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Dextranomer-Hyaluronic Acid and Polyacrylate-Polyalcohol Copolymer are Equally Efficient for Endoscopic Treatment of Vesicoureteral Reflux in Children

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Keywords: Deflux; dextranomer hyaluronic acid; endoscopic injection; polyacrylate polyalcohol copolymer; Vantris, vesicoureteral reflux
ABSTRACT

Purpose: To compare the efficacy of two bulking agents, Dextranomer-Hyaluronic Acid (DxHA) and Polyacrylate-Polyalcohol Copolymer (PPC) used for endoscopic treatment of vesicoureteral reflux (VUR).

Materials and Methods: We endoscopically treated 125 patients (89 girls and 36 boys) diagnosed with VUR grades I-V, comprising a total of 174 refluxing ureters (RUs). Patients were categorized into two groups, 99 (56,9%) RUs were treated with DxHA (Group 1) and 75 (43,1%) RUs with PPC (Group 2). RUs treated with both bulking agents were excluded. The success of treatment was evaluated with postoperative VCUG at 3- and 12-months after the endoscopic procedure, only complete resolution of VUR was considered as treatment success. Data was collected and analyzed retrospectively. Statistical calculations were performed using the Chi-square test.

Results: After a single injection 80,0% (60/75) and 68,7% (68/99 RUs) of RUs resolved completely when treated with PPC and DxHA, respectively \( (P = .094) \). A second injection of PPC healed another 10 RUs (total 93,3%), whereas DxHA resolved additional 16 RUs (total 84,8%) \( (P = .097) \). A third injection was needed for 1 RU, treated with PPC and another 3 RUs with DxHA. Twelve months post-operatively, we achieved a total resolution rate of 94,7% (71/75 RUs) with PPC, while DxHA successfully treated 87,9% (87/99) of RUs \( (P = .125) \).

Conclusions: DxHA and PPC showed no statistically significant differences neither in the number of injections needed nor in the total success rate after 12 months of follow-up.

INTRODUCTION

Vesicoureteral reflux (VUR) is a common urological condition in children, which can in the presence of urinary tract infections (UTI) lead to renal scarring, hypertension and renal...
failure\(^{(1)}\). Endoscopic treatment of VUR with injecting a bulking agent beneath the ureteral orifice and the distal ureter has become widely accepted and performed in several urological centers worldwide. Although no strict recommendations have been made regarding the indication for open surgical procedures versus endoscopic treatment \(^{(1)}\), some authors believe that endoscopic interventions should be first line treatment, regardless of VUR grade \(^{(2)}\). Although several reports on effectiveness of different bulking agents for treating VUR have been published, no clear consensus has been made, which bulking agent showed best results. It is not only VUR resolution rate, but also other aspects, such as protection against UTI, effective long-term results, treatment complications and others, that must be considered as an important factor of an effective bulking agent \(^{(3)}\).

The aim of our study was to compare the efficacy of two different bulking agents: a) Dextranomer-Hyaluronic Acid (DxHA) (Deflux®, Q-Med Scandinavia, Uppsala, Sweden) and b) Polyacrylate-Polyalcohol Copolymer (PPC) (Vantris®, Promedon, Córdoba, Argentina) used for endoscopic VUR treatment. This is, to our knowledge, the biggest study, that directly compared these two substances.

**MATERIALS AND METHODS**

*Study population*

Between January 2005 and July 2014, we endoscopically treated 125 patients (89 girls and 36 boys). VUR was unilateral in 76 patients (60.8%) and bilateral in 49 patients (39.2%), comprising a total of 174 refluxing ureters (RUs) (**Table 1**). Inclusion criteria were pediatric patients, with unilateral or bilateral VUR grade I – V (based on the international classification of VUR), with breakthrough febrile UTI, despite antibiotic prophylaxis with trimethoprim/sulfamethoxasol. Exclusion criteria were anatomical abnormalities of the urinary tract (including posterior urethral valves, double urinary collecting system or ectopic ureter), presence of hydronephrosis, functional bladder anomalies or treatment with both bulking agents
(DxHA and PPC). The study has been reviewed and approved by the Committee for medical ethics of the University medical centre Maribor.

**Study design**

Patients that met the inclusion criteria were enrolled in our study. We performed renovesical ultrasound and voiding cystourethrography (VCUG) on all patients preoperatively and 3-months and 12-months after the endoscopic procedure. Patient were categorized into two groups, based on the bulking agent which they were treated with. Data was collected and analyzed retrospectively. We treated 99 (56,9%) RUs with DxHA (Group 1) and 75 (43,1%) RUs were treated with PPC (Group 2). Patients received different bulking agents, based on the availability of each bulking agent in our medical centre. RUs treated with both bulking agents were excluded from our study.

**Surgical technique**

Endoscopic treatment was performed by two experienced urologists. Patients received general anesthesia and were placed in the lithotomy position. We performed the STING procedure, using a rigid, Ch 9 cystoscope with 0°optics to perform a subureteral injection of the selected bulking agent just below the ureteral orifice at 6 o’clock position. The method of administration of the bulking agent was the same for both treatment groups.

**Outcome assessment**

The success of treatment was evaluated using the postoperative VCUG at 3- and 12-months after the endoscopic procedure. To exclude potential VCUG evaluator influences on the postoperative VCUG assessments, the bulking agent used was only know to the surgeon. The treatment was considered as successful if 12-months postinjection VCUG showed complete VUR resolution. If during follow-up VUR persisted or was only downgraded, it was considered as a therapeutic failure. Statistical calculations were performed using the Chi-square test, with
IBM SPSS Statistics software (IBM, Armonk, USA). Values $P < .05$ were considered as significant.

**RESULTS**

Altogether we treated 174 RUs. Demographic data, together with the distribution of RUs among treatment groups and different VUR grades is shown in Table 1.

After a single injection 80.0% (60/75) of RUs resolved completely when treated with PPC, in contrast to a success rate of 68.7% (68/99 RUs) with DxHA ($P = .094$) (Table 2). A second injection of PPC healed another 10 RUs (total 93.3%), whereas DxHA resolved additional 16 RUs (total 84.8%) ($P = .097$). A third injection was needed for 1 RU, treated with PPC and another 3 RUs with DxHA. Twelve months post-operatively, we achieved a total resolution rate of 94.7% (71/75 RUs) with PPC, while DxHA successfully treated 87.9% (87/99) of RUs ($P = .125$). The treatment success within each VUR grade for both treatment groups are presented in Table 3 and Table 4.

Endoscopic treatment was unsuccessful in 5.3% (4/75 RUs) with PPC, of which 2 RUs (2.7%) were treated with open surgical procedures and 2 children (2 RUs) discontinued treatment. The failure rate of DxHA was 12.1% (12/99 RUs), of which 9 RUs (9.1%) were treated with open surgical procedures and 3 children (3 RUs) discontinued treatment.

We observed 2 complications after endoscopic treatment, one in each study group. In study group 1 (DxHA) one patient (1 RU, 1% RUs), who was successfully treated, with no signs of hydronephrosis or residual VUR, gradually worsened in kidney function, finally resulting in a non-functional kidney, thus we performed a nephrectomy. In study group 2 (PPC) we noticed a hydronephrosis in one patient (1 RU, 1.3% RUs) on the site, where the bulking agent was injected. An endoscopic revision was performed with a partial removal of the bulking agent. During follow-up hydronephrosis gradually resolved, with no signs of VUR. In the study we
observed the development of a new, contralateral VUR in 4 patients (4% RUs) that were treated with DxHA.

**DISCUSSION**

The first description of endoscopic VUR treatment with subureteral injection of Teflon was described in 1981 by Matouschek\(^4\). Since then several different bulking agents were described and the endoscopic technique nowadays represents an attractive, minimally invasive alternative to open surgical procedures. Although the success of endoscopic treatment versus open surgical techniques has always been questioned, recent studies confirmed that endoscopic treatment of VUR grades II to IV are as effective as ureteral reimplantation, during short- and long-term follow up\(^5\).

Several factors that affect the VUR resolution rate after endoscopic and surgical interventions have been identified. During the first 3 years of follow up, VUR resolution rates decrease with patients’ history of voiding dysfunction, breakthrough infections and “golf-hole” or “stadium” ureteral orifice appearance and increase with increased ureteral orifice distance\(^6\). With longer follow-up (up to 11 years), high VUR grade, but also ureteral orifice appearance and a history of pyelonephritis, have been identified as factors, contributing to a higher failure rate, with up to 67% failure rate for VUR grade V\(^7\).

Despite several published studies using different bulking agents, no clear consensus has been made, which bulking agent showed best results. The success rates of endoscopic VUR treatment with DxHA differ from one study group to another. The overall success rates described range from 68%-92% and the quite large success range interval is probably VUR grade depended\(^8\). Longer follow-up studies with promising short-term success rates of 84% show more recurrences during longer follow-up, with a decreased success rates to 74% during their mean follow-up time of 5 years, although the VUR grade in this study was grade 3 or greater\(^9\).
Our results with DxHA show a complete VUR resolution rate of 87.9% after 12 months of follow-up. Similar conclusions could be drawn from the study of Stradele et al., who also treated 99 RU (Grades II-IV) with DxHA. They report an initial 81.5% success rate with DxHA at 3-month post injection. Nevertheless 42 of 62 successfully treated children underwent another VCUG after 3 years, which showed that only 78.5% remained free of VUR\(^{(10)}\). One of the possible explanations for this late recurrence onset could be the biodegradable DxHA properties\(^{(11)}\).

On the other hand, PPC has a very high molecular mass and is classified as a non-biodegradable bulking agent\(^{(12)}\). That is why it is suspected to have better long-term results. Some authors even report no VUR recurrence of complex cases after a prospective, 3 years follow-up\(^{(13)}\), although the number of patients that completed the follow up is rather small. In another study, 81% of the initial 86 RUs were VUR free 3 months after endoscopic treatment with PPC, although the number slightly decreased to 77% after 12 months and stayed the same after 24 months of follow-up\(^{(14)}\).

Our results with PPC do correlate with other published studies, where treatment success with a resolution rate of more than 90% was described\(^{(3, 13, 15)}\). In our study we successfully treated 94.6% of the initial 75 RUs with PPC. Kocherov et al. report similar or even better total success rates of 97.5%, of which 93.7% resolved after the first injection and 3.8% required a total of up to 3 injections until complete resolution\(^{(15)}\). Also, Chertin et al. report a high success rate of 89.4% after single injection of PPC and another 5.4% after a second injection with a complete success rate of 94.8%\(^{(15)}\). The study of Corbetta et al. had a similar study design to our research and the results are comparable as well. They report an overall 92.3% success rate with PPC during their median follow-up time of 14 months\(^{(3)}\).

As presented in Table 1, 85.1% of our patients had VUR grades II-III, which could explain the high success rates of endoscopic treatment with both substances in our study. It was shown in
a meta-analysis that patient selection depending on VUR grade is an important factor that influences endoscopic treatment outcomes. The primary success rates of endoscopic treatment for VUR grades I and II was 78,5% and 72% for grade III, with furthermore decline rates of 63% and 51% for grade IV and V respectively\(^{(16)}\). Also our results, shown in Table 3 and 4, demonstrate that with higher VUR grade more repeated injections and higher treatment failure rates are observed for both treatment groups.

Another important factor of our study is that only two experienced endoscopic urologists performed the treatment, with both bulking agents. In that way the successfulness of treatment in both study groups was not compromised. This seems a rather important factor, since it has already been shown that not only the injected material and injection location, but also sufficient experience with the injection technique seems to correlate with the treatment outcome\(^{(17)}\).

Although the complications after endoscopic VUR treatment are rare, they should not be overseen. Most frequently ureteral obstruction and development of a new, contralateral VUR are described, but also dysuria, hematuria, fever, lumbar pain and UTIs without VUR \(^{(3, 14, 18)}\)\(^{(19, 20)}\). The reported ureteral obstruction rates for DxHA vary from 0,7% to 5,7% RUs\(^{(19, 21)}\) and for PPC from 1,2% to 4,6% \(^{(3, 15, 22)}\). We have observed 1 (1,3%) ureteral obstruction after PPC treatment, that was endoscopically cured with removing a part of the bulking agent. Another complication occurred in the study group 1 (DxHA), where we observed a gradually progressing kidney dysfunction without any signs of VUR or obstruction. As described in the literature, development of a new, contralateral VUR after a successful endoscopic treatment occurs in up to 10% of treated patients\(^{(23)}\). In our study, we detected 4 patients (4 RUs, 4%) who developed a new, contralateral VUR after treatment and all of them were treated with DxHA.

We strongly believe that the choice of a bulking agent does not affect the incidence of developing a new contralateral VUR and that it was only a coincidence that all these children were treated with DxHA.
Our results showed no statistically significant differences in success rates using DxHA versus PPC. Although it seems that PPC shows slightly better results, there is no statistically significant difference neither in the number of injections needed nor in the total success rate after 12 months follow-up, which does correlate to the results published by Blais et al\(^{(24)}\). On the contrary, some studies did show a statistical significant difference in the success rates in favor of PPC\(^{(25,26)}\), although the number of patients and RUs included in our study was bigger. Both substances have shown good success rates with low rates of complications. Nevertheless, there is a 15% price difference per ampule of the bulking agents in favor of PPC, at least in our country. Given the similar success results it does raise the question of cost effectiveness.

Despite efforts, our study has its limitations, one being the follow-up of 1 year. To objectify the treatment results we have performed two VCUGs after the procedure on each patient, the first at 3 and the second at 12 months post-operatively, with the investing radiologist being blinded for the bulking agent used. Even though pediatric nephrologists have followed-up all patients further on, no objective conclusions could be made for the follow-up past 1 year. Another limitation of our study is the fact that the data was collected retrospectively. Although patients were not randomized in a standard manner, they received the bulking agent based on the availability of each bulking agent in our medical center. The availability was not influenced by the researchers, which makes us certain, that this kind of patient allocation did not influence the results of our study.

**CONCLUSIONS**

Endoscopic treatment of VUR offers an attractive, minimally invasive alternative to open surgery. The treatment success rates are high and the complication rates are relatively low. Based on our result DxHA and PPC have shown no statistically significant differences neither in the number of injections needed nor in the total success rate after 12 months follow-up time.
Nevertheless, there is a tendency of better success rates with PPC and considering the costs, we prefer using PPC in our center.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

REFERENCES


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### Table 1. Demographic data and patient characteristics.

<table>
<thead>
<tr>
<th>Primary VUR cases (RUs)</th>
<th>174</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral</td>
<td>76  (43.7%)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>98  (56.3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients</th>
<th>DxHA</th>
<th>PPC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>22   (31%)</td>
<td>14  (26%)</td>
<td>36  (28.8%)</td>
</tr>
<tr>
<td>Female</td>
<td>49   (69%)</td>
<td>40  (74%)</td>
<td>89  (71.2%)</td>
</tr>
<tr>
<td>Total</td>
<td>71</td>
<td>54</td>
<td>125</td>
</tr>
<tr>
<td>Mean age</td>
<td>3.98 yrs</td>
<td>2.64 yrs</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VUR grade (RUs)</th>
<th>DxHA</th>
<th>PPC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>2    (2.0%)</td>
<td>1   (1.3%)</td>
<td>3   (1.7%)</td>
</tr>
<tr>
<td>II</td>
<td>36   (36.3%)</td>
<td>26  (34.7%)</td>
<td>62  (35.6%)</td>
</tr>
<tr>
<td>III</td>
<td>48   (48.5%)</td>
<td>38  (50.7%)</td>
<td>86  (49.5%)</td>
</tr>
<tr>
<td>IV</td>
<td>11   (11.1%)</td>
<td>9   (12.0%)</td>
<td>20  (11.5%)</td>
</tr>
<tr>
<td>V</td>
<td>2    (2.0%)</td>
<td>1   (1.3%)</td>
<td>3   (1.7%)</td>
</tr>
<tr>
<td>Total RUs</td>
<td>99</td>
<td>75</td>
<td>174</td>
</tr>
</tbody>
</table>

DxHA, Dextranomer-Hyaluronic Acid; PPC, Polyacrylate-Polyalcohol Copolymer; RUs, refluxing ureters; VUR, vesicoureteral reflux; yrs, years.

### Table 2. Treatment results.

<table>
<thead>
<tr>
<th>Nº RUs treated</th>
<th>DxHA</th>
<th>PPC</th>
<th>P - value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correction after</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st injection</td>
<td>68   (68.7%)</td>
<td>60  (80.0%)</td>
<td>0.094</td>
</tr>
<tr>
<td>2nd injection</td>
<td>16   (16.1%)</td>
<td>10  (13.3%)</td>
<td>0.097</td>
</tr>
<tr>
<td>3rd injection</td>
<td>3    (3.1%)</td>
<td>1   (1.3%)</td>
<td>/</td>
</tr>
<tr>
<td>Total</td>
<td>Success</td>
<td>87  (87.9%)</td>
<td>71  (94.6%)</td>
</tr>
<tr>
<td></td>
<td>Failure</td>
<td>12   (12.1%)</td>
<td>4    (5.3%)</td>
</tr>
</tbody>
</table>

*Chi-square test
DxHA, Dextranomer-Hyaluronic Acid; Nº, number of; PPC, Polyacrylate-Polyalcohol Copolymer; RUs, refluxing ureters.

### Table 3. Treatment results per VUR grade for Dextranomer-Hyaluronic Acid (DxHA).
Table 4. Treatment results per VUR grade for Polyacrylate-Polyalcohol Copolymer (PPC).

<table>
<thead>
<tr>
<th>VUR grade</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>N° RUs treated</td>
<td>1</td>
<td>26</td>
<td>38</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Correction after</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st injection</td>
<td>1 (100,0%)</td>
<td>24 (92,3%)</td>
<td>31 (81,6%)</td>
<td>4 (44,4%)</td>
<td>0</td>
</tr>
<tr>
<td>2nd injection</td>
<td>0</td>
<td>2 (7,7%)</td>
<td>5 (13,1%)</td>
<td>3 (33,3%)</td>
<td>0</td>
</tr>
<tr>
<td>3rd injection</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (100,0%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Success</td>
<td>1 (100,0%)</td>
<td>26 (100,0%)</td>
<td>36 (94,7%)</td>
<td>7 (77,8%)</td>
<td>1 (100,0%)</td>
</tr>
<tr>
<td>Failure</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

N°, number of; RUs, refluxing ureters; VUR, vesicoureteral reflux.