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ORIGINAL ARTICLE

Injection volumes of dextranomer/hyaluronic acid are increasing in the endoscopic management of vesicoureteral reflux

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Abstract
Purpose Dextranomer/hyaluronic acid (Deflux®) has been increasingly used for the treatment of vesicoureteral reflux (VUR). Experience has shown that injecting more volume of material is necessary to achieve greater success. We evaluate trends in the number of vials being used to treat VUR using a multi-institutional database and data from patients treated at our own institution.
Methods Children of age 0–19 years in the Pediatric Health Information System (PHIS) database from 2003 to 2008 were extracted with a VUR diagnosis (ICD-9 593.7x) and subureteric injection procedure code (CPT 52327). We identified children with reflux treated with endoscopic injection at Seattle Children's Hospital from 2005 to 2008. Hospital trends of the number of vials used were evaluated using multivariate linear regression.
Results From 2003 to 2008, we identified 4,078 endoscopic injection procedures in PHIS. There was a 33% increase in the average number of vials used per patient ($p < 0.0001$) with more than a threefold increase in the number of patients receiving three or more vials per procedure. All institutions increased the average vials used per patient with the most pronounced increase at the highest-volume centers. These trends were also present in the 186 children treated at our own institution.
Conclusion Over the study period there was an increase in the number of vials of dextranomer/hyaluronic acid being used per patient to treat children with VUR. This practice may improve success rates but will increase the cost of treatment due to the inherent expense of the material.

Keywords Vesicoureteral reflux · Dextranomer/hyaluronic acid · Urinary tract infection · Cost-effectiveness · Practice patterns

Abbreviations
VUR Vesicoureteral reflux
PHIS Pediatric health information system

Introduction

Vesicoureteral reflux (VUR) is estimated to occur in 1–3% of children [1]. Treatment of reflux with a goal of preventing pyelonephritis episodes is the standard of care in pediatric urology. Treatment options include close observation, antibiotic prophylaxis, minimally invasive endoscopic injection procedures, and surgical ureteral reimplantation.

Minimally invasive injection therapies have had historical success, but due to durability and safety concerns many of these materials have been abandoned [2, 3]. Since

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the approval of dextranomer/hyaluronic acid copolymer (Deflux®) in 2001 by the United States Food and Drug Administration, endoscopic management of VUR has been embraced by the pediatric urologic community and parents as an alternative to antibiotic prophylaxis and surgical reimplantation.

Our center previously evaluated the impact of the introduction of dextranomer/hyaluronic acid in the endoscopic management of VUR using the Pediatric Health Information System (PHIS) database. We identified a 288% increase in endoscopic injections for VUR over a 3 year time period [4]. Since this publication, others have demonstrated that the success of injection therapy for VUR has been shown to improve with increased surgeon experience, alternative injection techniques, and more injected volume of material [5, 6]. The cost-effectiveness of endoscopic injection has also been evaluated [7–9]. Clearly, success rates are the major determinant of the cost-effectiveness of this therapy. These rates determine the number of additional procedures that are necessary, whether it be a repeat injection procedure or surgical reimplantation. Given the significant cost of the material, the number of vials of injected material used per procedure is another important factor in determining cost-effectiveness and most cost analyses have accounted only modest average injection volumes.

The purpose of this study was to evaluate if some of these factors have changed practice patterns nationally. We used a large multi-institutional database, which includes hospitals from all regions of the United States, to evaluate trends in the number of vials used per endoscopic procedure to treat VUR. We then compared these trends with patients treated at our own institution to provide important clinical information lacking in the PHIS database.

Materials and methods

Study setting and subjects

The PHIS database was created by the Child Health Corporation of America (Shawnee Mission, KS). The database was initially created to assess hospital practices as they relate to other institutions. The database composition, geographic representation and subject inclusion have been reported previously and are reviewed here in brief [4, 10].

After Institutional Review Board approval was obtained, the database was queried for children of age 0–19 years encountered at hospitals enrolled in the PHIS database between 2003 and 2008 with a diagnosis code for VUR (ICD-9 593.7x) [11] and a procedure code for subureteric injection of implantable material (CPT 52327) [12]. Within the "supply charges" field, we identified each hospital's unique charge code for dextranomer/hyaluronic acid for each year. In 2003, 37 (67%) of the 50–55 free-standing pediatric acute care hospitals in the United States submitted data to PHIS. However, not all institutions submitted ambulatory surgery data, performed subureteric injection procedures and/or provided an identifiable charge code for dextranomer/hyaluronic acid (Fig. 1). Over the study period, 13 institutions provided data for at least four consecutive years and were included in this study. In 2002, the year following FDA approval of dextranomer/hyaluronic acid, only 111 procedures at eight institutions were captured and thus data from this year were not included.

Children undergoing subureteric injection of dextranomer/hyaluronic acid from 2005 to 2008 at Seattle Children's Hospital were identified. After retrospective review, we evaluated and compared our institutional trends to those in the PHIS database. We evaluated temporal trends of the average grades of reflux for those undergoing endoscopic treatment. We also evaluated the proportion of children treated for bilateral reflux and those who had injection of a contralateral non-refluxing ureter.

Number of vials

Institutions in PHIS provided data regarding material charges and the number of units of dextranomer/hyaluronic acid material billed. The number of vials of material was checked for consistency against the material charges and for the majority of institutions, the material charges and reported units correlated exactly. For those institutions where the units did not correlate exactly, it was possible to compare the material charges to the charge for a single vial of dextranomer/hyaluronic acid. For example, in 2003 there was an institution where a single vial had a material

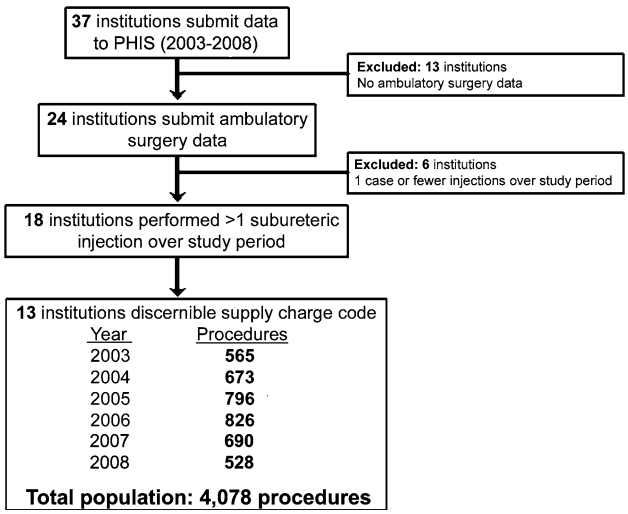

Fig. 1 Institution participation in PHIS and enrollment of included hospitals

charge of $2,065.24, followed by a series of patients with exactly double the material charge $4,130.48, followed by a series of patients with exactly triple the material charge $6,195.72. For these procedures the number of vials used was determined as 1, 2 and 3 vials, respectively. Overall, 92% of procedures had perfectly duplicating charges with the number of units reported correlating with the number of vials calculated for comparison. The charge per unit of dextranomer/hyaluronic acid varied considerably between institutions, but was consistent within an institution from year to year.

Patients were excluded if they underwent additional concurrent procedures, such as renal transplantation or bladder augmentation, or if the number of vials injected were indiscernible through the methods mentioned above.

Statistical analyses

Chi-squared analyses were performed for binary outcomes, and Student's *t* tests were performed for continuous variables. Linear regression analyses with robust standard error calculations were used to evaluate annual trends with a priori adjustment for age. All analyses were performed using StataIC 10.0 (Statacorp, TX) with two-tailed *p* values and statistical significance set at <0.05.

Results

A total of 4,078 procedures for VUR were identified in the PHIS database over the 6 year time period. The mean age of patients was 5.5 ± 3.6 years (range 42 days to 18 years) and did not vary significantly by year. Over the study period, the 13 institutions identified in the PHIS database had a shift to an increased proportion of patients receiving more vials (Fig. 2). In 2003, 46% of children received a single vial of material, while 43% received 2 vials and the remaining 11% received ≥3 vials. By 2008, the number of patients receiving 1 vial of material dropped to 27%, the number receiving 2 vials remained stable at 38% and the number of subjects receiving ≥3 vials had more than tripled to 36%. The mean vials used per procedure increased 33% over the study period (1.67–2.22 vials/procedure from 2003 to 2008, respectively, $p < 0.0001$, Fig. 3).

All hospitals analyzed increased their average vials used per procedure. The highest-volume centers (75th percentile) increased their average vials injected by 52% over the study period while the lowest-volume centers (25th percentile) increased their average vials injected by only 9% after adjustment for age.

The number of children undergoing a second injection was 7–9% each year, at an average of 8 months after their first injection. Patients who underwent repeated injections tended to receive the same number of vials injected at subsequent injections as their first procedure.

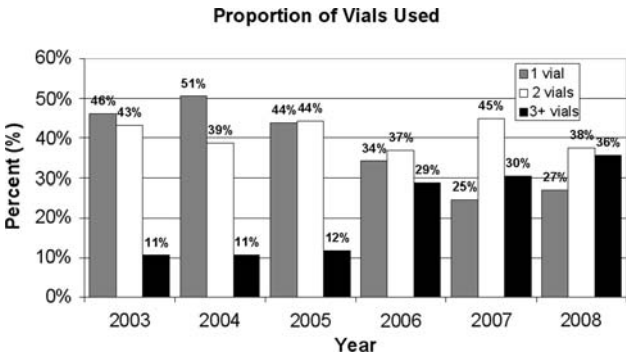

Fig. 2 Proportion of vials used by study year with an increase in the number of subjects receiving ≥3 vials per injection

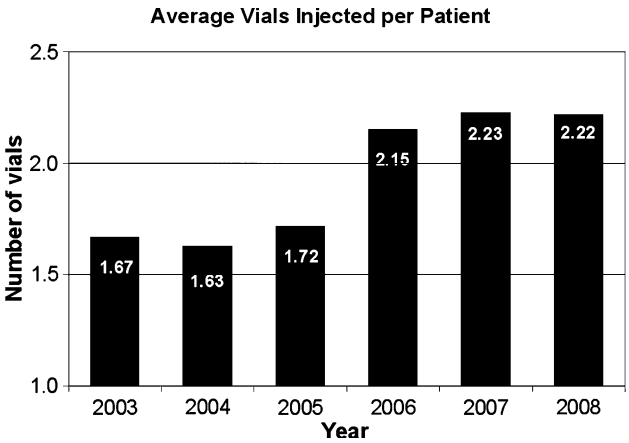

Fig. 3 Mean vials used per patient for each study year. There was a statistically significant increase ($p < 0.0001$) in the mean number of vials injected from 2003 to 2008

By comparison, at Seattle Children's Hospital from 2005 to 2008 there was a similar shift to an increased proportion of children receiving more vials. In 2005, 54% of children received a single vial of material while 31% received 2 vials and the remaining 15% received ≥3 vials. By 2008, the number of patients receiving 1 vial of material dropped to 20%, with 53% receiving 2 vials and the number of children receiving ≥3 vials had almost doubled to 27%. Over the study period, there was a 30% increase in the average vials used per procedure (1.68–2.17 vials/procedure from 2005 to 2008, respectively, $p = 0.03$). The mean age was similar to the PHIS cohort (5.2 ± 3.4 years) and did not vary significantly by year ($p = 0.65$). The average grade of reflux was 2.7 ± 0.8 (median 3) and did not vary by year ($p = 0.41$). Overall 39% of patients were treated for bilateral reflux with no significant differences by year ($p = 0.24$). We adopted the Hydrodistention Implantation Technique in June 2006 and noted a 20% increase in vials used (1.69 vs. 2.0 vials, $p = 0.04$) after adopting this technique.

Discussion

Using the PHIS database we previously identified a national increase in procedures for vesicoureteral reflux fueled by more than a threefold increase in patients undergoing endoscopic injection procedures [4]. As this treatment modality has become established, practitioner patterns of care have become increasingly important. Due to the significant cost of the material, we felt it valuable to explore the number of vials used per procedure over time at multiple institutions as endoscopic injections have increased in popularity.

This study demonstrates that multiple institutions have changed their intraoperative approach to vesicoureteral reflux with respect to the volume of injected material. There was a shift towards children receiving more vials per procedure. In 2003, most patients were treated with a single vial and only 11% received 3 or more vials, but by 2008 it was most common for a subject to receive 2 vials and the number of subjects that received ≥3 vials more than tripled (36%). These trends were most pronounced at the highest-volume centers and all 13 hospitals increased their average vials used per procedure over the study period.

The PHIS database is missing many of the important clinical variables helpful to interpret these data. Thus, we compared the trends identified in the PHIS database to a recent cohort of patients at our own institution undergoing subureteric injection. We found that the identified trends were mirrored at our own institution where there was a shift in the proportion of patients receiving more vials of material and a 30% increase overall in the average vials used per procedure. The average age and distribution of children treated at Seattle Children's Hospital was similar to those in the PHIS database. We feel the similarities between the patient populations and the identification of similar trends in the PHIS database and our own patients provide validity to the extrapolation of clinical data.

Using more vials per procedure increases the cost of endoscopic injection. At the time of these analyses, each 1 mL syringe of dextranomer/hyaluronic acid costs $1,045. There were no volume discounts and no changes in price since the product was released in the US in 2001 [13]. According to cost analyses, using more vials of material markedly increase the success rate necessary for injection therapy to achieve equal cost-effectiveness to ureteral reimplantation, but if more than 3 vials of material are required, endoscopic injection therapy can never be as cost-effective as ureteral reimplantation [7, 14].

The total cost of endoscopic injection depends largely on the material expense for the dextranomer/hyaluronic acid but the cost-effectiveness of any treatment for VUR must consider both cost and efficacy [15]. Studies have shown that injecting more material increase the success of subureteric injection, in addition to surgeon experience and injection technique [5, 6]. Therefore the ultimate potential benefit of injecting more material will depend on the balance between the additional cost and potential increase in success.

There are many possible explanations for the increase in the average vials used per procedure. This may be due to practitioners adopting new injection techniques such as the Hydrodistention Implantation Technique since this technique requires more material be injected to obtain the success rates that rival the gold standard of surgical reimplanation [5, 6, 16]. Some of the increase may be due to providers injecting higher grades of reflux, although high-grade refluxers make up a small proportion (2–3%) of the refluxing population [17]. Practitioners may be treating more bilateral reflux, or treating contralateral ureters in order to prevent de novo contralateral reflux.

An analysis of patients treated at our own institution reveals that over this 4 year time period, there was no difference in the average grade of reflux in patients treated with injection therapy, with no identifiable shift towards treating higher grades of reflux. There was also no increase in the proportion of patients with bilateral reflux. Only 13% of our patients undergoing an injection procedure had treatment of a non-refluxing contralateral ureter. After adopting the Hydrodistention Implantation Technique in June 2006 we did notice a 20% increase in vials used ($p = 0.04$) after adopting this technique.

This study has limitations. This is a retrospective study and is thus subject to the inherent biases and limitations of such a study design. The PHIS database is not population-based and not all hospitals reporting data to PHIS were able to be included due to the lack of ambulatory surgery data. The dataset does not include clinical data, and despite the similarities in our patient population and similar injection trends, we had to extrapolate clinical data from a single institution. Despite these limitations, this is the largest study of its kind in the literature. It includes children from multiple institutions in all regions of the US over several years, allowing us to analyze the temporal trends of injection therapy for a descriptive analysis of utilization trends of a material that is relatively expensive and unlikely to be missed in the billing process.

The goal of this study was not to evaluate success rates with newer injection techniques, but rather to identify changes in practice patterns at multiple institutions. There are important clinical and economic ramifications for the changes identified in this study. These data argue for the need for prospective studies and should be incorporated into future cost analyses. Economically, success due to increased volumes comes at the price of increased material costs. If increased injection volumes, despite the increased material costs, are associated with a significant, durable,

and sustained improvement in success rates, injection therapy may prove cost-effective and continue to serve as a primary invasive therapeutic option in patients with VUR [7, 14].

Conclusions

The number of vials of dextranomer/hyaluronic acid material used per procedure increased 33% from 2003 to 2008 while the number of children receiving 3 or more vials of material more than tripled. Studies have shown that injecting more material increase the success of subureteric injection but this comes at the price of increased material costs.

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