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Efficacy and safety of Hyadex for treatment of vesicoureteral reflux: a multicenter experience

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Abstract

Objective: This study was performed to evaluate the efficacy and safety of dextranomer/cross-linked hyaluronic acid (Hyadex) in patients with a clinical diagnosis of vesicoureteral reflux (VUR).
Methods: In this cross-sectional multicenter observational study, Hyadex was used in four different centers for the endoscopic treatment of VUR from 2020 to 2022. The study involved 74 patients (93 renal units) who were diagnosed with VUR according to voiding cystourethrography (VCUG) findings and were considered suitable for subureteric endoscopic treatment. The follow-up time (control VCUG time) was 3 months.
Results: In the VCUG evaluation, grade I VUR was found in 13 renal units, grade II in 23 renal units, grade III in 42 renal units, and grade IV in 12 renal units. The success rates of Hyadex treatment according to the degree of VUR were as follows: 84.6% for grade I, 82.6% for grade II, 71.4% for grade III, and 66.0% for grade IV. No major complications were observed.
Conclusion: Endoscopic subureteric Hyadex injection had high success rates in appropriately selected patients with VUR and may be used as the first-line treatment for children with VUR.

Keywords

Vesicoureteral reflux, subureteric injection, dextranomer, cross-linked hyaluronic acid, Hyadex, voiding cystourethrography

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Introduction

Vesicoureteral reflux (VUR) is a condition characterized by retrograde urine flow from the bladder into one or both ureters and then into the kidneys.[1] Approximately 30% of children with urinary tract infections (UTIs) are diagnosed with VUR, and such children may experience recurring UTIs and long-term renal scarring.[2] There are several possible causes of VUR, including congenital anomalies at the ureterovesical junction, pathological conditions that may cause voiding dysfunction, or illnesses that disturb the function of the ureterovesical junction or bladder.[3] Voiding cystourethrography (VCUG) is the imaging modality of choice for diagnosing VUR, and the diagnosis is confirmed by observing the movement of contrast dye through the ureters and kidneys.[4]

Most cases of VUR in children resolve spontaneously; however, patients with more severe VUG (bilateral grades III, IV, and V) require antibiotic prophylaxis or surgical interventions.[5] For some patients in whom conservative treatment with antibiotic prophylaxis fails, however, surgical intervention may not be suitable for the patient or their family. The surgical treatment options for VUR include endoscopic subureteric injection and open or laparoscopic corrective surgery.[6]

Polytetrafluoroethylene (PTFE) was found to have a high risk of migration, leading to the requirement for an alternative substance. This led to the discovery of dextranomer/hyaluronic acid, which was approved by the Food and Drug Administration for the treatment of VUR in 2001.[7] Dextranomer/hyaluronic acid is nonimmunogenic and biocompatible, and it carries no risk of migration or transformation into a malignant growth. Hyaluronic acid dissolves completely 3 months after injection, and the volume of material decreases by 25% over 12 months. However, endogenous tissue augmentation may occur due to ingrowth of collagen and fibroblasts between the microspheres.[8] Jaafar and Hussein[9] reported that Deflux (Palette Life Sciences, Inc., Stockholm, Sweden) has dextranomer microspheres ranging in size from 80 to 250 μm (average, 130 μm), whereas Dexell (Istem Medikal, Ankara, Turkey) has dextranomer microspheres ranging in size from 80 to 120 μm. The authors stated that the therapeutic outcome of these two agents is not significantly different and that the ideal injectable bulking agent should be durable, effective, safe, stable, non-migrating, biocompatible, non-antigenic, and non-carcinogenic.[9] Hyadex (dextranomer/cross-linked hyaluronic acid) is a new product that is biochemically similar to Deflux, with dextranomer microspheres ranging in size from 80 to 250 μm (average, 130 μm). Like Deflux, Hyadex has larger microspheres, making migration less likely to occur.[10]

Because Hyadex is a newly developed agent with minimal available information, the present study was planned to investigate the mid- and long-term results of the efficacy and safety of Hyadex when used as a treatment for VUR.

Materials and Methods

Compliance with ethical standards

This multicenter clinical evaluation was designed as a cross-sectional observational study involving 74 patients (total of 93 renal units) with VUR to examine the efficacy and safety of Hyadex treatment. This study was carried out from 2020 to 2022 and performed to assess the efficacy and safety of Hyadex in treating patients with grade I to IV VUR.

In the creation of our medical device called "Injectable Gel for Treatment of VUR and Stress Urinary Incontinence," we followed the ISO 13485 standards for design, development, and manufacturing management. CE certification was obtained

in July 2020. We received permission from the Turkish Ministry of Health Ethics Committee (2020/49) to perform a clinical trial involving the use of this device. Written informed consent was obtained from the parents of the patients included in the study before beginning treatment. This clinical study was conducted in accordance with the Helsinki Ethical Guidelines.

Hyadex was chosen as the injectable material for all patients included in this study. Hyadex is a new product with a domestic production certificate, and its research and development/formulation were carried out in İnönü University in Malatya Technopolis, Turkey. It has been registered in the Product Tracking System with a CE Certificate by the Turkey Medicine and Medical Device Agency of the Ministry of Health (Figure 1).

Study design

Hyadex was administered to patients who had a confirmed diagnosis of VUR and were considered suitable for endoscopic treatment. Suitable patients were considered to be those with recurrent UTIs despite antibiotic prophylaxis, persistent VUR after a >2-year period of observation, poor compliance with antibiotic prophylaxis, new renal scarring, and no requirement for open surgery. Patients from four major centers were included: the Departments of Urology at the Atatürk University Erzurum, Harran University Şanlıurfa, and Inonu University Malatya and the Department of Pediatric Surgery at Inonu University Malatya. The surgeons in these four centers had been working in the field of pediatric urology for about 5 years. In accordance with a report by Baydilli et al.,[11] we excluded patients with reflux accompanied by anatomical problems such as duplication and obstruction, patients with neurogenic bladder, and patients who had been diagnosed with secondary VUR according to the degree of reflux, age, and whether scarring was present. Secondary VUR is defined as VUR secondary to functional or organic abnormalities of the urinary tract. Neurogenic functional abnormalities include neurogenic bladder due to spinal cord disorders (e.g., spina bifida) and brain disorders (e.g., cerebral palsy), whereas non-neurogenic organic abnormalities include posterior urethral valves and ureteroceles.[12]

Figure 1. Hyadex is a sterile, viscous gel available in 1-mL disposable syringes containing dextranomer microparticles with a diameter of 80 to 250 μm and a non-animal-based, cross-linked hyaluronic acid with CE certificate.

Hyadex is a sterile, viscous gel available in 1-mL disposable syringes containing dextranomer microparticles with a diameter of 80 to 250 μm and a non-animal-based, cross-linked hyaluronic acid that functions as a carrier gel for the dextranomer microparticles. The dextranomer microparticles form an augmentation on the connective tissue at the injection site, which gradually becomes surrounded by host connective tissue.

Hyadex application

For prophylaxis, a single dose of sulfamethoxazole/trimethoprim was orally administered before the operation. The Hyadex injection procedure was carried out with the patient under general anesthesia in the cystolithotomy position. A rigid fine needle marked at 0.8 cm was inserted into the urethral orifice at the 6-o'clock position. The needle was advanced 0.8 cm, until the orifice appeared to be closed. Hyadex was administered until achievement of a "volcanic" appearance at the injection site. The quantity of endoscopic subureteric Hyadex injection used for one ureter was 0.5 to 1.0 mL. Figure 2(a)–(d) shows this dome-like appearance of the ureteral orifice after subureteric injection. Upon completion of the injection, the needle remained in place for a further 60 s to ensure no extravasation or freezing of the injection contents occurred. Patients were discharged from the hospital 24 hours postoperatively. Following the procedure, each patient underwent a physical examination, total urine test, and urine culture on a monthly basis for 3 months. Additionally, each patient underwent VCUG 3 months after the procedure. The resolution of VUR as confirmed by negative VCUG was considered a successful outcome. All records obtained during the procedure and after the control visit were analyzed by another researcher who was unaware of the details of the study process.

The factors affecting treatment success in our study were the absence of infection, the presence of primary VUR, and the absence of additional disease.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA). The patients' age is presented as mean ± standard error, and their sex is shown as a proportion (male/female) (Table 1). A graphic of the reflux resolution rate (%) according to the VUR grade was drawn using SPSS software.

Results

No complications were observed or reported during or after the surgical procedure. Additionally, after subureteric Hyadex injection, no patients developed UTIs and none

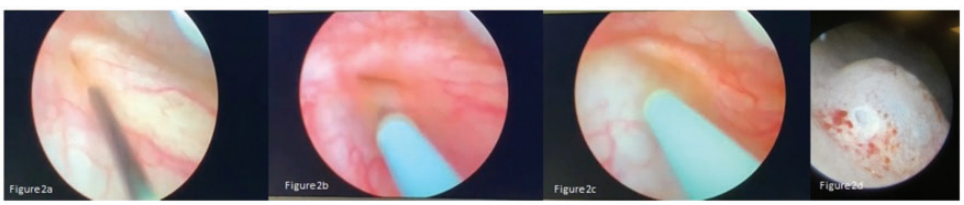

Figure 2. (a) Appearance of refluxing ureter and needle. (b) The needle is introduced under the bladder mucosa, 2 to 3 mm below the refluxing orifice at the 6-o'clock position. (c) The injection is continued until a prominent bulge is observed and the ureteral orifice has assumed a crescent-like shape and (d) After endoscopic injection, a bulge is seen (mound shape).

Table 1. Endoscopic subureteric injections with Hyadex in VUR treatment and reflux resolution rate.

Number of patients	74
Sex, male/female	23/51
Mean age, years	8.3 ± 7.5
VUR grade (number of renal units)	Grade I (13) Grade II (23) Grade III (42) Grade IV (15)
Total renal units	93

VUR, vesicoureteral reflux.

complained of flank pain suggesting ureteral obstruction or late failure (complications) up to 3 months postoperatively.

The study results are summarized in Table 1. Briefly, the study involved 74 children (93 renal units) with a confirmed diagnosis of VUR who were deemed suitable for endoscopic treatment. The patients comprised 51 girls and 23 boys with a mean age of 8.3 ± 7.5 years. The VUR grade ranged from I to IV; grade I VUR was present in 13 renal units, grade II in 23 renal units, grade III in 42 renal units, and grade IV in 15 renal units. Two patients had type 1 diabetes, 3 had celiac disease, and 69 had no additional disease. None of the patients had undergone previous surgery for VUR. Fifteen patients had grade 1 hydronephrosis, 12 patients had grade 2, and 3 patients had grade 3. None of the patients had any additional urinary tract abnormality. All 74 patients were treated with Hyadex as described above. The VCUG results obtained 3 months following the procedure demonstrated that the resolution rates according to the VUR grade were 84.6% for grade I VUR, 82.6% for grade II, 71.4% for grade III, and 66.0% for grade IV (Figure 3).

Discussion

Our goal when planning this study was to provide new information to researchers considering working with this new medical product, and we aimed to contribute valuable insights for further research in this field. The results of this study indicate that our newly developed dextranomer/cross-linked hyaluronic acid agent Hyadex is effective and safe. The cause of the early obstructions reported in the literature may be the physical obstruction caused by the injected material.[13] Rossini et al.[14] reported that VUR in children can predispose patients to febrile UTIs. Repeated UTIs can lead to renal scarring, hypertension, and ultimately end-stage renal disease. Therefore, VUR is a long-term condition that may require medical treatment. One approach to the medical management of VUR is a regimen of long-term antibiotics; however, long-term antibiotic use can lead to resistance and treatment failure. Furthermore, a lack of patient or family compliance with long-term antibiotic regimens may result in unsuccessful treatment.[15] Surgical management includes endoscopic and open or laparoscopic surgery. Although the resolution rate with open or laparoscopic surgery reportedly ranges from 90% to 98%, such treatment also has disadvantages such as the risks associated with invasive surgeries and a relatively long hospital stay.[14]

Endoscopic subureteric injections have several advantages, including ease of administration, low cost, and proven safety. Even in the event of treatment failure, injections can be safely repeated. Several materials are available for subureteric injection, including PTFE, collagen, autologous fat, polydimethylsiloxane, silicone, chondrocytes, dextranomer/hyaluronic acid, and a recently developed material, polyacrylate polyalcohol.[6] Although the resolution rate after using PTFE is very high, this material is not approved for use in children because of the risk of particle migration.[16] Despite most subureteric injection components

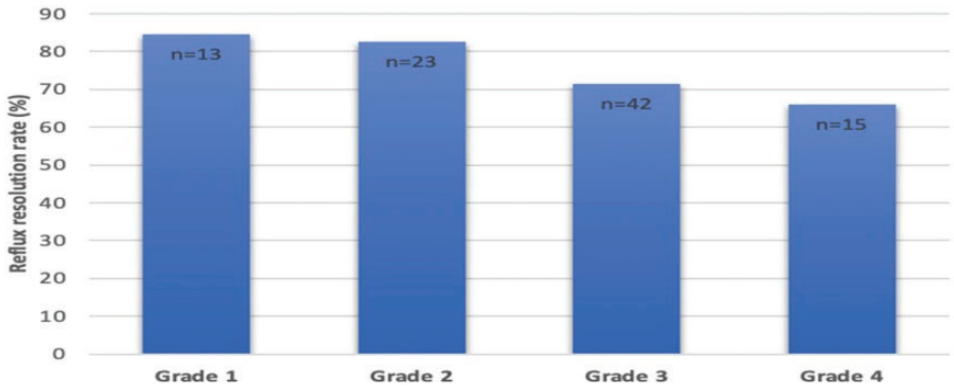

Figure 3. Reflux resolution rate (%) according to grade of vesicoureteral reflux.

being biocompatible, materials such as collagen and chondrocytes are associated with relatively low rates of resolution.[17] Lavelle et al.[18] recently reported that endoscopic treatment of VUR with multiple different substances has been evaluated in the past with mixed results. More recently, Doğan et al.[19] reported that although many bulking agents have been used (including PTFE, silicone, and bovine collagen), many have been abandoned because of skepticism and complications. They stated that the most commonly used bulking agents in the endoscopic treatment of VUR are dextranomer/hyaluronic acid copolymer and polyacrylate-polyalcohol copolymer.[19] Hyadex is a new product that is biochemically similar to Deflux, containing dextranomer microspheres that range in size from 80 to 250 μm. For this reason, migration of Hyadex is less likely to be a problem.

Research has shown that Deflux is effective in the treatment of VUR. One study demonstrated that the resolution rates after using Deflux in treatment of VUR were 81.8% for grade I VUR, 83.8% for grade II, 77.7% for grade III, and 72.7% for grade IV.[18] In a meta-analysis involving 5527 patients (8101 renal units) treated with different materials, the reflux resolution rate for grades I and II reflux was 78.5%, that for grade III was 72.0%, that for grade IV was 63.0%, and that for grade V was 51.0% following one treatment round.[20] In the current study, the resolution rate after use of Hyadex for treatment of VUR was 84.6% for grade I (n = 13), 82.6% for grade II (n = 23), 71.4% for grade III (n = 42), and 66.0% for grade IV (n = 15) (Table 1). Therefore, our clinical results are consistent with the above-mentioned studies in terms of VUR treatment according to grade. Chung et al.[10] reported that although many injection techniques have been described and many factors have been evaluated (e.g., degree of hydrodistension, depth of needle penetration, and volume of material injected), the final "volcano" appearance is considered the main predictor of success at most centers. Therefore, in the current study, we paid very close attention to achievement of the volcano appearance. Additionally, because Kim et al.[21] reported that surgeon experience is another important factor for obtaining successful results, we designed our study to involve experienced surgeons at four centers for the endoscopic treatment of VUR. All of these surgeons had been working in the field of pediatric urology for about 5 years.

In a study investigating the long-term follow-up of children treated with

dextranomer/hyaluronic acid copolymer for VUR, 228 patients underwent endoscopic treatment.[22] The efficacy population comprised 221 children, including 67 children who received two implantations and 8 children who received three implantations. The patients were clinically followed for 2.0 to 7.5 years (mean, 5 years). On the last VCUG examination, 68% of the patients had a positive response to therapy (grade $\leq$I) and 81% had no dilation reflux. Corresponding outcomes for treated ureters were 75% and 85%, respectively. Only 27 (12%) patients were referred for open surgery. Delayed VCUG was performed in 49 patients at 2 to 5 years after treatment. Dilated reflux was not observed in 96% of reflux-free ureters (grade 0) at 3 to 12 months after treatment.[22] The long-term follow-up results of our study have not yet been published.

In one study of the use of dextranomer/hyaluronic acid copolymer, the patients were followed for 3 months to 1 year, and the initial results were obtained.[23] The reflux resolved in 143 (86%) of 166 ureters after a single injection and in 22 (13%) and 1 (1%) of 166 ureters after the second and third injections, respectively. No procedure-related complications were observed in any of the patients. Of 113 patients, 11 (9.7%) completed 1 year of follow-up, and VCUG showed no reflux. Follow-up ultrasonography showed no evidence of the delayed appearance of vesicoureteral junction occlusion in any of the treated ureters or any change in the sonographic appearance of the dextranomer/hyaluronic acid copolymer implants.[23]

Despite some limitations of injection therapy, such as migration and durability, this treatment still has a role in the treatment of VUR. We agree with the following recent statement by Kim et al.[21]: "In light of recent studies reporting the low effectiveness of antibiotic prophylaxis and concerns about antibiotic-resistant strains, we believe injection therapy still has an important role in VUR treatment."

Our study had several limitations, including the small number of patients, the inability to perform the second and third injections, and the inability to perform ultrasonography because of early postoperative discharge. We are aware that the most valid method to show the absence of ureteral obstruction is the performance of ultrasonography immediately after surgery. Unfortunately, this study was carried out under the conditions of the COVID-19 pandemic, and the patients had to be discharged from the hospital because of the risk of infection during postoperative hospitalization; therefore, ultrasonography could not be immediately performed. Additionally, follow-up clinical assessments of all patients were carried out 1 week later. One important advantage of using Hyadex is that it is among the most competitively priced products among the options considered in the tender for subureteric injection material at our university hospital. At least two surgeons were involved in the operation; the mean operation time was 20 minutes, and 1 mL of injection material was enough for a single application.

Further prospective randomized studies involving larger numbers of patients and longer-term follow-up should be performed to assess the long-term efficacy and safety of endoscopic injection therapy in the treatment of VUR.

Conclusions

Endoscopic subureteric injection is an effective treatment option for patients with VUR, and the average hospital stay was only 1 day. Additionally, Hyadex was determined to be easily injected, safe, therapeutically effective, and cost-effective in the treatment of VUR, with no risk of migration or toxicity. Moreover, no complications associated with Hyadex injection

occurred in this study. We believe that endoscopic subureteric injection of Hyadex may be considered among the first-line treatment options in children with VUR.

Declaration of conflicting interests

The authors declare that they have no conflicts of interest.

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