Review article
Korean J Pediatr 2013;56(4):145-150
http://dx.doi.org/10.3345/kjp.2013.56.4.145
eISSN 1738-1061•pISSN 2092-7258

Korean J Pediatr

Endoscopic treatment of vesicoureteral reflux in pediatric patients

Jong Wook Kim, MD, PhD, Mi Mi Oh, MD, PhD
Department of Urology, Korea University Guro Hospital, Seoul, Korea

Endoscopic treatment is a minimally invasive treatment for managing patients with vesicoureteral reflux (VUR). Although several bulking agents have been used for endoscopic treatment, dextranomer/hyaluronic acid is the only bulking agent currently approved by the U.S. Food and Drug Administration for treating VUR. Endoscopic treatment of VUR has gained great popularity owing to several obvious benefits, including short operative time, short hospital stay, minimal invasiveness, high efficacy, low complication rate, and reduced cost. Initially, the success rates of endoscopic treatment have been lower than that of open antireflux surgery. However, because injection techniques have been developed, a recent study showed higher success rates of endoscopic treatment than open surgery in the treatment of patients with intermediate- and high-grade VUR. Despite the controversy surrounding its effectiveness, endoscopic treatment is considered a valuable treatment option and viable alternative to long-term antibiotic prophylaxis.

Key words: Vesico-ureteral reflux, Endoscopy

Corresponding author: Mi Mi Oh, MD, PhD
Department of Urology, Korea University Guro Hospital, 148 Gurodong-ro, Guro-gu, Seoul 152-703, Korea
Tel: +82-2-2626-1310
Fax: +82-2-2626-1321
E-mail: mamah77@paran.com

Received: 12 September 2012
Accepted: 2 November 2012

Introduction

The management goals for children with vesicoureteral reflux (VUR) are to prevent febrile urinary tract infection (UTI) and renal scarring and to minimize patient morbidity[1-3]. Ideally, the treatment choice should be evidence-based and may vary depending on each child's age, sex, reflux grade, history of recurrent UTI, ipsilateral renal function, associated ureterorenal anomalies, and associated bladder/bowel dysfunction, in addition to parental and provider experience and preference. In general, VUR treatment can be either conservative or interventional and may include continuous antibiotic prophylaxis (CAP), endoscopic treatment, or open antireflux surgery[4].

CAP has been the cornerstone of VUR treatment since its initial success in the mid-1970s[5]. However, CAP involves the risk of bacterial resistance accompanied by breakthrough UTIs and depends on patient compliance, which has been reported to be poor. Hensle et al.[6] revealed that only 17% of pediatric patients with VUR who were receiving prophylactic antibiotics were compliant with therapy. Of these patients, 58% had a diagnosis of a UTI within 1 year. Furthermore, several large prospective randomized controlled trials have shown medical therapy to have little to no benefit in terms of decreasing the incidence of febrile UTI or renal scarring[3].

Open antireflux surgery remains the treatment of choice for high-grade reflux. There have been reports of a correlation between reflux grade and frequency of renal damage[7] and between reflux grade and acute photon defects[8]. The various intravesical and extravesical techniques that have been described share the basic principle of lengthening the intramural part of the ureter and have been shown to be safe, with low complication

rate and excellent success rates[9]. Although open antireflux surgery offers a high cure rate, this procedure usually requires a prolonged hospital stay and is not without complications. The American Urological Association (AUA) reported that the rate of ureteral obstruction requiring operation after open antireflux surgery was 0.3% to 9.1%, on the basis of 33 studies[10]. Moreover, the AUA reported the persistence of VUR after open antireflux surgery for grade V VUR in 19.3% of the cases.

Endoscopic treatment is a minimally invasive management of VUR. Endoscopic subureteric injection was first described in 1981[11] and later popularized by O'Donnell and Puri[12]. Subsequently, several bulking agents have been used for endoscopic treatment, such as polytetrafluoroethylene (PTFE; Teflon, DuPont Co., Wilmington, DE, USA), bovine collagen, polyacrylate-polyalcohol copolymer (Vantris, Promedon, Cordoba, Argentina), polydimethylsiloxane (Macroplastique, Uroplasty Inc., Geleen, The Netherlands), and calcium hydroxyapatite (Coaptite, BioForm Medical Inc., Franksville, WI, USA). Currently, dextranomer/hyaluronic acid (Dx/HA; Deflux, Oceana Therapeutics Inc., Edison, NJ, USA) is the only bulking agent approved by the U.S. Food and Drug Administration (FDA) for treating VUR. Endoscopic treatment has increased rapidly after the approval of the Dx/HA copolymer for its use in the United States after 2001[13,14]. Although the per-patient administered volumes of Dx/HA have steadily increased, the use of endoscopic treatment seems to have currently plateaued[15]. Some providers may have increased the administered volume to treat high-grade reflux.

Materials for endoscopic treatment

1. PTFE

PTFE is one of the most widely used biomaterials in medicine. The medical applications of PTFE include vascular grafts, heart valves, and tissue replacement patches[16]. PTFE was the first biomaterial used for endoscopic treatment of VUR and was commonly used in European countries owing to its relatively inexpensive price and long-term durability. However, injection of PTFE requires special equipment because of its high viscosity. The size of a PTFE molecule is only approximately 4–100 μm; thus, it has a high potential to spread to other organs. In an experimental model and some clinical studies, numerous particles of PTFE were recovered from the lungs and brain after PTFE injection for VUR. Although no adverse neurological effects have been reported clinically, some particles may lodge in the brain, where they can block cerebral microcirculation[17,18].

2. Cross-linked bovine collagen

Collagen was intensively used in the medical industry for the manufacturing of cardiac valves and hemostatic agents. Cross-linked bovine collagen (Zyplast, Inamed Co., Santa Barbara, CA, USA) can be injected even with a small-diameter injection needle and cause minimal tissue reaction when locally injected. Injection of this compound also induces collagen production by infiltrating fibroblast cells and therefore causes less inflammation. Moreover, collagen particles migrate minimally[16]. Owing to these features, collagen initially seemed a promising substance for VUR. However, Haferkamp et al.[19] showed that the volume of the injected collagen decreased in long-term follow-up. The success rate was 93% at 1 month after the injection but decreased to 35% after 1 year. Moreover, there have been reports of the development of connective tissue diseases subsequent to collagen injection, including systemic lupus erythematosus, polymyositis, and dermatomyositis[20].

3. Polydimethylsiloxane

Polydimethylsiloxane is a solid, elastomeric, silicone, soft tissue bulking material that has been incorporated into a patented medical device called Macroplastique. The injectable material comprises soft, flexible, highly textured implants of heat-vulcanized polydimethylsiloxane suspended in a bioexcretable polyvinylpyrrolidone carrier hydrogel. The carrier gel is a pharmaceutical-grade, water-soluble, low-molecular-weight povidone that has been studied and safely used clinically for many years[21].

Polydimethylsiloxane has been found to have a mean maximum particle diameter of 209 μm[22]. Because it is highly viscous, its injection requires an administration gun that can withhold high pressure. To minimize particle migration, polydimethylsiloxane is engineered to create an elastomer instead of the less cross-linked silicone gels or the noncross-linked silicone oils used in breast implants. After injection, its consistency allows the polydimethylsiloxane implant to be held in place. The carrier gel is then absorbed and exchanged for a natural reactive transudate into which host fibroblasts and macrophages subsequently deposit collagen, thus encapsulating the implant. The absorbed hydrogel is removed from the implantation site via reticuloendothelial cells and excreted unmetabolized by the kidneys[21]. In animal experiments, silicone was found to migrate locally and distantly[23,24]; therefore, the FDA did not approve its use for VUR treatment. In addition, it has been found that silicone particles cause neuropathy by inducing fibrosis around nerve cells[25]. Because of this major side-effect, its use has greatly diminished.

4. Autologous chondrocytes

The use of autologous chondrocytes for the endoscopic treatment of VUR was proposed after successful animal experiments. Caldamone and Diamond[26] harvested chondrocytes from ear cartilage and incubated them for 6 weeks. However, the need to

 http://dx.doi.org/10.3345/kjp.2013.56.3.145

perform 2 procedures under anesthesia, the first for harvesting cartilage cells for the preparation of the injection solution and the second for the endoscopic implantation, reduced the popularity of the substance. Moreover, a considerably high recurrence rate in children after 1 year raised a serious question about the reliability of this tissue-augmenting substance[16,26].

5. Calcium hydroxyapatite

Calcium hydroxyapatite has been used as an implant for dental restoration and bone healing for longer than 25 years. It comprises smooth 75- to 125-µm spheres of synthetic calcium hydroxyapatite suspended in a gel composed mainly of glycerin and water, with a chemically modified, naturally occurring polysaccharide sodium carboxymethylcellulose as support[27]. It can be easily injected with a small-diameter injection needle. However, although the short-term success rate of subureteric injection of calcium hydroxyapatite for 23 ureters was favorable, the 47- to 60-month long-term success rate was decreased to 47.4%; hence, its durability was questioned. Particularly in 1 reported case, the migration of the injected material resulted in a nonfunctioning kidney[28].

6. Dx/HA

After it was introduced by Stenberg and Lackgren[29] in 1995, Dx/HA has been the most widely used bulking agent for the endoscopic treatment of VUR. It is also the most studied endoscopic material, and there are enough available long-term data to clearly understand its efficacy[16]. Currently, Dx/HA is the only material approved by the FDA for treating VUR. Deflux is composed of dextran polymer microspheres and nonanimal hyaluronic acid mixed to form a viscous gel with 2 components, both of which are made up of polysaccharide (sugar-based) molecules. Dextranomer microspheres are formed by cross-linking dextran polymers into porous beads of 80–250 µm in diameter[16]. After injection, dextranomer microspheres cause deposition of fibroblasts and collagen. Dx/HA is a biodegradable material that can be easily injected, with most of its molecules larger than 80 µm, thus having less potential of migrating to other organs. In addition, it is known to not cause inflammation and mutation. Moreover, Dx/HA can be well encapsulated and maintained in injected sites.

The overall success rate of Dx/HA use ranged from 68% to 92%, depending on the VUR grade[30-32]. Kirsch et al.[31] revealed that the short-term results with the hydrodistention implantation technique (HIT) may be close to those after open antireflux surgery. Whether Dx/HA has long-term durability is not clear, but the current long-term follow-up data are insufficient. Lackgren et al.[33] reported that although Dx/HA was shown to resolve reflux in the short-term, their 2- to 5-year long-term trace study revealed a recurrence rate of almost 13%.

Developments of the endoscopic treatment

The original subureteric Teflon injection (STING) procedure was originally designed for injecting PTFE. The suggested injection site is 2 to 3 mm below the affected ureteric orifice, at the 6 o'clock position. The needle enters the bladder mucosa and advances 4 to 5 mm into the submucosal plane, creating a mound that elongates the intramural ureter[12]. This method has been shown to be safe and minimally invasive for VUR treatment[30,33].

The modified STING procedure, later known as the HIT, was introduced in 2004. Kirsch et al.[31] modified this procedure by inserting the needle into the submucosal tunnel of the ureter via hydrodistention. The investigators reported a success rate of 92% using the HIT procedure compared with the 79% using the conventional STING procedure, with better results in patients with high-grade reflux.

In recent years, the HIT procedure has been modified to include 2 tandem intraluminal ureteric tunnel injections (double HIT)[34,35]. Before injection, the bladder is emptied, and the ureteral orifices are hydrodistended and graded according to the hydrodistention grading system (H0–H3)[36]. The first injection is made at the 6 o'clock position mid tunnel and coapts the proximal tunnel. A second injection is made at the distal aspect of the tunnel at the location of the ureteral orifice and serves to coapt the ureteral meatus[34]. Kalisvaart et al.[34] evaluated 54 patients who underwent double HIT and revealed 93% clinical and 93% radiographic intermediate/long-term success rates.

Endoscopic treatment for VUR has gained great popularity owing to its low invasiveness and high efficacy. Some investigators have suggested endoscopic treatment as a first-line treatment alternative to CAP or surgical treatment[30-32,37-39]. Several obvious benefits are driving this trend, including the short operation time, short hospital stay, minimal invasiveness, low complication rate, and reduced cost[40]. Although the medical cost may vary, the physical and mental burdens are significantly decreased[41]. Another advantage involves the high success rates in low-grade reflux, making endoscopic treatment a viable alternative to long-term antibiotic prophylaxis[42]. This hypothesis has been proven in a study performed among 91 families with children who had reflux with a mean duration of 2 years[43]. If a child was predicted to have VUR for up to 1 year, most parents chose prophylactic antibiotics with yearly voiding cystourethrography. However, if the duration of prophylactic antibiotic use were to exceed 3 years, 60% of the parents would choose endoscopic treatment over open surgery, although the child may have to undergo repeat injections, with a 20% risk of persistent reflux. Meanwhile, the increased use of endoscopic treatment have not resulted in decreased use of open antireflux surgery[13,14], indicating a shift in surgical indications in some centers or

regions[37].

In a meta-analysis that examined several types of injections (including Dx/HA) in 8,101 ureters, primary success rates of 78.5% for grades I and II, 72.0% for grade III, 63.0% for grade IV, and 51.0% for grade V reflux were demonstrated. In cases of failed first treatment, the second and third injections had success rates of 68% and 34%, respectively[44].

One major disadvantage of the endoscopic management of reflux is its poor therapeutic outcome in patients with high-grade reflux as compared with open antireflux surgery; therefore, endoscopic treatment may not be used in this clinical scenario[42]. Most treatment failures are due to extrusion of the material immediately after injection, postoperative decrease in volume, and migration of the implant[45]. However, a recent study showed very high success rates repetitive injections were administered in children with intermediate- and high-grade VUR compared with those in open surgery[46].

Investigators have reported a variable success rate (50–94%)[31,47], indicating differences in methods and study design, including differences in patient selection in addition to surgeon or technical factors[48]. Independent of the technique used, there has been a learning curve associated with endoscopic VUR correction[49]. Kirsch et al.[50] reported a 60% success rate in their first 20 patients compared with the 80% success rate in their most recent 20 patients. Herz et al.[21] achieved a success rate of 46% in 28 refluxing ureters during the first 6 months of their study. In the subsequent 18 months, the overall correction rate was 93% in 84 ureters. Using multivariate analysis, Lorenzo et al.[51] demonstrated that physician experience was an independent predictor of VUR correction rates.

There is significant dissent as to what constitutes a successful endoscopic treatment. In the United States, successful endoscopic treatment is typically defined as the absence of VUR[47,52]; however, in several European studies, the presence of grade I or II VUR (downgrading) after injection is considered successful[33,53,54]. If the goal is the prevention of recurrent febrile UTIs, the clinical success rate is high (>90%) in most modern series. However, if success is defined radiologically as the absence of VUR after 1 treatment, then the success rate falls between 50% and 93%. Combining these 2 definitions (i.e., no VUR and no febrile UTI after a single treatment) may result in an even lower success rate[55].

Recently, the effectiveness of CAP has been intensely discussed. Some studies comparing the conservative management with or without CAP suggested that there was no significant difference between the 2 groups in patients with low-grade VUR[56-58]. Owing to controversies, the new guideline does not universally recommend CAP for children with VUR. Paradoxically, "downgrading to the level of no antibiotics" can be used to define treatment success.

Conclusions

There are several options for managing VUR in pediatric patients. Treatment options should be evidence-based and should depend upon the condition of each patient. Endoscopic treatment of VUR has developed rapidly, and has replaced some aspects of the antibiotic treatment and open surgery. Many researchers have been engaged in developing new techniques and safe materials. Open antireflux surgery remains the treatment of choice for high-grade reflux. However, endoscopic treatment has several advantages for grade II to IV reflux. Although its effectiveness for high-grade VUR has been inconsistent, endoscopic treatment is currently considered a valuable treatment option and viable alternative to long-term antibiotic prophylaxis.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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