Antireflux surgery does not change ongoing renal functional deterioration

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ABSTRACT

Aim: Treatment modalities of vesicoureteral reflux (VUR) consist of antimicrobial prophylaxis and antireflux surgery. In this study, we aimed to determine if antireflux surgery changes the course of renal functional deterioration in children with VUR and urinary tract infections (UTI).

Methods: Medical files of patients with VUR diagnosed during evaluation for UTI were evaluated retrospectively for gender, age, follow-up period, and renal ultrasonography (US) and serial 99mTc-dimercaptosuccinic acid (99mTc-DMSA) scintigraphy findings. Estimated glomerular filtration rate and urinary protein levels were determined at the initial and last visits, and before the operation in children who had antireflux surgery. The patients were divided into two groups as solely medically treated (Group 1) and both medically and surgically treated (Group 2). Group 2 was further divided as those with stable renal function (Group 2a) and with progressive renal injury (Group 2b).

Results: There were 140 patients (77 female; mean age 51.6 ± 51.9 months). Group 1 and Group 2 included 82 and 58 patients, respectively. In Group 2, the number of patients with the abnormal US, DMSA scintigraphy, and renal function was higher than in Group 1. Recurrent UTI rate was similar, but progressive scarring was more prominent in the antireflux surgery group. In Group 2, 31 patients had a stable renal function (Group 2a) while 27 had progressive deterioration of renal functions (Group 2b). These subgroups were not different with respect to the rate of high-grade VUR, the presence of a renal scar in DMSA, and UTI recurrence. However, the bilateral renal scar was more common in Group 2b.

Conclusion: Antireflux surgery does not change the course of ongoing renal injury and renal functional deterioration.

Introduction

Vesicoureteral reflux (VUR), retrograde flow of urine, is a predisposing factor for urinary tract infections (UTI) and permanent renal injury.1 Treatment modalities of VUR consist of long-term antimicrobial prophylaxis and/or antireflux surgery, which are believed to help prevent end-stage renal disease attributable to reflux nephropathy.2 In this study, we aimed to determine if antireflux surgery changes the course of renal functional deterioration in children with VUR and UTI.

Methods

Medical files of patients with VUR diagnosed during an evaluation for UTI at the Pediatric Nephrology Department of Dokuz Eylül University Medical School between 1998 and 2015 were evaluated retrospectively. Patients with secondary reflux (neurogenic bladder dysfunction, bladder outlet obstruction), double collecting system, comorbid ureteropelvic obstruction, and a follow-up period of less than 12 months were excluded. The patients were evaluated for gender, age, follow-up period, and urinary tract ultrasonography (US) and serial 99mTc-DMSA scintigraphy findings. In addition, estimated glomerular filtration rate (eGFR) and urinary protein levels were determined at the initial visits, before surgery, and at last visits. Renal injury was defined as eGFR <90 mL/min/1.73 m² and/or proteinuria >4 mg/m²/h or >0.2 mg/m² creatinine.

UTI was diagnosed when symptoms were associated with a growth of single bacterium ≥10⁵ cfu/mL in urine collected by catheter and midstream clean-void samples from infants and older toilet-trained children, respectively. All of the patients underwent US examination. The presence of reflux was determined by voiding cystourethrography and was graded (I–V) according to the International Reflux Study Committee.3 Grades I–II and III–V VUR were considered mild and severe reflux, respectively. Renal parenchymal involvement was assessed by 99mTc-DMSA scan. All children with

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impaired differential uptake (>10% uptake difference between renal units) or hypoactive foci in the first DMSA scan underwent a second imaging 4–6 months later for determination of the persistence of globally low uptake or hypoactive foci compatible with hypoplasia or scarring, respectively. Goldraich et al.4 underline four separate types for classifying progressively increasing tissue damage. Renal scarring was classified as “Type 1,” indicating no more than two scarred areas. “Type 2” class indicated effects on more than two areas with an intact, normal parenchyma, whereas “Type 3” meant a generalized parenchymal damage and “Type 4” referred to a shrunken end-stage kidney. DMSA findings were defined as “a normal/mild renal scar” (Goldraich 1–2) and “a severe renal scar” (Goldraich 3–4). Surgery indications were high-grade reflux, recurrent pyelonephritis during antibiotic prophylaxis, new scar development, and patient’s non-compliance on antibiotic prophylaxis.

The patients were divided into two groups as solely medically treated (Group 1) and both medically and surgically treated (Group 2). Surgical correction was performed by either subureteric injection or by open surgery. In the case of subureteric injection, the success of the procedure was controlled by repeat radionuclide scintigraphy after 3 months of surgery. Group 2 was further divided as those with stable renal function (Group 2a) and with progressive renal injury (Group 2b). Group 1 versus Group 2 and Group 2a versus Group 2b were compared for the parameters described above.

**Statistical analysis**

The mean values of numeric variables were compared by Mann–Whitney U test and Student’s t-test. The analysis of interrelation between categorical variables was done with the χ² test. This study received ethical approval from the local ethics committee (2015/19-13).

**Results**

There were 140 patients (77 female; mean age 51.6 ± 51.9 months). Group 1 and Group 2 included 82 and 58 patients, respectively. Table 1 shows demographic features, recurrent UTI, reflux status, US, and DMSA findings of Groups 1 and 2. Presenting age was significantly higher in Group 2. Two groups were not different with respect to gender, unilateral/bilateral VUR, mild/severe VUR, and UTI recurrence. Almost one-third to one-half of the patients had recurrent UTI in both groups.

The abnormal US was more common in Group 2. Out of 68 patients with normal US findings, 30 (44%) had a renal scar by DMSA. This is especially more prominent in Group 2 where 20 out of 22 (90%) renal patients with the normal US had a scar in DMSA.

Renal scar rate was 2.6 times higher in Group 2 (91%) compared to Group 1 (35%). Severe scar (Goldraich 3–4) was also significantly higher in Group 2 than in Group 1 (16/58 vs. 7/82 respectively, p = 0.003). Importantly, the renal scar was identified in 10 of 29 (4%) patients with mild VUR, whereas renal scar was not present in 38 of 99 (38%) renal units with severe VUR. The rate of new renal scar formation was also higher in Group 2.

Table 2 shows recurrent UTI, reflux status, US, and dimercaptosuccinic acid (DMSA) findings of Groups 2a and 2b. Both subgroups were not different statistically with respect to the abnormal US, VUR grade, total and severe scar rate, recurrent UTI, and new scar development (albeit new scar development rate was twice higher in Group 2b). On the other hand, bilateral renal scarring was higher in Group 2b in comparison to Group 2a. In Group 2, 31 of the patients did not develop renal insufficiency/proteinuria while, 13 patients had new renal insufficiency/proteinuria. Follow-up period of these patients were not different (p 0.655).

**Discussion**

Development of reflux nephropathy and renal scarring is a multifactorial process. Risk factors for renal scarring are different with respect to gender, unilateral/bilateral VUR.

**Table 1.** Comparison of the medically (group 1) and surgically (group 2)-treated group.

|                | Group 1 (n = 82) | Group 2 (n = 58) | p       |
|----------------|-----------------|-----------------|---------|
| Age            | 35.6 ± 47.7     | 74.2 ± 49.6     | <0.001  |
| Male/female    | 39/43           | 24/34           | 0.469   |
| Bilateral VUR  | 49 (60%)        | 31 (53%)        | 0.458   |
| Severe VUR (3–5) | 17 (21%)       | 28 (48%)        | 0.001   |
| Abnormal ultrasonography | 36 (44%) | 36 (62%) | 0.034 |
| Recurrent UTI  | 38 (46%)        | 22 (38%)        | 0.322   |
| Abnormal DMSA  | 29 (35%)        | 53 (91%)        | <0.001  |
| New/progressive scar in DMSA | 4 (5%) | 11 (19%) | 0.008 |
| Renal insufficiency/proteinuria onset | 3 (4%) | 14 (24%) | <0.001 |
| Renal insufficiency/proteinuria final visit | 3 (4%) | 27 (47%) | <0.001 |

**Table 2.** Comparison of the patients with stable renal function (Group 2a) with the patients with a progressive decline in renal function (Group 2b).

|                | Group 2a (Renal function stable) | Group 2b (Renal function decline) | p       |
|----------------|---------------------------------|----------------------------------|---------|
| VUR (>3)       | 16 (52%)                        | 14 (52%)                         | 0.986   |
| Recurrent UTI  | 10 (32%)                        | 12 (44%)                         | 0.340   |
| DMSA           |                                 |                                  |         |
| Scar           | 27 (87%)                        | 25 (93%)                         | 0.493   |
| Severe scar    | 10 (32%)                        | 6 (22%)                          | 0.394   |
| Bilateral scar | 1 (3%)                          | 7 (26%)                          | 0.012   |
| New scar       | 4 (13%)                         | 7 (26%)                          | 0.207   |
VUR, UTI, and previous scar/dysplasia. 5,6 Although ante-natal US can help identify up to 30% of newborns with VUR, exposing detectable renal damage prior to UTI, US imaging can miss detection of approximately half of the scars. In accordance with this data, US was normal in 44% of our patients with abnormal DMSA.

The management of VUR aims to prevent UTI-induced damage. The best form of treatment for children with VUR is a debated subject, taking into account cases with no treatment, long-term antibiotic prophylaxis, surgery, or a combination of both. 7–11 A study with a long-term follow-up of patients with VUR demonstrated that antibiotic prophylaxis decreased recurrent UTI by 60% for the first 5 years. 12 However, RIVUR (renal scarring in the Randomized Intervention for children with Vescicoureteral Reflux) study has recently shown that antibiotic prophylaxis does not prevent renal scar development. 7 In our study, despite antibiotic prophylaxis recurrence rate for UTI of was 46% in Group 1. On the other hand, UTI recurrence (38%) was not different in patients undergoing surgical correction. Likewise, the 2011 Cochrane database on VUR reported only a 60% reduction in febrile UTI cases between “antibiotic prophylaxis only” and “combined antibiotic prophylaxis and surgery” groups. 10

It has been stated that neither medical treatment nor surgical correction of VUR does not effectively prevent recurrent UTI and new scar formation and progression to end-stage renal disease. Thus, physicians should focus on the prevention of initial renal scarring. 2,11,13 Renal scar rate was significantly higher in Group 2 already before surgical correction of VUR. Although UTI recurrence was not higher in Group 2 after surgery, progressive scar formation was significantly higher in this group. This result is in accordance with our previous data that the most important predictor of new/progressive scarring is the presence of renal scar. 5

Reflex nephropathy has been associated with long-term renal dysfunction like proteinuria and/or renal insufficiency. 7,9,10,14 Neither medical nor surgical treatment of VUR prevented renal function deterioration. 9,10,14 The patients in surgically treated group had already a higher rate of renal dysfunction compared to solely medically treated group. However, at the end of follow-up, the number of patients with renal dysfunction doubled in the surgically treated group; indicating that presence of renal scar is the most important determinant of renal functional deterioration.

Comparison of the children with stable and deteriorating renal functions in the surgically treated group showed that the only difference between these groups was the high rate of bilateral renal scar in the latter children. While one-fourth of children with deteriorating renal functions had a bilateral renal scar, this rate was negligible in those with stable renal functions. Copper et al. 14 previously reported that despite surgical correction, children with bilateral reflux and renal scar had increased microalbuminuria.

**Conclusion**

Antireflux surgery does not prevent progressive renal scar development and renal functional deterioration. This is true especially in children with bilateral renal scarring. If there is indeed a lack of preventative benefit with continuous antibiotic prophylaxis and/or antireflux surgery for acute pyelonephritis and progressive renal injury in children with VUR, one may question the value of treating, or even diagnosing, VUR.

**Declaration of interest**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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