates and coapts the orifice is the most important factor determining the success of EIT (4, 29). This volcano mound after the injection morphology of ureteral orifice is associated with a statistically significant increase in reflux resolution (19, 22, 45). The achievement of a mound mass height measuring 9.8 mm in maximal vertical diameter, at intraoperative ultrasound simultaneously with endoscopic procedure, maintains a significant correlation with EIT success (47). On the other hand, moderate injected volume >1 ml is a significant predictor of treatment failure (22). Intraoperative cystography following injection may help to determine immediate success and identify cases of new contralateral reflux but there is insufficient correlation with the standard 3-month postoperative VCUG (48). Thus, intraoperative cystography fails to show clinical utility to predict the EIT outcome (49).

LEARNING CURVE OF EIT

Independently of the technique used, there has been a learning curve associated with endoscopic VUR correction (50). EIT cure rates related to the surgeon are increasing and the requirement for reinjections decreasing as experience with the technique is improved (21, 46, 51). A combination of adequate experience and great skill in EIT is required to obtain results that could be favorably comparable to ureteral reimplantation, because there is a strong belief that nearly all endoscopic failures are related to unrecognized or unappreciated technical errors (9). In one study, success rates increased from 60% for the first 20 of 134 patients, to 80% for the last 20 cases (52). With increasing experience, not only high grade primary VUR, but also secondary reflux (duplex system), are considered eligible for EIT (51, 53). A multivariate analysis demonstrates that physician experience is an independent predictor of endoscopic VUR correction rates (54). Physician's experience and adjustments in clinical-surgical practice are associated with a reduced ureteral reimplantation rate (51, 55).

VUR GRADE AND MULTIPLE INJECTIONS

VUR grades II–III are considered as middle grade reflux and grades IV–V as high. In systematic reviews the reported success rates were 80–90% for grade I, 79–84% for grade II, 72% for grade III, 59–63% for grade IV, and 51–62% for grade V (56, 57). Lower success rates are presented in higher grades of VUR (19, 21, 46, 57, 58), and application of second and third injections increases the success rates (21, 46, 57). EIT is successful in about 50% of children with high grade VUR, and multiple injection procedures are frequently necessary to achieve a success rate about 85% (16). In a study, reflux was cured after the first STING injection in 100% of the ureters with grade II reflux, 65% of the ureters with grade III reflux and 50% of the ureters with grade IV reflux (28). The overall success rate increased with the second STING injection to 73% and 67% for grades III and IV reflux (28). Reflux was cured after the first HIT injection in 100% of the ureters with grade II reflux, 74% of the ureters with grade III reflux and 55% of the ureters with grade IV reflux (28). The overall success rate increased with the second HIT injection to 85% and 76% for grades III and IV reflux (28). Repeated EIT procedures are found to be successful in grade III and IV VUR, but children presenting with grade V should undergo ureteral reimplantation if the first trial of EIT results in failure as repeated injections have been proved unsuccessful in this grade (59). Recently, increasing evidence has been emerging to support the use of EIT in children with grade V VUR (24, 43, 60).

OTHER PREOPERATIVE FACTORS

Age is found to be a significant predictive factor of EIT success (40). Puri et al. presented their experience with endoscopic treatment of VUR in infants less than 12 months of age, asked about the necessity to overcome general anesthesia in such young patients with increased rate of VUR resolution over time (61). We can perform EIT in infants (62, 63), but we should rather not, because the effectiveness is lower than in children treated at an older age, there is not much experience, and the incidence of high-grade VUR is significantly higher as DMSA changes too (62). Age ≥6 years is a positive predictor (22), and age <1 year is a negative predictor of EIT success (33, 64). Younger age, especially age of 0–12-month-old, is a significant predictor of postoperative febrile UTI recurrence (65).

Radiologic success of EIT is statistically less common in males compared to females (66). There is a significant positive correlation between grade, bilaterality, recurrent preinjection UTIs, history of voiding dysfunction, defects on DMSA scan, and persistent or recurrent VUR after EIT (67). A study revealed that younger age, grade IV–V VUR and renal scarring are significant variables for the failure of endoscopic treatment after the first injection (68).

VCUG timing for VUR is found to be an independent factor for VUR resolution after EIT, and a filling reflux has significant lower success rate than a voiding reflux, especially in children with high grade VUR (69). Ureters that refluxed during the voiding phase have an approximately threefold independent odds of successful EIT, compared to those that refluxed during bladder filling (70). Distal ureteral diameter ratio at preoperative VCUG provides an objective measurement of VUR and appears as a predictive tool for clinical outcome and success after EIT (71, 72). It is significantly higher in children with high grade VUR and/or DMSA renal uptake ≤40% (72). Its predictive value for EIT success is more significant than VUR grade (72).

Renal scars on preoperative scintigraphy are significantly associated with postoperative febrile UTI and possible EIT failure (15, 21). Renal units with preoperative DMSA changes (hypoplasia, scars, uptake ≤40%) are at higher recurrence and lower cure risk, as a possible result of maldevelopment (15, 19, 46, 72, 73).

A factor that influences VUR resolution is voiding dysfunction, which refers to the presence of bladder filling and/or emptying lower urinary tract symptoms (urge, incontinence, weak stream, hesitancy, frequency, accompanying bowel problems) (1). Bilaterality is also a significant prognostic factor for the success rate of EIT (65–71). The success rate of EIT is significantly reduced in the presence of abnormal voiding habits, and additional injections are needed (21, 33, 74, 75). Duplicated systems and complex cases of VUR have lower cure rates (4, 31, 45), but are not associated with EIT failure (29, 31, 55). More recent studies have reported better success rates after a single injection (43, 55, 60, 76, 77).

It seems clear that a girl with high grade VUR and DMSA changes is at relatively high risk for recurrence than a boy with low grade VUR and no DMSA changes (15). Children aged less than two years or with ≥3 preoperative febrile UTI or with documented voiding dysfunction or with grade IV–V VUR, are 13 times more likely to have EIT failure (78). Children with ≥2 predictive factors, including febrile UTI, voiding dysfunction, and/or defects on DMSA, may not be optimal candidates for EIT (67).

POSTOPERATIVE FACTORS

Postoperative febrile UTI is significantly associated with EIT failure (21). Recurrences of febrile UTI may occur after 3 years of follow up and within the first 5 years after EIT (79, 80). Children with >3 episodes of recurrent preinjection UTI are 8.5 times more likely than those with only one episode to have an infection after EIT (67, 81). Female sex, older children and voiding dysfunction are the most important risk factors in the development of febrile UTI during long-term follow-up after successful EIT correction of VUR (81, 82). Furthermore, reinjections in children with postoperative febrile UTI and grade III-IV VUR seem to be unsuccessful (21). Mound detection at the first postoperative ultrasound is most critical factor than the intraoperative mound shape, and a strong and more reliable predictor of a successful EIT outcome (19, 45, 66). Calculated ellipsoid volume (CEV) of injected agent mounds is defined as $4/3\pi \times \text{height}/2 \times \text{length}/2 \times \text{width}/2$, based on 3-months postoperative ultrasound dimensions (22, 45). CEV>25% of injected agent volume is a positive predictor of EIT success (22, 31). The achievement of a maximal mound height in transverse vesical section measuring

at least 10 mm at three months postoperative ultrasound suggests a major predictive parameter for VUR resolution after EIT (64).

CONCLUSIONS

With the wide use of EIT and long-term follow-up, more treatment failures are being encountered, despite the accumulated endoscopic experience and the apparent by time success rates improvement. There is no agreement on which factors are the most influential for EIT successfulness. The risk factors affecting the outcome of EIT management for VUR studied herein are summarized in Table 1. The high grade VUR and treatment at infancy, as well as the presence of positive DMSA or urinary dysfunction, are factors associated with reflux persistence or recurrence after EIT. The preoperative filling than voiding VUR and the large ureteral diameter at VCUG are strong independent predictive factors for EIT failure. Duplex ureters are no longer considered as a contraindication for EIT. Even with widespread experience, the success rate in high grade VUR with a single injection of any of the available agents still fails to equal that of following ureteral reimplantation. Vantris is a new promising bulking agent for additional improvement of the double HIT method's results. Postoperative febrile UTI and/or poor ultrasound visualization of the ureteral orifice mound suggest negative predictive parameters for VUR cure after EIT. The endoscopic VUR approach should be risk-adapted to current knowledge. More experience and longer-term follow-up are needed. More prompt and aggressive approach with ureteral reimplantation is mandatory for children who have grade V VUR and low success rate at the beginning.

Tab. 1 Risk factors affecting the outcome of VUR endoscopic injection therapy.

VUR grade
Re-injections
Endoscopic technique
Bulking agent
Surgical endoscopic experience
Age (≥ 6 or ≤ 1 years old)
Gender
DMSA scan defects (hypoplasia, renal scar, uptake ≤40%)
Recurrent preinjection UTIs
Post-injection UTIs
Voiding dysfunction history
Bilateral VUR
Double ureteral system
VCUG timing of VUR (filling vs voiding)
Preoperative-VCUG distal ureteral diameter ratio
Endoscopically showed shapes of the ureteral orifice
Hydro-distension grade of the ureteral orifice
Endoscopically creation of a volcano mound
Moderate injected volume >1 ml
Intraoperative ultrasound mound mass height
Postoperative ultrasound mound volume (3 months)
Postoperative ultrasound mound mass height (3 months)

Abbreviations: vesicoureteral reflux (VUR), urinary tract infection (UTI), hydrodistension implantation technique (HIT), voiding cystourethrography (VCUG).

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