

Research Article / Araştırma Makalesi

Results of Preference of Subureteric Injection or Ureteroneocystostomy As the Initial or Subsequent Surgical Intervention in Vesicoureteral Reflux

Vezikoureteral Reflüde İlk veya Sonraki Cerrahi Girişim Olarak Subüreterik Enjeksiyon veya Üreteroneosistostomi Tercihinin Sonuçları

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Abstract: The incidence of vesicoureteral reflux (VUR) in childhood is 0.4-1.8%. Among the surgical treatment options, there are two different approaches: Subureteric injection (SUI) and ureteroneocystostomy (UNC). In this study, we evaluated the operation results of patients who underwent SUI and UNC for VUR. Patients who underwent surgical treatment for vesicoureteral reflux in a tertiary university hospital between 2010-2018 were retrospectively analyzed. The surgical techniques applied to the patients, whether the procedure was successful or not, and additional interventions needed afterwards were recorded. The success rates of the two different techniques applied were compared. Of the 274 patients included in the study, 219 received SUI as the first procedure, 57% of patients did not need additional intervention. After the first SUI, 13.1% of patients underwent UNC as the second procedure. A second SUI was given to 21.2% of patients. UNC was given to 5.5% of patients who received two injections, and 4% of patients were underwent a third SUI. 59.8% patients were treated with SUI alone. Reflux was treated in 65.6% of patients with a single procedure. In VUR patients, SUI should be the first treatment choice because of its high success rate, low complication risk and not preventing UNC.

Keywords: Vesicoureteral reflux, Subureteric injection, Ureteroneocystostomy

Özet: Çocukluk çağında vezikoureteral reflü (VUR) görülme sıklığı %0,4-1,8'dir. Cerrahi tedavi seçenekleri arasında iki farklı yaklaşım bulunmaktadır: Subüreterik enjeksiyon (SUI) ve üreteroneosistostomi (UNC). Bu çalışmada, VUR nedeniyle SUI ve UNC uygulanan hastaların operasyon sonuçlarını değerlendirdik. Üçüncü basamak bir üniversite hastanesinde 2010-2018 yılları arasında vezikoureteral reflü nedeniyle cerrahi tedavi uygulanan hastalar retrospektif olarak analiz edildi. Hastalara uygulanan cerrahi teknikler, işlem başarısı ve sonrasında ihtiyaç duyulan ek müdahaleler kaydedildi. Uygulanan iki farklı tekniğin başarı oranları karşılaştırıldı. Çalışmaya dahil edilen 274 hastanın 219'una ilk işlem olarak SUI uygulandı, %57 hastaya ek müdahale gerekmedi. İlk SUI'den sonra hastaların %13,1'ine ikinci prosedür olarak UNC uygulandı. Hastaların %21,2'sine ikinci bir SUI uygulanmıştır. İki kez enjekte edilen hastaların %5,5'ine UNC, %4'üne ise üçüncü SUI uygulandı. Hastaların %59,8'i tek başına SUI ile tedavi edildi. VUR %65,6 hastada tek işlemlerle tedavi edildi. VUR hastalarında SUI, yüksek başarı oranı, düşük komplikasyon riski ve UNC'yi engellememesi nedeniyle ilk tedavi seçeneği olmalıdır.

Anahtar Kelimeler: Vezikoureteral reflü, Subüreterik enjeksiyon, Üreteroneosistostomi

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1. Introduction

The prevalence of vesicoureteral reflux (VUR) is reported to be 0.4%–1.8%. Patients are diagnosed in the examinations performed after urinary tract infection (UTI), evaluating a patient diagnosed with hydronephrosis, or investigating voiding dysfunction [1]. VUR-related nephropathy is one of the most common causes of childhood hypertension. It also causes end-stage kidney disease [2-4].

The first target in the treatment of VUR is to prevent refluxing of infected urine to the kidney [2]. The treatment options include continuous antibiotic prophylaxis, SUI, and UNC. The choice of treatment depends on many factors such as the degree of VUR severity, ipsilateral kidney function, additional anomalies in the bladder and ureter, patient age, treatment compliance, parental preference, surgeon's preference, and experience [5].

In our study, we aimed to investigate the effect of the management preferences on the success rate by comparing the results of patients with VUR who underwent subureteric injection (SUI) or ureteroneocystostomy (UNC) as initial or subsequent interventions with review of the literature.

2. Materials and Methods

This study was conducted with the approval of the Non-Interventional Clinical Research Ethics Committee (date 31.07.2017 and number 13).

The data of 298 patients who underwent SUI and/or underwent UNC for VUR between June 2010 and August 2018 at our clinic were retrospectively evaluated. A total of 24 patients who received SUI more than three times, or underwent UNC more than once, as well as patients who underwent SUI following UNC were excluded from the analysis.

Preoperative and postoperative records of the operated patients were reviewed. Patients who were examined for UTI, voiding dysfunction, or antenatal hydronephrosis and diagnosed with VUR were selected.

Surgical intervention was conducted in patients with UTI despite antibiotic prophylaxis, presence of diseases causing secondary VUR (such as ureterocele, diverticulum, double collecting system, etc.), cessation of renal growth expected according to patient age, development of new kidney scar, failure of regular and safe medication administration, older age at the diagnosis of reflux, or long duration of reflux.

The factors considered in decision making process were age, the patient's other diseases, anesthesia-related risks, additional anatomical anomalies in the urinary system, reflux degree, presence of parenchymal scarring and loss of function, lower urinary system dysfunction, parental preference, and patient compliance. The basic approach was to specify the treatment according to the patient's condition; however, SUI was recommended to families as the primary choices in appropriate cases or following the cystoscopy. UNC was preferred as the initial procedure in patients with additional anomaly (cloaca exstrophy, bladder exstrophy, etc) and in those with ectopic localization and/or severely tortuous ureter on cystoscopy or with the family's preference.

Some patients were informed that they would start the operation with diagnostic cystoscopy. All patients were informed that they could transition to open surgery if necessary. Information about both procedures was provided, including hospital stay, probability of treatment failure and follow up process. Consent forms for both procedures were signed. Open surgery was offered to some patients, either due to higher success rate, the presence of additional anomalies, difficulty in reaching the hospital, or non-compliance with treatment. Only those who were recommended open surgery signed consent for UNC.

The urethra, bladder, and ureteral openings were evaluated in the lithotomy position during cystoscopy for SUI. Dextranomer microparticles and cross-linked hyaluronic acid gel solution (Dexell) were preferred as injection material for SUI. Polyacrylate–

polyalcohol copolymer (Vantris) was used as injection material for a short period.

Intravesical Cohen technique was utilized in those who underwent UNC. A DJ stent or feeding tube was placed in the operated ureter and a foley catheter was placed in the bladder in all patients. According to the urine output and hematuria follow-up in patients who had a feeding catheter inserted into the ureter, the feeding catheter followed by the foley catheter was removed after an average of 1–5 days. In cases with DJ stent, the foley catheter was removed during the early postoperative period according to the urine output and hematuria monitoring. The DJ stent was typically removed approximately 3 weeks later under general anesthesia using cystoscopy.

Patients who underwent SUI were assessed using ultrasonography (USG) in the first month and voiding cystourethrogram in the 3rd month after the procedure. All patients were followed up with antibiotic prophylaxis until the treatment of VUR was terminated. Nitrofurantoin or trimethoprim-sulfamethoxazole was used as prophylactic antibiotics. Control VCUG was not routinely performed in patients who underwent UNC unless additional findings were present, and the patients were followed up with clinical findings, urine analysis, and USG.

Data analysis was performed using IBM SPSS 21 package program. The conformity of quantitative variables to normal distribution was investigated using Shapiro–Wilk test. Quantitative variables with normal distribution were reported as mean \pm standard deviation, and those without normal distribution were reported as median and quartile ranges (Q1–Q3). During the comparison of the pre and post measurements, dependent sample *t* test was used if the distribution of the differences was normal, and Wilcoxon test was used if it was not normally distributed. Qualitative variables are shown as frequency and percentage (%). The relationship between qualitative variables was examined by chi-square analysis. A *p* value of <0.05 was considered statistically significant.

3. Results

Of 274 patients, 25.5% had isolated right VUR ($n = 70$), 27% isolated left VUR ($n = 74$), and 47.4% had bilateral VUR ($n = 130$). As the initial intervention, SUI was performed in 219 (79.9%) of the 274 patients while UNC was performed in the remaining 55 (20%).

As soon as vesicoureteral reflux was diagnosed in all patients, prophylaxis was initiated. Nitrofurantoin or trimethoprim-sulfamethoxazole was recommended for prophylaxis. Prophylaxis was continued until reflux completely resolved in all patients or until all stents used were removed.

The screenings conducted prior to the initial intervention were reviewed. It was observed that scarring scan (DMSA-dimercaptosuccinic acid scintigraphy) was performed on 408 ($n=204$) renal units. Scarring was detected in a total of 76 renal units.

Dextranomer was used in patients (74%) and polyacrylate–polyalcohol was used 57 (26%) were used in SUI for the first time. Among patients treated with polyacrylate-polyalcohol or other patients, no cases requiring emergency surgical intervention due to obstruction were reported. The injection material information of 20 patients could not be obtained.

The mean age of 219 patients who received SUI for the first time was 64.1 ± 47.1 months, and 35 (16%) patients who had their first injection were under the age of one. Among the patients injected under the age of one, female/male ratio was 13/22, while in the 184 patients over the age of one who received injections, the female/male ratio was 115/69.

First injection was successful, and there was no need for second intervention in 125 out of 219 patients (57%). Our study revealed that for patients with advanced dilatation in the ureteral orifice, double collecting system, diverticulum or ureterocele during the initial intervention as well as for those with frequent UTIs, severe increase in renal function loss, and insufficient tumefaction, UNC was preferred as a second intervention instead of

SUI. UNC was performed in 36 (13.1%) patients after the first injection. Overall, 58 (21.2%) patients had SUI for the second time. Following two SUI procedures, 15 patients (5.5%) underwent UNC as a subsequent intervention, and 11 patients (4%) received a third injection. Only four (1.5%) patients underwent UNC after three SUIs. In total, 55 patients (20.1%) who received SUI for the first, second, or third time were followed by UNC (Figure 1).

The success rate after a single injection was 57%; however, successful results were obtained in 55% and 63.6% patients who received the second and third injections, respectively. Overall, 180 patients (65.6%) were treated with a single intervention (UNC or SUI); 248 (90.5%) were treated with at most two interventions; and 270 patients (99.2%) were treated with at most three interventions (Table 1).

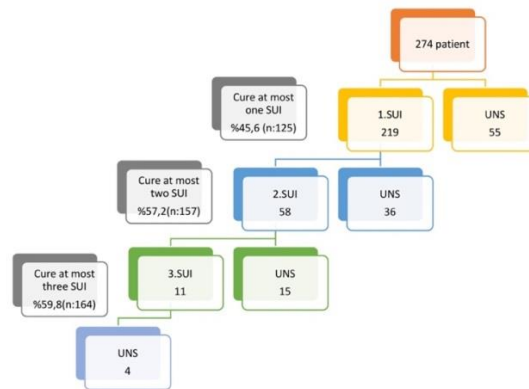


Figure 1. Flow Chart

The total number of patients successfully treated with only SUI was 164 (59.8%). In total, 110 patients underwent UNC. The mean age at which UNC was performed was 110 months. Eight (7.2%) patients under the age of one underwent UNC. During clinical and

USG follow-up of the patients underwent UNC, VCUG was performed if additional complaints or signs were found. The number of the patients who required VCUG after UNC was 24 (21.8%) and none of those studies have showed the reflux.

Table 1. Success rates according to the number of interventions (SUI or UNC)

Success rates according to the number of interventions n(%)	
Cure at most one intervention	180 (%65,6)
Cure at most two intervention	248 (%90,5)
Cure at most three intervention	270 (%98,5)

The difference and significance between choosing SUI or UNC as the initial procedure was compared using two proportion tests and the preference of SUI was found to be significant ($p < 0.001$), whereas the difference

and significance between choosing SUI and UNC as the second and third procedure were not found to be significant ($p = 0.148$ and $p = 1.000$), respectively.

4. Discussion and Conclusion

The main aim in the treatment of VUR is to prevent infected urine from reaching the ureters and kidney from the bladder [1]. Kidney damage resulting from VUR, known as reflux nephropathy, stands as one of the most prevalent causes of hypertension in childhood. About 10%–20% children with reflux nephropathy progress to hypertension or end-stage renal disease [2,3].

The likelihood of renal cortical scarring following pyelonephritis subsequent to VUR has tripled [6,7]. In 2006, Polito et al. reported that permanent kidney damage after febrile UTI is attributed to existing VUR. In a comparison study of pediatric patient groups including 206 with VUR and 77 without VUR, assessing renal damage, significantly higher results were observed in the VUR group [8]. In a study evaluating renal scarring in VUR, encompassing 197 children with VUR with a mean age of 4.26 years, renal damage occurred in 67% of 282 kidney units with VUR and in 16% of 112 kidney units with no VUR [9].

In a meta-analysis published in 2019, 12 studies comparing continuous antibiotic prophylaxis with placebo were examined, and continuous antibiotic prophylaxis did not show a significant difference in the risk of developing symptomatic UTI [10]. Similarly, an analysis of eight separate studies found little or no difference in new kidney scar formation between continuous antibiotic prophylaxis and placebo [10]. In six studies examining bacterial antibiotic resistance, bacterial resistance was found to be approximately three times higher in children who received continuous antibiotic prophylaxis than in those who did not [10]. Spontaneous resolution was evaluated in three studies and that there was little or no reflux resolution in the 2-year follow-up [10]. In this study, continuous antibiotic prophylaxis administered to all patients when reflux was detected to prevent infection and scar formation. Additionally, intervention was also recommended for eliminating reflux. Until reflux was eliminated, all patients remained under continuous antibiotic protection.

SUI treatment with cystoscopy is a simple outpatient treatment approach with well-established safety [11]. Elder et al. reported a success rate of 67.1% after the first injection. This rate gradually decreased in the second and third procedures; it was 54.4% and 33.9% after the second and third injections, respectively [12]. In the study of Chertin et al., 507 pediatric patients treated with subureteric injection were examined, and successful outcomes observed in 473 renal units (68 %) after first injection, 161 renal units after second injection (23 %) and 25 (3.6 %) after third injection [13]. In this study, the success rate of treatment after single and second injection was consistent with the literature, whereas the success rate in patients who received the third injection was higher than that reported in other studies; additionally, no patient was received a fourth injection [12, 13].

In a study published in 2013 comparing ureteral reimplantation (Cohen technique) and endoscopic treatment, a success rate of 91% was achieved with endoscopic treatment and 100% with ureteral reimplantation [14]. This study concluded that multiple injection therapy was as effective as ureteral reimplantation after a 5-year follow-up of patients. Prioritizing cystoscopic evaluation in our study enabled a detailed examination of the lower urinary tract anatomy and existing pathology. Determining the anatomical features of the lower urinary tract by cystoscopy first helped to determine which method could be preferred as the first intervention. In our study, VUR treatment was completed in 59.8% of patients by performing only SUI with one to three injections. The results of the present study and the literature show that endoscopic evaluation and SUI allow appropriate patient selection, enabling many patients to respond to treatment without the need for open surgery, and it should be considered as the first line diagnosis and treatment approach in VUR [12, 14].

In patients planned for surgical intervention due to VUR, the choice of the first intervention as SUI or UNC is based on preoperative clinical and radiological

examinations, cystoscopic evaluation, and anatomy of the lower urinary tract. The treatment decision for the second and third intervention based on the response to initial intervention, determines the success of the treatment. In the present study, 65.6% of patients obtained successful results with a single intervention (UNC or SUI), 90.5% with two interventions, and 99.2% after three interventions. This outcome underscores the importance of factors influencing the decision-making process for the method to be used at each stage of VUR treatment. Determining the patient-specific second and third approach according to the clinical course, existing anatomy, and response to the first intervention will increase the success rate.

SUI technique has gained popularity due to its minimally invasive nature, easy of learning, and has a significant success rate with a low complication rate. [15]. The decision for the surgeon to choose SUI as the first endoscopic treatment depends on various factors such as laterality, additional anatomical anomalies, age of presentation, reflux degree, presence of parenchymal scarring, lower urinary system dysfunction, parental preference, and patient compliance. However, it is unclear which

treatment to choose when these factors are examined at the individual patient level. Injection therapy was preferred as the first choice in the present study. The absence of significant complications during the early and late postoperative periods and the recovery of VUR in our patients who underwent UNC after SUI show that SUI does not adversely affect the surgical course and success rate of these patients.

This study has a retrospective design, so we could not access complete data for all patients. This situation may have prevented us from accessing some important data. The lack of screening for vital signs and hypertension data is a significant limitation that may restrict the comprehensive evaluation of the results. However, we are aware of these limitations and have attempted to interpret our results based on the available data to enhance the reliability of our study.

In conclusion; in cases of VUR, SUI can be considered as the first treatment option due to its high success rate, low complication risk, and non-interference with subsequent open surgery.

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Ethics

Ethics Committee Approval: The study was approved by Eskişehir Osmangazi University Noninterventional Clinical Research Ethical Committee (Decision no: 13, Date: 31.07.2017).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

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