

ORIGINAL PAPER
ΕΡΕΥΝΗΤΙΚΗ ΕΡΓΑΣΙΑ

**Endoscopic injection treatment
of vesicoureteral reflux in children
A ten-year initial experience
at a single Greek institution**

OBJECTIVE To present our initial experience with endoscopic vesicoureteral reflux (VUR) management and investigate the predictive value of factors that could influence its outcome. **METHOD** The records of 79 children who had undergone endoscopic injection treatment (EIT) during the last ten years were examined. The following were included into the study as investigated and analyzed parameters: sex, age, VUR grade, VUR side, VUR bilaterality, VUR timing on voiding cystourethrogram (VCUG), preoperative relative renal function in dimercaptosuccinic acid (DMSA) scintigraphy, presentation of ureteral duplication, reinjection attempts, postoperative febrile urinary tract infection (UTI) and outcome. **RESULTS** VUR was successfully resolved with endoscopy in 88/120 ureters (73.3%) after 1–3 injections, and finally, 24/120 ureters (20%) underwent reimplantation. Children ≥6 years of age, girls, left-sided ureters, and ureters or children without duplication system, seem to be better candidates for successful EIT. Children with bilateral VUR, children presenting post-injection febrile UTI, and ureters with higher grade VUR, presented significant failure in EIT cure rates. **CONCLUSIONS** EIT is a safe and viable alternative option against open surgical ureteral reimplantation and long-term antibiotic prophylaxis. Reflux grades II–III present successful outcomes after EIT. Repeated injections after EIT failure were less satisfactory in grade IV and unsuccessful in grade V reflux. EIT needs further evaluation of long-term outcomes to implement predictive risk factors.

Vesicoureteral reflux (VUR) is the most common and controversial urological abnormality in children, with a prevalence of 1–2% for primary VUR.¹ Treatment options are often individualized and risk-based.¹ Many children with VUR may have spontaneous resolution of the disease with time. Treatment options in children present great variability, ranging from watchful waiting through antibiotic

prophylaxis administration and minimally invasive endoscopic procedures, to open or laparoscopic surgical ureteral reimplantation. The recently established and promising endoscopic injection treatment (EIT) initially became a popular alternative to open surgical ureteral reimplantation and long-term antibiotic prophylaxis in pediatric VUR management, and is currently recommended in selected

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Η ενδοσκοπική μέθοδος αντιμετώπισης της κυστεοουρητηρικής παλινδρόμησης στα παιδιά: Η δεκαετής αρχική εμπειρία μιας παιδοχειρουργικής κλινικής

Περίληψη στο τέλος του άρθρου

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centers as the first-line therapy.^{2,3} Parents of children with VUR are very likely to express a preference for EIT after all options have been explained to them,⁴ because of its minimal invasiveness, reduced morbidity and hospital stay. EIT presents variable reported cure rates between 67–93%,⁵ indicating differences in study design-methodology and inclusion criteria of patients. Concerns about its long-term efficacy and delayed complications have resulted in a controversy over its real usefulness in recent years.² One or multiple reinjection procedures are frequently necessary in 10–30% of cases with failed EIT.⁶ Furthermore, reflux recurrence is reported in 5–25% of children after a successful EIT.⁷

Many preoperative, intraoperative, and postoperative factors have been implicated with EIT success rates, with controversial assumptions. The endoscopic approach should be risk-adapted to current knowledge, but there is not any agreement on which predictive factors are the most determinant for its effectiveness yet.⁸ EIT needs further evaluation of long-term outcomes and has not gained momentum in Greek pediatric surgical practice yet. The aim of this study is to present our initial experience with endoscopic VUR management and discuss the predictive value of factors affecting the outcome.

MATERIAL AND METHOD

Study population

We reviewed the records of children who had undergone endoscopic correction of VUR at the Department of Pediatric Surgery of the “Hippocrateion” General Hospital at Thessaloniki, during a period of ten years (2010–2019). The following were included as studied factors: gender, age, VUR grade, bilaterality, presentation of reflux in the filling or voiding phase of preoperative voiding cystourethrogram (VCUG), preoperative dimercaptosuccinic acid scintigraphy (DMSA) defects, ureteral duplication, reinjections, postoperative febrile urinary tract infection (UTI) and final outcome.

Inclusion criteria

All patients enrolled in the study presented VUR of grades II–V, confirmed by voiding cystourethrogram following febrile UTI incidents. International system of radiographic grading of VUR was used. Patients with duplex ureter were also included in this study. DMSA was performed preoperatively in all patients for renal scarring detection, and relative renal function measurement (relative renal function less than 44% was defined as deficient, independently of scar presence). Indications for endoscopic intervention included persistent VUR grade \geq II or febrile UTI breakthrough with the patient being on medical treatment for at least 12–24 months, DMSA defect or new renal scars, and parental preference. Children presenting voiding dysfunction were not included in the study.

Injection technique

A combination of hydro-distension injection (HIT) and sub-ureteral transurethral injection (STING) technique (one submucosal injection under hydrodistension inside the ureteral tunnel and a second submucosal injection below the refluxing ureteral orifice) was used. For double ureters HIT technique was applied at the refluxing proximal ureter and STING technique at the distal ureter.

Follow-up

All patients were on a postoperative follow-up period from 12 months to 3 years. Postoperative control VCUG was performed in the third month after endoscopic injection. VUR resolution was defined as complete cessation, or downgrading from grades IV–V to grade I. In patients with persistent or recurrent VUR, a repeated second, and if necessary, a third injection attempt after six months were performed, respectively. Every patient with subsequent febrile UTI during the follow-up period underwent further VCUG and DMSA assessment. The diagnosis of a febrile UTI was set in every child who presented with temperature more than 38 °C and positive urine culture (bacterial count more than 10^5 of a single organism).

All patients were kept on prophylaxis with antibiotics until VCUG-determination of VUR resolution after the last endoscopic injection, or until ureteral reimplantation. Antibiotic prophylaxis was stopped in patients with persistent grade II primary VUR after three failed endoscopic attempts. These patients remained under surveillance. Open ureteral reimplantation was recommended for patients with persistent grade III or greater of VUR after three failed endoscopic attempts, for duplex system with persistent grade I–II VUR after three failed endoscopic attempts, and for patients with persistent grade II primary VUR who presented new renal scar and or deterioration of relative renal function after a new febrile UTI.

Statistical analysis

Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS) (IBM SPSS Statistics, version 24.0, Chicago, IL, USA). Categorical variables were compared by Chi-square test. Statistical significance was considered as $p < 0.05$.

RESULTS

Patient characteristics

A total of 79 children –58 (73.3%) female and 21 (26.6%) male patients– with a mean age of 5.6 years (range 12 months to 15 years, 36 patients <6 years, 43 patients \geq 6 years) underwent EIT for VUR correction during the study period of ten years. VUR was unilateral in 38 (48.1%) and bilateral in 41 (51.9%) patients, and combined with a duplex ureteral system in 8 patients. The corresponding total number of refluxing ureters comprised 120 units, of which 55 (45.8%) were right-sided and 65 (54.2%) left-sided. The

refluxing grades of the ureters were II (n=52, 43.3%), III (n=38, 31.7%), IV (n=21, 17.5%), and V (n=9, 7.5%).

Outcomes

VUR was successfully resolved in 55 (45.8%) refluxing ureters after a single injection, in 75 (62.5%) after a second one, and in 88 (73.3%) ureters after three injections. Detailed EIT outcomes in association with the number of attempts and the ureteral refluxing grades are shown in table 1 and figures 1–2.

A total of 11 (16.5%) patients presented febrile UTI after the injections. One patient presented ureteral obstruction which was managed with endoscopic placement of a double J catheter for 4 weeks.

Out of the 32 (26.7%) refluxing ureters in which reflux correction failed, 24 (20%) needed reimplantation surgery.

All patients remained under surveillance by a pediatric nephrologist, evaluating postinfectious upgrading of VUR or new DMSA scanning in terms of scar formation and relative renal function deterioration.

Outcome associated factors

All children with VUR managed with EIT were studied to identify possible predictive factors of success. Based on univariate analysis, bilateral VUR and post-injection febrile UTI were found to have statistically significant (p<0.05) association with failed injection treatment. Children aging ≥6 years, female gender, and those without duplex system VUR, though no statistically significant, presented more successful reflux resolutions compared to children <6 years, of male gender, and children with duplex system, respectively (tab. 2). DMSA relative renal function ≤44% and VUR timing on VCUG did not affect the success rate of the EIT procedure.

Table 1. Endoscopic injection treatment outcomes in association with the number of attempts and the ureteral refluxing grades.

VUR grades	Refluxing ureters		Single injection resolution		Second injection resolution		Third injection resolution	
	n	%	n	%	n	%	n	%
II	52	43.3	38	73.1	46	88.5	49	94.2
III	38	31.7	17	44.7	24	63.2	30	78.9
IV	21	17.5	0	0	5	23.8	8	61.9
V	9	7.5	0	0	0	0	1	11.1
Total	120	100.0	55	45.8	75	62.5	88	73.3

VUR: Vesicoureteral reflux

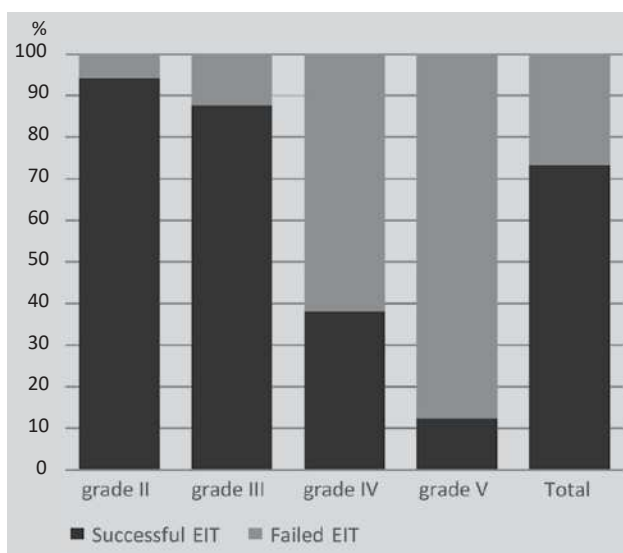


Figure 1. Endoscopic injection treatment (EIT) outcomes: Final correction outcomes of refluxing ureters after EIT in association with the grade of reflux.

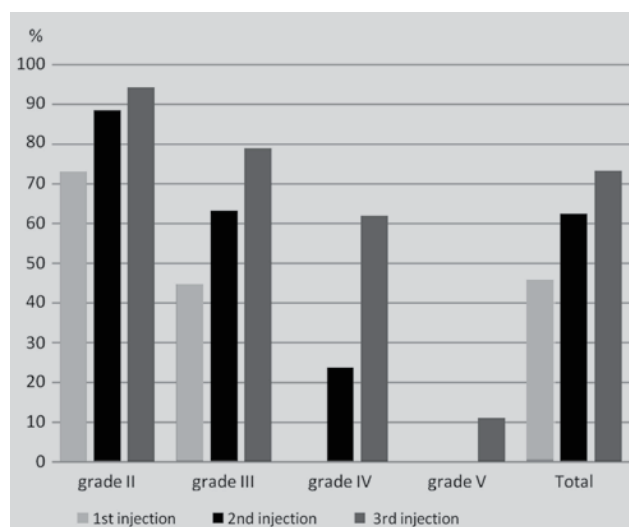


Figure 2. Endoscopic injection treatment (EIT) outcomes: Final correction outcomes of refluxing ureters after EIT according to vesicoureteral reflux (VUR) grade. Reflux correction percentages shown after one (white columns), two (black columns) and three (grey columns) injections.

Refluxing ureters with high grade (IV and V) of VUR were found to have a statistically significant ($p < 0.05$) failed EIT rate compared to lower grades. Left-sided ureters and those without duplex system presented, though non-statistically significant, more reflux resolutions than right-sided ureters and these of a duplex system, respectively (tab. 3).

DISCUSSION

With the wide use of EIT and long-term follow-up, failed

treatments are being encountered, despite the added endoscopic experience and the apparent success rates improvement over time. Accumulated endoscopic experience affected the VUR resolution rates, in association with a variety of characteristics or risk factors.⁹ The HIT technique seems to have statistically significant success rates compared to the traditional STING for high grade VUR cases,¹⁰ with double HIT technique currently achieving the highest success rates.¹¹ A combination of HIT and STING techniques can be performed,¹² and we chose this

Table 2. Factors associated with endoscopic injection treatment outcomes in the children ($n=79$) of the study. Significant outcomes are indicated.

Factors n (%)	Total	Successful		Failed		Surgery		Significance p value
	n	n	%	n	%	n	%	
Study population	79	50	63.3	29	36.7	21	26.6	
Age <6 years	36	21	58.3	15	41.7	13	36.1	0.403
Age ≥6 years	43	29	67.4	14	32.6	8	18.6	
Female patients	58	40	69.0	18	31.0	13	22.4	0.082
Male patients	21	10	47.6	11	52.4	8	38.0	
Unilateral VUR	38	35	92.1	3	7.9	3	7.9	0.000
Bilateral VUR	41	15	36.6	26	63.4	18	43.9	
Filling VCUG	48	29	60.4	19	39.6	14	29.2	0.510
Voiding VCUG	31	21	67.7	10	32.3	7	22.6	
DMSA ≤44%	49	30	61.2	19	38.8	13	26.5	0.626
DMSA >44%	30	20	66.7	10	33.3	8	26.7	
Single ureteral system	71	46	64.8	25	35.2	17	23.8	0.411
Duplex ureteral system	8	4	50.0	4	50.0	4	50.0	
Post-injection UTI	11	1	9.1	10	90.1	8	72.7	
Without post-injection UTI	68	49	72.1	19	27.9	13	19.1	0.000

VUR: Vesicoureteral reflux, VCUG: Voiding cystourethrogram, DMSA: Dimercaptosuccinic acid scintigraphy, UTI: Urinary tract infection

Table 3. Factors associated with endoscopic injection treatment outcomes in the refluxing ureters ($n=120$) of the study. Significant outcomes are indicated.

Factors n (%)	Total	Successful		Failed		Surgery		Significance p value
	n	n	%	n	%	n	%	
Refluxing ureters	120	88	73.4	32	26.7	24	20.0	
Right sided reflux	55	39	70.1	16	29.9	13	23.6	
Left sided reflux	65	49	94.2	16	24.6	11	16.9	0.581
Grade II	52	49	94.2	3	5.8	3	5.8	
Grade III	38	30	78.9	8	11.1	6	15.8	
Grade IV	21	8	38.1	13	61.9	8	38.1	0.000
Grade V	9	1	11.1	8	78.9	7	77.8	
Grades II and III	90	79	87.8	11	12.2	9	10.0	
Grades IV and V	30	9	30.0	21	70.0	15	50.0	0.000
Single ureteral system	112	84	75.0	28	25.0	20	17.6	
Duplex ureteral system	8	4	50.0	4	50.0	4	50.0	0.122

method as initial VUR endoscopic treatment of all cases, aiming to the accomplishment of better results. The most significant potential complication of EIT for VUR includes a risk of ureteral obstruction of less than 1%.³

We can no longer view VUR as a homogeneous entity affecting all children equally, and we should consider individual parameters and specific factors for a case-by-case, risk-to-benefit-based deciding VUR management.^{1,13} Studies have attempted to define and suggest prognostic factors for EIT success, but with contradictory results. We herein report studies with positive correlation of factors with EIT cure rate, though many present contradictory results.

Grades II–III are considered as mid-grade, and grades IV–V as high-grade reflux. In certain systematic reviews, the reported success rates were 80–90% for grade I VUR, 79–84% for grade II, 72% for grade III, 59–63% for grade IV, and 51–62% for grade V.^{14,15} Lower success rates were encountered in higher grades of VUR, and application of second and third injections were needed to increase them.^{16,17} Studies reported VUR resolution per ureter rate (53–89%) after a single endoscopic injection.^{6,18} Patients with grade V reflux tended to have primary reimplantation surgery. Recently, increasing evidence has been emerging to support the use of EIT in children with grade V VUR,¹⁹ but high grade VUR is a predisposing factor for endoscopic treatment failure, performing by less experienced surgeons.⁹ Our results were consistent with other reports and concurred with the declined success rate at extended follow-up. High grade VUR, duplicated systems, and reduced experience comply with any lower cure rates observed.

There is a significant positive correlation between grade, bilaterality, recurrent pre-injection UTIs, history of voiding dysfunction, defects on DMSA scan, and persistent or recurrent VUR after EIT.²⁰ The success rate of EIT is significantly reduced in the presence of abnormal voiding habits, and additional injections are needed.^{16,21} Bilaterality is also a significant prognostic factor for the success rate of EIT.^{22,23} Preoperative VCUG timing for VUR is found to be an independent factor for VUR resolution after EIT, and a filling reflux has a significant lower success rate than a voiding reflux, especially in children with high-grade VUR.^{24,25}

Renal units with preoperative DMSA changes (hypoplasia, scars, uptake $\leq 40\%$) are at a higher recurrence and a lower cure risk, as a possible result of maldevelopment.^{11,17,22,26} Renal scars on preoperative scintigraphy are significantly associated with postoperative febrile UTI and possible EIT failure.^{11,16} A DMSA-based division could assist in selecting children with VUR who would benefit from early intervention.²⁷

Postoperative febrile UTI is significantly associated with EIT failure.¹⁶ Recurrence of febrile UTI may occur after three years of follow-up and within the first five years after EIT.^{28,29} Female gender, older age, and voiding dysfunction are the most important risk factors in the development of febrile UTI in children during long-term follow-up after successful EIT correction of VUR.^{30,31} In children with post-injection UTI who underwent a repeated VCUG, the incidence of recurrent VUR is reported between 35% and 82%.³²

Radiologic success of EIT is statistically less common in males compared to females.²² On the other hand, females are more favorable to post-injection UTI than males.⁵ Age ≥ 6 years is a positive predictor,³³ while age < 1 year is a negative predictor of EIT success.²⁷

EIT outcomes are more favorable and significantly higher in patients with single versus double ureters.¹⁵ Duplicated systems as complex cases of VUR have lower cure rates but are not associated with EIT failure.^{2,12,34} Boys, and children with bilateral VUR or duplex ureteral system should be treated by more experienced endoscopic surgeons.⁹

The study presented certain limitations. A larger series of patients would give more powerful statistically significant results regarding age, gender, side of ureter, and duplex system. Our results implied a correlation between these parameters and EIT success. DMSA scarring evaluation and cut-off about 40% in relative renal function could possibly give more important results. Follow-up period of children who underwent EIT the last year of the study was shorter. Retrospective nature of data based on case records was another limitation, rendering the need of performing more prospective studies.

In conclusion, our initial experience with EIT has been promising. By identifying the prognostic factors, pretreatment counseling could be improved. EIT, with rare postoperative complications, is a favorable alternative against open surgical ureteral reimplantation and long-term antibiotic prophylaxis, provides satisfactory reflux resolution rates that decreases with increasing grade and bilaterally presentation. Grades II–III of reflux gain a successful outcome of EIT. High VUR grade is the most well-known factor that can affect the success rate of the procedure. Repeated injections after EIT failure were less satisfactory in grade IV reflux and unsuccessful in grade V reflux. EIT needs further evaluation of long-term outcomes for predictive risk factors determination.

Ethical approval

The study has been approved by the Bioethics Committee of the institution where it was performed.

ΠΕΡΙΛΗΨΗ

Η ενδοσκοπική μέθοδος αντιμετώπισης της κυστεο-ουρητηρικής παλινδρόμησης στα παιδιά: Η δεκαετής αρχική εμπειρία μιας παιδοχειρουργικής κλινικής

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ΣΚΟΠΟΣ Η παρουσίαση της αρχικής μας εμπειρίας με την εφαρμογή της ενδοσκοπικής μεθόδου αντιμετώπισης (ΕΙΤ) της κυστεο-ουρητηρικής παλινδρόμησης (ΚΟΥΠ) και η διερεύνηση της προγνωστικής αξίας παραγόντων που θα μπορούσαν να επηρεάσουν την τελική της έκβαση. **ΥΛΙΚΟ-ΜΕΘΟΔΟΣ** Διεξήχθη αναδρομική ανασκόπηση των ιατρικών φακέλων των παιδιών που υποβλήθηκαν σε ενδοσκοπική διόρθωση της ΚΟΥΠ στην Παιδοχειρουργική Κλινική του Γενικού Νοσοκομείου «Ιπποκράτειο» Θεσσαλονίκης κατά την περίοδο των τελευταίων 10 ετών (Ιανουάριος 2010–Ιανουάριος 2019). Εξετάσαμε την πιθανή στατιστικά σημαντική επίδραση στην τελική έκβαση της ενδοσκοπικής θεραπείας των παρακάτω παραγόντων: ηλικία, φύλο, βαθμός ΚΟΥΠ, πλευρά εντόπισης ΚΟΥΠ, κυστεογραφικά (εμφάνιση ΚΟΥΠ στη φάση πλήρωσης ή κένωσης) και σπινθηρογραφικά (σχετική νεφρική λειτουργία <44% ανεξάρτητα της παρουσίας νεφρικής ουλής) ευρήματα, παρουσία διπλού συστήματος ουρητήρων, αμφοτερόπλευρη ΚΟΥΠ και μετεγχειρητική ουρολοίμωξη. **ΑΠΟΤΕΛΕΣΜΑΤΑ** Η ΚΟΥΠ διορθώθηκε επιτυχώς ενδοσκοπικά σε 88 (73,3%) παλινδρομούντες ουρητήρες μετά από 1–3 συνολικά εγχύσεις. Από τους 32 (26,7%) παλινδρομούντες ουρητήρες στους οποίους απέτυχε η ΕΙΤ, 24 (20%) υποβλήθηκαν σε ανοικτή χειρουργική επέμβαση μετεμφύτευσης. Η αμφοτερόπλευρη ΚΟΥΠ και η ανάπτυξη εμπύρετης ουρολοίμωξης μετά την ενδοσκοπική έγχυση είχαν στατιστικά σημαντική σχέση με την αποτυχημένη έκβαση της ΕΙΤ. Οι ουρητήρες με υψηλού βαθμού (IV και V) ΚΟΥΠ βρέθηκαν να έχουν στατιστικά σημαντικά αυξημένο ποσοστό αποτυχίας της ΕΙΤ. Τα παιδιά ηλικίας ≥6 ετών, το θήλυ φύλο και εκείνα με ΚΟΥΠ μονήρους ουρητήρα, αν και όχι στατιστικώς σημαντικά, παρουσίασαν καλύτερα ποσοστά ενδοσκοπικής διόρθωσης ΚΟΥΠ. **ΣΥΜΠΕΡΑΣΜΑΤΑ** Η αρχική μας εμπειρία με την ενδοσκοπική θεραπεία έγχυσης ήταν πολλά υποσχόμενη. Τα ποσοστά επιτυχίας της μειώνονται με την αύξηση του βαθμού και την αμφοτερόπλευρη προσβολή της ΚΟΥΠ. Οι επαναληπτικές εγχύσεις μετά την αποτυχία της μεθόδου είναι λιγότερο αποτελεσματικές στην παλινδρόμηση βαθμού IV και ανεπιτυχείς στην παλινδρόμηση βαθμού V. Απαιτείται περαιτέρω αξιολόγηση των μακροπρόθεσμων αποτελεσμάτων για τον προσδιορισμό των προγνωστικών παραγόντων κινδύνου αποτυχίας της μεθόδου.

Λέξεις ευρετηρίου: Ενδοσκοπική θεραπεία, Κυστεο-ουρητηρική παλινδρόμηση, Παράγοντες κινδύνου, Πρόγνωση

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