

Revisiting the EAU Paediatric Urology Guideline Risk Grouping On Vesicoureteral Reflux: Shall We Challenge Ourselves?

Vezikoüreteral Reflüde Risk Gruplandırması Konusunda EAU Çocuk Ürolojisi Kılavuzlarının Yeniden Gözden Geçirilmesi: Kendimizi Sorgulamalı mıyız?

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ABSTRACT

Objective: To challenge retrospectively the treatment outcomes of vesicoureteral reflux (VUR) management according to new EAU Paediatric Urology Guideline Risk Grouping on VUR.

Methods: The records of the patients who received medical and/or surgical treatment between 2009-2012 due to VUR were reviewed. History, demographic variables, diagnostic features (presence of renal scar, grade of reflux, laterality), clinical course, causes of failure, secondary intervention type and follow-up variables were analyzed. The patients were classified as low, moderate and high-risk groups according to EAU paediatric urology guideline. Treatment failure is defined as new urinary tract infection and presence of new renal scar during follow-up.

Results: A total of 157 patients with 232 renal units (RU) were treated due to VUR. 33(71.7%) of 46RU's were treated with sub-ureteric injection and 18(39.1%) unsuccessful RU's were treated with re-injection in low risk group. Only 2(11.1%) re-injected RU's had postoperative UTI and/or new renal scar at follow-up. In moderate risk group, 54 and 7 of 61 unsuccessful RU's were treated with re-injection and ureteral re-implantation, respectively. 4(7.4%) of 54 had postoperative UTI and/or new renal scar at follow-up. In high-risk group, 13 and 12 of 25 unsuccessful RU's treated with re-injection and ureteral re-implantation, respectively.

Conclusion: We detected over treatment in low risk group. Success of the surgical correction was evident in moderate and high-risk group. The surgeon should be more pursuer in low risk and more invasive in moderate and high-risk group.

Key Words: Vesicoureteral reflux, treatment, risk

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ÖZET

Amaç: Vezikoüreteral reflüde (VUR) risk gruplaması konusundaki yeni EAU kılavuzlarına göre VUR için yaptığımız tedavilerin sonuçlarının tekrar değerlendirilmesi.

Yöntem: 2009-2012 yılları arasında VUR nedeniyle medikal veya cerrahi tedavi görmüş hastaların kayıtları tekrar incelendi. Hikaye, demografik veriler, tanı esnasındaki klinik özellikler (renal skar varlığı, reflü derecesi, reflü yönü), klinik seyir, başarısızlık nedenleri, ikincil girişim tipi ve takipte elde edilen veriler değerlendirildi. EAU kılavuzlarına göre hastalar düşük, orta ve yüksek risk gruplarına ayrıldı. Tedavi başarısızlığı, yeni tanımlanan üriner sistem enfeksiyonu ve takipte yeni oluşan renal skar olarak kabul edildi.

Bulgular: VUR nedeniyle 159 hastanın 232 renal ünitesi tedavi edilmişti. Primer tedavi ile elde edilen sonuçlar tablo 1'de özetlenmiştir. Düşük risk grubunda olan 46 RÜ'nün 33(%71.7)'ü subüreterik enjeksiyon ile tedavi edilmişti. Bu hastalar arasında başarısız ilk tedavi nedeniyle re-enjeksiyon yapılan 18(%39.1) hasta mevcuttu. Re-enjeksiyon yapıp takipte yeni renal skar tespit edilen veya üriner sistem enfeksiyonu geçiren sadece 2(11.1%) hasta vardı. Orta risk grubunda ilk tedavisi başarısız olan 61 hastanın 54'ü re-enjeksiyon, 7'si üreteral re-implantasyon ile tedavi edildi. 54 hastanın 4(%7,4)'ünde takipte yeni renal skar veya üriner sistem enfeksiyonu tespit edildi. Yüksek risk grubunda ilk tedavisi başarısız olan 25 hastanın 13'ü re-enjeksiyon, 12'si üreteral re-implantasyon ile tedavi edildi.

Sonuç: Düşük risk grubunda gereksiz tedavi uygulanmış olduğunu söyleyebiliriz. Orta ve yüksek risk grubu hastalarda cerrahi tedavinin başarısı daha belirgindi. Cerrah, düşük risk grubunda daha sık takip kararı vermeli, orta ve yüksek risk grubunda ise daha girişimsel davranmalıdır kanaatindeyiz.

Anahtar Sözcükler: Vezikoüreteral reflü, tedavi, risk

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INTRODUCTION

Vesicoureteral reflux (VUR) is a very common urological anomaly that affects nearly 1% of children in the population (1). In fact, management of VUR is one of the most controversial issues in paediatric urology. Preventing renal damage is the main goal of treatment. However, new renal scars can be occurred due to presence of febrile urinary tract infection (UTI), high-grade reflux, bilateral VUR, cortical abnormalities and lower urinary tract dysfunction (LUTD). Current treatment options include re-implantation of the ureters, continuous antibiotic prophylaxis (CAP), sub-ureteric endoscopic injections by using different materials, or a combination of interventions. The presence of renal scars, renal functions, clinical course, grade and laterality of reflux, associated anomalies, lower urinary tract functions, age, compliance, and parental preference are the key factors for determining best management of VUR (2). The optimal management of VUR is controversial and has been discussed over more than thirty years several times in the literature. The traditional approach of initial medical treatment after diagnosis and shifting to interventional treatment in case of breakthrough infections and new scar formation needs to be challenged.

Although medical therapy with antibiotics and surgical correction are both recommended to treat VUR, until now it is not clear which type of treatment is superior because there are contradictory studies. It is not clear that the interventional treatments are really necessary in patients with low grade reflux or is there an overtreatment issue in these patients. On the other hand, the question is, in the patients with high grade reflux; if the conventional therapies are sufficient enough to protect the kidney from reflux nephropathy.

European Urology Association (EAU) guideline committee established a new risk grouping for VUR patients to provide a better decision-making process (1). We thought that it would be valuable to refer the differences between our clinical daily practices and actual recommendations of VUR treatment. In this study, we endeavored to review our treatment strategies based on EAU Paediatric Urology Guideline of risk grouping in children with VUR.

MATERIALS AND METHODS

The records of the patients who received medical and/or surgical treatment between 2009-2012 due to VUR were reviewed. History of disease, demographic variables, diagnostic features (presence of renal scar, grade of reflux, laterality), clinical course, causes of failure, secondary intervention type and follow-up variables were analyzed. The patients with VUR were classified as low, moderate and high-risk groups according to EAU paediatric urology guideline (1). Treatment failure is defined as new urinary tract infection and presence of new renal scar during follow-up.

The children were investigated with ultrasound, VCU, and DMSA scintigraphy as diagnostic tools and excretory urography if needed. Study exclusion criteria were previous urogenital surgery, malformation (duplication of ureter orifices), known neurological disease and stone disease. An experienced radiologist in paediatric urology reevaluated all radiological investigations. VCU was done and VUR was graded according to International Reflux Study in Children standards (3). The highest VUR grade was used to classify each case.

For endoscopic injection, we used Dextronamer/Hyalunoric acid (Dx/HA) copolymer. In cases of persistent dilating VUR, the endoscopic procedure might be repeated for a maximum of 3 injections. Ultrasound was done at 1 month after each injection. VCU was repeated if new urinary tract infection and presence of new renal scar were occurred during follow-up or results of the VUR might be changed the treatment decision. The endoscopic procedure was performed at 2 pediatric surgical centers. Treatment was done using general anesthesia. Injection was performed according to standard technique (4,5). Dx/HA was injected submucosally in or below the ureteral orifice at the 6 o'clock position to create a prominent bulge and raise the distal ureter and ureteral orifice. The children who received CAP were prescribed trimethoprim/sulfamethoxazole as the first choice. DMSA scintigraphy were repeated within 1 year period in follow-up. The re-implantation of ureters was performed by Cohen surgical techniques (6).

Statistical analysis

Statistical analyses were done in a computer based statistical program. Statistical differences were calculated by chi-square test and One-way ANOVA between risk groups and initial treatment variables. The differences between demographic and disease specific features with nominal values were analyzed with Mann-Whitney U test. Statistical significance was accepted as $p < 0.05$.

RESULTS

A total of 157 patients with 232 renal units (RU) were treated due to VUR. Mean age of the children was 6.78 ± 5.5 years. The demographic features of the patients at primary treatment were shown in table 1. The distribution of the patient's outcome with primary treatment was shown in table 2. 33(71.7%) of 46RU's were treated with sub-ureteric injection and 18(39.1%) unsuccessful RU's were treated with re-injection in low risk group. Only 2(11.1%) re-injected RU's had postoperative UTI and/or new renal scar at follow-up. In moderate risk group, 54 and 7 of 61 unsuccessful RU's were treated with re-injection and ureteral re-implantation, respectively. 4(7.4%) of 54 had postoperative UTI and/or new renal scar at follow-up. In high-risk group, 13 and 12 of 25 unsuccessful RU's treated with re-injection and ureteral re-implantation, respectively.

Table 1. Demographic features of the patients at primary treatment

| | Continued Antibiotic Prophylaxis(CAP) (n=16) | Injection (n=88) | Ureteral re-implantation (n=12) | CAP and CIC (n=1) | CAP and anti-muscarinics (n=24) | Injection+anti-muscarinics (n=16) | p |
|--|--|------------------|---------------------------------|-------------------|---------------------------------|-----------------------------------|--------|
| Age (median/ years) | 4.5 | 6.5 | 3.5 | 8 | 6 | 5.5 | |
| Gender | Male (n%) | 5 (31.2) | 17(19.3) | 7 (58.3) | 0 | 4 (16.7) | 0.058 |
| | Female (n%) | 11(68.8) | 71 (80.7) | 5 (41.7) | 1(100) | 20(83.3) | |
| Side of VUR | Right (n%) | 3 (18.8) | 16(18.2) | 5(41.7) | 1(100) | 9 (37.5) | 0.221 |
| | Left (n%) | 3(18.8) | 28(31.8) | 2(16.7) | 0 | 6(25) | |
| Presence of renal scar in initial DMSA | Bilateral (n%) | 10(62.5) | 44(50) | 5(41.7) | 0 | 9(37.5) | <0.001 |
| | yes (n%) | 9(56.2) | 55(62.5) | 11(91.7) | 1 (100) | 15(62.5) | |
| | no(n%) | 7(43.8) | 33(37.5) | 1 (8.3) | 0 | 9(37.5) | |

Table 2. The distribution of the patient's outcome with primary treatment according to VUR risk grouping

| | | Continued Antibiotic Prophylaxis (CAP) | Injection | Ureteral re- implantation | CAP and CIC | CAP and anti- muscarinics | Injection+ anti- muscarinics | p |
|---------------------------|---------------|--|-----------|------------------------------|----------------|------------------------------|---------------------------------|--------|
| Low risk(n=46RU) | Success(n(%)) | 0 | 26(78.8) | | | 0 | 2(100) | <0.001 |
| | Failure(n(%)) | 9(100) | 7(21.2) | | | 2(100) | 0 | |
| Moderate risk(n=144RU) | Success(n(%)) | 0 | 62(76.5) | 11(100) | 0 | 0 | 10(66,7) | <0.001 |
| | Failure(n(%)) | 8(100) | 19(23.5) | 0 | 1(100) | 28(100) | 5(33,3) | |
| High risk(n=42RU) | Success(n(%)) | 0 | 9(50) | 7(100) | | 0 | 1(25) | <0.001 |
| | Failure(n(%)) | 9(100) | 9(50) | 0 | | 4(100) | 3(75) | |

DISCUSSION

Vesicoureteral reflux is the most common urological anomaly in children with potentially serious consequences such as hypertension, renal scarring and renal failure. Reflux nephropathy is a major cause of growth impairment, childhood hypertension and renal insufficiency (7). The main purpose of VUR treatment is to protect the patient from febrile UTI, renal injury and accompanying morbidities. Therefore, elements such as age, gender of the patient, the reflux grade, history of recurrent UTI, renal dysfunction and associated bladder-bowel dysfunction must be evaluated and a decision must be made with the family. The treatment approaches are divided into conservative and interventional methods (8). Continued antibiotic prophylaxis, endoscopic injection of bulking agents and ureteral reimplantation procedures are the common treatment modalities of VUR. The medical management of VUR is based upon the observation that there is a natural evolution to improvement of the grade of reflux or disappearance of the VUR (9).

In a Cochrane systematic review, 20 RCTs with 2324 children were reviewed on treatment options of VUR (3). The authors found that long-term low-dose antibiotic prophylaxis didn't have any superiority compared to no treatment/placebo regarding repeat symptomatic UTI or febrile UTI at two years. However, antibiotic prophylaxis reduced the risk of new or progressive renal damage on ^{99m}Tc-DMSA (dimercaptosuccinic acid) scintigraphy (DMSA scan) in that period. According to risk analysis, that means 33 children would need long-term antibiotic prophylaxis to prevent one more child developing kidney damage over the course of two to three years. When they compared long-term antibiotic prophylaxis and surgical or endoscopic correction of VUR plus antibiotics, the risk of symptomatic UTI and progressive renal damage was not significantly different at any time point. However, combined surgical and antibiotic treatment caused a 57% reduction in febrile UTI by five years. It meant that 8 children would require combined surgical and antibiotic treatment to prevent one additional child developing febrile UTI by five years (2). In the recent prospective trial, 203 children aged 1-2 years with grade III/IV reflux randomized in three treatment arms including endoscopic injection, antibiotic prophylaxis and surveillance. The resolution rates of patients in the prophylaxis, endoscopic and surveillance groups are 39%, 71% and 47% after 2 years' follow-up, respectively. The highest rate of febrile UTIs and scar formation was seen in the surveillance group at 57% and 11%, respectively. The recurrence rate of endoscopic treatment was found as 20%. Any patient had new scar formation in antibiotic prophylaxis group (4).

These results showed us that the treatment should be tailored to different risk groups. According to risk classification, the children who have symptomatic high-grade reflux and abnormal kidney with/without LUTD need a more aggressive early intervention. The authors recommended open re-implantation for the children. However, all children who have low-grade reflux with normal kidneys and lower urinary tract function don't require any treatment or only CAP.

In our study, when we classified the patients into the risk groups, according to the EAU classification system, we saw that we treated the vast majority of the low risk group patients with subureteric injection. That finding shows a great overtreatment in this group as the EAU guideline recommends no treatment or only CAP in this group. There are two randomized controlled trials, one from Garin et al. and one from Pennesi et al., demonstrating that prophylactic use of antibiotics does not prevent for acute pyelonephritis and thus not the incidence of renal damage (10,11). Even more, Garin suggested that prophylactic antibiotics increased the risk of acute pyelonephritis and contribute to antibiotic resistance of the infecting bacteria. Immediate

recognition and treatment of urinary tract infections is probably the most important factor to prevent renal scarring.

These findings show us that we have to reconsider the accurate risk grouping of children to conservatively treat the patients. In our study, 11 of 18 treatment failures were not treated with injection or surgical interventions in low risk group which is compatible with EAU guideline recommendations. That may be due to inaccurate risk grouping of these children because of the missing data's or shows that we have to reevaluate the patients if there is a real treatment failure condition or if it is just a follow up mistake.

The treatment options are variable with a wide spectrum of patient characteristics in moderate risk group. In this group, it is favorable to start the treatment with CAP and endoscopic injection and ureteral reimplantation can be preferred as interventional treatment in case of breakthrough infections and persistent VUR (1). In moderate risk group, recent treatment recommendations according to the risk grouping system is consistent with the conventional idea of the management of VUR that interventional therapy should be considered if there is not sufficient reply to conservative treatment (12). In our study we analyzed that we had no successful attempt of CAP without subsequent intervention. Endoscopic injection and ureteral reimplantation treatment success rates were %75 and %100, respectively in this group. We treated 107 (%74) of 144 renal units in moderate risk group with interventional approaches. It may seem like that there is an overtreatment in this group as well, but unlike low risk group, interventions are more critical because of high possibility of persistent VUR and reflux nephropathy (13). In contrast to our findings, in the Swedish Reflux Study, 203 children were included in this prospective randomized controlled multicenter study (14). They all were 1 to younger than 2 years old during recruitment and had a grade III-IV VUR. They were randomized to prophylaxis, endoscopic treatment or surveillance. The main study end points were recurrent febrile urinary tract infection, renal status on dimercaptosuccinic acid scintigraphy and reflux status. There were febrile recurrences in 19% of girls on prophylaxis, in 23% in the endoscopic therapy group and in 57% of the surveillance group, so there was no difference between the prophylaxis and endoscopic groups. In girls the recurrence rate was associated with persistent reflux after 2 years. The recurrence rate in boys was very low and showed no differences between treatment groups. This study shows us that neither prophylaxis nor endoscopic treatment is of value to decrease recurrence after age 1 year. The very low success rate of conservative treatment in moderate risk group in our study can be explained with our tendency of advancing to an interventional treatment especially to endoscopic injection without following these patients for sufficient duration.

The high success rate of open ureteral reimplantation is well documented. According to the Pediatric American Urological Association Guideline Panel Summary published in 1997 (15), the success rates of open ureteral reimplantation for VUR grades I to V are 99.1%, 99.0%, 98.3%, 98.5%, and 80.7%, respectively. The success rate per patient is 95.1%, and the success rate per ureter is 95.9%. In addition, VUR recurrence is not observed except in those children with severe bladder bowel dysfunction. The success rate of endoscopic treatment is low compared with that of open surgery. Several authors have reported high success rates with injection therapy that are comparable with those of open ureteroneocystostomy (16-18). However, it should be remembered that these excellent results were attained by expert surgeons and that universally, there is a certain period of time required to overcome the steep learning curve necessary to perform these procedures. In high risk VUR patients it is recommended to approach more aggressively, as intervention should be considered early. Open ureteroneocystostomy is said to be superior to endoscopic treatment (1).

According to our data, we preferred conservative treatment in 13, injection in 22 and ureteral reimplantation in 7 of 42 high risk renal units. Success rates were %0, %45 and %100 respectively. It looks like we were not aggressive enough to perform sufficient initial interventional treatment. While there is an increased risk of reflux nephropathy in patients with high risk VUR, the surgeons should consider ureteral reimplantation more frequently.

CONCLUSION

Vesico-ureteric reflux is a frequent diagnosis in children and until now the optimal treatment is not always clear. To determine the most favorable treatment option in each individual VUR patient, it should be wise to check out EAU guidelines' risk grouping system and manage the patients according to this system. In our study we detected over treatment in low risk group. Success of the surgical correction was evident in moderate and high-risk group. Further studies with large quantity of subjects and with long term follow up, the consistency between the recommendations for each risk group and treatment success rates should be clarified.

Conflict of interest

No conflict of interest was declared by the authors

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