Recent Advances in the Endoscopic Treatment of Vesicoureteral Reflux

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The management of vesicoureteral reflux, the most common urological anomaly in pediatric patients, has changed dramatically in the past decade due to the increasing acceptance of endoscopic injection therapy as a minimally invasive and valid form of therapy. Advances in the composition of injectable materials allow easier placement with favorable safety profiles. Specifically, dextranomer/hyaluronic acid has emerged as the favored bulking agent, with quick acceptance and prevalent use soon after its introduction in different countries. However, there are few clear clinical rules to follow, and the choice of management is usually guided by informed parental preferences and the surgeon’s treatment philosophy. Important factors that have fostered improvements in endoscopic injections include increased success through advances in injection techniques and better patient selection. Furthermore, clinicians are generally concerned about the possibility of postoperative ureteral obstruction, the durability of the implant volume, and the long-term effects after implantation of dextranomer/hyaluronic acid. In this review, we present the current status of treatment outcomes with endoscopic injection therapy. (JTUA 19:1-4,2008)

Key words: vesicoureteral reflux, dextranomer/hyaluronic acid copolymer, endoscopic treatment.

INTRODUCTION

Vesicoureteral reflux (VUR), the most common urological anomaly in pediatric patients, affects 1% of children and may be present in 30%~50% of those who present with urinary tract infection. Treatment options for VUR include observation with antibiotics prophylaxis, an open or laparoscopic ureteroneocystotomy, and the subureteral injection of bulking agents. To prevent such complications as recurrent pyelonephritis, renal scarring, and renal impairment, VUR must be identified and appropriately treated. Two of the big challenges clinicians face today are deciding who needs treatment and which modality is the best one for a particular child. We all probably agree on the fact that not all VUR needs surgical intervention and that treatment does not always prevent complications. In recent years, long after its first description, the widespread acceptance of endoscopic subureteral injection therapy has revolutionized the management of VUR in children. The developing paradigm shift offers surgical correction on an outpatient basis and avoids the prolonged antibiotics prophylaxis or the invasiveness and morbidity of ureteral reimplantation. Although endoscopic management of VUR is popular among parents and practitioners, appropriate skepticism and concerns over the indiscriminate use of subureteral injection therapy have been raised. In this review, we present outcomes and durability for the endoscopic treatment of VUR using dextranomer/hyaluronic acid copolymer (Dx/HA) based on recently published literature (2003~2007).

Success Rate and Complications

In a recent meta-analysis, Elder et al. demonstrated resolution rates of 79% for ureters with grades I and II, 72% with grade III, and 65% with grade IV following 1 injection; all of these are inferior to the overall success rate of approximately 96% for open surgical procedures. However, a different or higher success rate was observed in recent publications reported in different groups (Table 1).

Puri et al. prospectively studied the use of Dx/HA in 113 children with 166 affected ureters. Eighty-one girls and 32 boys, aged between 3 months and 10 years with primary VUR grades II–V, received an endoscopic injection of Dx/HA. Early results with a median follow-up of 6 months revealed the correction of reflux in 143 of 166 ureters, or 86%, after a single injection. The suc-

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The success rate of multiple injections was 100%, and there were no complications from the injections. Although a 100% cure rate is encouraging, the authors defined "correction" as a reduction in reflux to grade 0 or I on the International Reflux Classification. Obviously, correction does not mean grade 0 in that study. Furthermore, another study showed that most relapse occurs within the first year, but can occur up to 3 years after the injection.6

In 2003, Kirsch et al. reported on 134 patients, aged 7 months to 15 years, with at least 3 months of post-injection follow-up. Success was defined as grade 0 VUR confirmed on a postoperative voiding cystourethrogram (VCUG) at 3 months. After 1 endoscopic treatment, 72% of patients achieved success. Treatment success rates for grades I–IV were 90%, 82%, 73%, and 65%, respectively. However, new contralateral reflux was seen in 6 patients (4.5%) with no history of VUR on previous studies. A learning curve for the procedure was revealed, with an overall success rate of 60% for the first 20 cases vs. an 80% success rate for the last 20 patients.7 Recently, Kirsch et al.8 described a modification to the subureteral injection procedure that may have contributed to their later success. In 2004, they reported that 122 patients had undergone a subset analysis comparing traditional injections (n = 52) with modified injections (n = 70). The simple modification of the procedure revealed a statistically significant improvement in the outcome of the procedure, with an overall success rate of 89% in the modified group compared to 71% in the standard group.

Capozza et al.6 retrospectively reviewed 1244 patients (with 1694 refluxing ureters) treated with endoscopic injections in Rome, Italy. Since 1995, 788 patients with 1050 ureters have undergone a subureteral injection with Dx/HA for VUR grades II–IV. VCUGs were obtained at 3 and 12 months postoperatively. The length of follow-up was a minimum of 12 months, with an average of 7.5 years. The overall success rate (defined as grades 0–1 reflux) with a Dx/HA injection was 82% for all grades. Two types of complications occurred with prolonged, severe hematuria in 1 child and temporary obstruction of the ureterovesical junction in 8 patients. The overall complication rate was 0.5% (9/1694). The authors stated that the success rate of endoscopic treatment was significantly reduced by the presence of abnormal voiding habits and recommended correction of voiding dysfunction prior to surgical management. In 2006, Prui et al.9 reported prospective results on 692 children with a median age of 2.1 years with VUR grades II–V who underwent endoscopic injections of Dx/HA. After 1 injection, 86.5% of patients achieved success. Ultimately, 96% of patients achieved success after multiple injections. Reflux recurred in 2 ureters (0.2%) after an initially successful injection.

In general, the reported rate of major complications from subureteral injections is very low and compares favorably with complications reported after open surgery. Vandersteen et al.10 retrospectively reviewed the records of all symptomatically obstructed patients undergoing a Dx/HA injection at 4 institutions. They concluded that a Dx/HA injection is associated with a small risk of postoperative ureteral obstruction requiring endoscopic intervention, with an overall incidence of < 0.7% of patients injected. All patients with obstruction achieved complete resolution of symptoms after removal of the temporary ureteral stents. Specifically, obstruction is an uncommonly detected problem, as is transient voiding dysfunction seen in patients after extravesical reimplantation. Furthermore, despite concerns about fibrosis and difficulty with future interventions, reimplantation does not appear to be particularly difficult after a failed endoscopic injection.11

Table 1. Outcomes of recent studies of endoscopic injections

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>VUR grades</th>
<th>No. of cases</th>
<th>No. of ureters</th>
<th>Follow-up duration</th>
<th>Success (w/ a SI)</th>
<th>Success (w/ MIs)</th>
<th>Complications</th>
<th>NCVUR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>Puri et al.</td>
<td>2–5</td>
<td>113</td>
<td>166</td>
<td>6 mo</td>
<td>86%</td>
<td>100%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2003</td>
<td>Kirsch et al.</td>
<td>1–4</td>
<td>134</td>
<td>NA</td>
<td>3 mo</td>
<td>72%</td>
<td>NA</td>
<td>0</td>
<td>0.5%</td>
</tr>
<tr>
<td>2004</td>
<td>Kirsch et al.</td>
<td>1–4</td>
<td>181</td>
<td>NA</td>
<td>3 mo</td>
<td>76%</td>
<td>89%</td>
<td>0</td>
<td>4.5%</td>
</tr>
<tr>
<td>2004</td>
<td>Capozza et al.</td>
<td>2–4</td>
<td>788</td>
<td>1050</td>
<td>7.5 yr</td>
<td>82%</td>
<td>NA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2005</td>
<td>Lavelle et al.</td>
<td>1–4</td>
<td>52</td>
<td>80</td>
<td>3 mo</td>
<td>80%</td>
<td>NA</td>
<td>0</td>
<td>0.5%</td>
</tr>
<tr>
<td>2006</td>
<td>Routh et al.</td>
<td>1–4</td>
<td>225</td>
<td>NA</td>
<td>3 mo</td>
<td>64%</td>
<td>NA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2006</td>
<td>Puri et al.</td>
<td>2–5</td>
<td>692</td>
<td>1102</td>
<td>3 mo</td>
<td>89%</td>
<td>96%</td>
<td>0</td>
<td>8.3%</td>
</tr>
</tbody>
</table>

NCVUR, new contralateral vesicoureteral reflux; SI, single injection; MIs, multiple injections; NA: not available.
Durability and Predictors of Outcomes

One vial of Dx/HA (1 ml) contains 50 mg dextranomer microspheres and 17 mg hyaluronic acid. Basically, dextranomer is slowly degraded by hydrolysis, whereas hyaluronic acid acts as a transport medium and disappears within several weeks. A giant-cell inflammatory reaction and fibrotic pseudo-encapsulation contribute to the durability. Sternberg et al.12,13 observed that the implant volume was reduced by 23% 1 year after subcutaneous implantation in rats.

As we know, the successful mound formation after injection is indicated that the implantation is located over submucosal space. A recent article indicated that Dx/HA implants become fixed after 2 weeks with no further significant loss after 2 weeks. The percentages of Dx/HA retained were 79% at 2 weeks, 78% at 12 weeks, and 65% at 36 months. They concluded that Dx/HA implants remained durable with insignificant volume reduction for up to 36 months postoperatively.14 However, the few long-term studies available suggest that the implant does not prevent later recurrence of VUR in all cases. Not uncommonly, patients return for follow-up evaluation with persistent VUR after an endoscopic injection. In a multi-institutional study, review of failures of endoscopic treatment showed that 49% of cases had a shifted mound, 22% an absent mound, and 10% loss of volume of the mound. Most failures of endoscopic correction are associated with mound shifting. However, the presence of a perfect mound does not predict success.15

In 2002, Capozza et al.16 reported on 45 patients who received Dx/HA injections that failed to resolve VUR, and implicated dysfunctional voiding as the responsible mechanism for mound displacement. On the contrary, Barker et al.17 in a comparison of 83 patients with failed injections without bladder dysfunction and 17 patients with failed injections who had bladder dysfunction found no correlation between the presence or absence of bladder dysfunction and mound appearance. In a prospective evaluation of factors predicting the success of endoscopic injections, Lavelle et al.18 identified the appearance of the mound at the time of the initial injection to be the only predictive factor. Lorenzo et al.19 revealed that the most important successful determinants of VUR correction after an endoscopic subureteral injection in a large, single-institution series were lower grades of preoperative VUR, surgeon experience, and fewer (means fewer times of previous subureteral injections for VUR) previous injections. There are multiple factors that may lead to failure of endoscopic correction, including material characteristics, technical factors of delivery, and bladder dynamics. Most failures are associated with a shift in the injection mound, although some failed mounds may appear perfect. The appearance of the mound is not predictive of the success or failure of a second injection, as the second injection success is generally high. However, dysfunctional voiding predicts a lower success rate with a second injection.

CONCLUSIONS

The data encouraging endoscopic injections for VUR using Dx/HA are impressive in recent years. However, some criticisms persist. First, direct comparisons with open surgery are often defective as success is often differently defined between the 2 therapies. Calling grade I reflux a success is misleading compared with complete surgical cure with no reflux and a success rate of 98%. Second, beginning endoscopic management as first-line therapy over antibiotics prophylaxis would mean using excessively aggressive treatment in a few patients in whom the reflux would spontaneously resolve. This would certainly increase the overall costs of VUR management in the long term. Third, the belief that open surgery requires prolonged hospitalization is also changing after unilateral extravesical reimplantation has been performed on an outpatient basis.

Treatment options continue to develop, and we must constantly remind ourselves that instead of trying to generalize 1 intervention for all patients with VUR, the treatment should be individualized, selecting an option that best fits each particular child. Our focus should include paying attention to voiding habits, constipation, the presence of renal dysplasia or acquired scars, acceptance or compliance with medication, potential treatment morbidities, the possibility of spontaneous resolution, and the potential for significant renal injury. The balance may eventually tip towards an endoscopic injection as the surgical approach of choice. It is up to us to study the issue scientifically and provide strong data to support our interventions. The need for long-term, carefully planned prospective studies should be kept in mind. Our endpoints should go beyond short-term evidence of resolution and focus on patient morbidity, treatment risks and benefits, and impacts on long-term outcomes.

REFERENCES


