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Antibiotic prophylaxis in vesicoureteric reflux in children

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Abstract

Urinary tract infection (UTI) is known entity and a common problem in pediatric age group. Children at risk for (UTI) such as vesicoureteric reflux (VUR), pelvi-ureteric junction obstruction (PUJO) and other urinary tract anomalies commonly receive prophylactic antibiotics to prevent nephropathy such as renal scaring ,hypertension and renal failure. Prolonged use of prophylactic antibiotics is common for recurrent (UTI), but this has not been assessed in well-controlled prospective studies. Different antibiotics such as nitrofurantoin, trimethoprim/sulfamethoxazole and nalidixcic acid have been used as prophylactic antibiotics to prevent (UTI) in pediatric age group which proved to be safe in long term prophylactic therapy without major complications. Although it is not easy to perform prospective studies in children because both clinical course and prognosis may be affected by many factors. Infant and children with factors need prolonged use of antibiotic prophylaxis, until there is evidence that these patients are not at risk without prophylaxis. We reviewed thoroughly the up to date literatures and practice guidelines to make sure that we are implementing appropriate use of antibiotic prophylaxis in pediatric urology in our institution being the referral pediatric hospital dealing with the vast majority of pediatric urology/ nephrology cases in the kingdom. We focus on the evaluation and actual benefits of prophylactic antibiotics in vesicoureteric reflux (VUR) in pediatric age group to reach consensus and recommendations for in hospital protocol on the basis of current best evidence. Over the past 3 years we selected a group of patients (N=130), 50 males and 80 females , age 4-7 years ,median age 5, 2 years with grad I-III (VUR). All patients with abnormal voiding , neurogenic bladder and urinary tract anomalies were excluded from the study. All patients who had breakthrough (UTI) or deterioration in the renal function were excluded from the study and managed by surgery or endoscopic injection. All patients were treated by prophylactic antibiotics for 18 months (first trial) then stopped and followed up for another 18 months on no prophylaxis (second trial). At the end of both trials, 100 patients met the inclusion criteria and the results were analyzed. There was no significant break though infection in the second trial and no significant drop in the renal function. Multi resistant bacterial growth was encounter in the first trial, while less resistant bacterial growth was encountered in the second trial. In conclusion, routine use of prophylactic antibiotics for low grade I-III (VUR) in normal urinary tract is not indicated after the age of 4 years without any significant health compromise.

Keywords: Antibiotic prophylaxis, child, vesicoureteric reflux.

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Introduction

Vesicoureteral reflux (VUR), is the back flow of urine from the bladder into the ureter. The recognition of an association between urinary tract infection (UTI), the presence of (VUR), and the risk to develop pyelonephritis resulting in the formation of renal scarring which will lead to the concept of reflux nephropathy[1]. VUR is an anatomic and functional disorder with potentially serious consequences. The Primary VUR encountered in normally functioning lower urinary tract, whereas

secondary VUR is associated with abnormal lower urinary tract due to obstruction or poor function, such as posterior urethral valves or a neurogenic bladder. In both conditions, failure of the function of ureterovesical junction as one way valve will occur. (VUR) considered one of the commonest causes of febrile urinary tract infections (UTIs) in pediatric age. The frequent outcome of this serious bacterial infection in childhood is the formation of renal scarring [2]. The American Academy of Pediatrics (AAP) established evidence based guidelines for diagnosis, treatment and evaluation of the initial urinary tract infection helpful for the practitioner caring for children between the ages of 2 months to 2 years but there is no such guidelines existing for older children. Different studies revealed that infants with urinary tract infection usually present with fever as the only symptom [3, 4]. Uncircumcised (male) with previous history of UTI presenting with illness and temperature above 39°C lasting more than 2days with no obvious focus of infection and tender suprapubic area should be managed and evaluated for high possibility (UTI) [5, 6]. Infants with (UTI) should be hospitalized when they have evidence of urosepsis or immunocompromised state. However, the majority of infants and young children can be treated as outpatients with up to 40% diagnosis of (VUR) [7]. Prophylactic antibiotics at one quarter to one third of the therapeutic dose have been used with the aim of preventing recurring (UTI) [8-10]. Other studies [11, 12] suggest that prophylaxis may moderately protect from recurrent symptomatic urinary tract infections, at least in some subgroups of children. Different antibiotics such as nitrofurantoin, trimethoprim/sulfamethoxazole, cephlexin and nalidixcic acid have been used as prophylactic antibiotics to prevent (UTI) in pediatric age group which proved to be safe in long term prophylactic therapy without major complications. There is no strong support for this approach based on evidence from randomized controlled clinical trials, instead many recent randomized controlled studies have doubted the efficacy of this approach but with limited validity and generalization [13-16]. Many studies published were suboptimum and poorly designed with controversies, resulted in failure of any reliable input this field. The appropriate diagnosis of (VUR), timely initiation of appropriate treatment and careful follow up will help to minimize the acute and long term complications of chronic renal disease. Few series suggest that antibiotic prophylaxis in children with low grade VUR may not be necessary without any health compromise. In our review, we focus on the evaluation and actual benefits of prophylactic antibiotics in grade I-III (VUR) after the age of 4 years to reach consensus and recommendations for in hospital protocol on the basis of current best evidence.

Materials and methods

With Institutional Review Board approval, the data of all patients with the diagnosis of grade I-III vesicoureteric reflux (VUR) at Queen Rania Hospital for Children / King Hussein Medical Center were retrospectively reviewed of prospectively collected data over 3 years period October 2010-2013.We selected a group of patients (N=130), 50 males and 80 females, age 4-7 years, mean age 5, 2 years with grad I-III (VUR). After agreement we explain all details for the parents regarding the aim and method of the trial .All patients with abnormal voiding, neurogenic bladder and urinary tract anomalies were excluded from the study. All patients who had breakthrough (UTI) or deterioration in the renal function were excluded from the study and managed by surgery or endoscopic injection. All patients were treated by prophylactic antibiotics for 18 months (first trial) then stopped and followed up for another 18 months on no prophylaxis (second trial). In the first trial, all patients received prophylactic oral trimethoprim/sulfamethoxazole for 3 months then cephlexin for 3 months at one forth to one third of the therapeutic dose given as single dose of drug at bedtime, so that the antibiotic can be retained all night in the bladder, thus enhancing its effectiveness which continued on the same sequel till the end of the first trial to minimize the chance of resistant bacterial growth. Urine culture obtained every 4 weeks in both trials, kidney function test, electrolytes assessment and blood pressure measurement every 6 weeks. Nuclear scan DMSA and micturating cystourethrogram (MCUG) were obtained in the beginning of the study then after 18 months and by the end of the study at 36 months. The follow up investigations performed by order and supervision of pediatric nephrologists & pediatric urologist. At the end of the study, 100 patients committed to the requirements of the study and met the inclusion criteria and the results were analyzed.

Results

A total of 100 patients completed with commitment the requirements of both trials and met the inclusion criteria .There was no significant break though infection in the second trial and no significant

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drop in the renal function. Multi resistant bacterial growth was encounter in the first trial. The commonest bacterial growths encountered were Gram-negative organisms. E.Coli found in (84% of bacterial growth) followed by Klebsiella and Pseudomonas, while less resistant bacterial growths were encountered in the second trial. Patients on oral cephlexin showed increased rate of resistant bacteria compared to those on oral trimethoprim/ sulfamethoxazole. Nitrofurantoin was the drug of choice for resistant bacteria. The accumulative change in the grade of (VUR) and DMSA scan, renal function test as well as blood pressure were nearly the same in both trials.

Discussion

Prophylactic antibiotics at one quarter to one third of the therapeutic dose have been used with the aim of preventing recurring (UTI) [8-10]. Other studies [11, 12] suggest that prophylaxis may moderately protect from recurrent symptomatic urinary tract infections, at least in some subgroups of children. There is no strong support for this approach based on evidence from randomized controlled clinical trials, instead many recent randomized controlled studies have doubted the efficacy of this approach but with limited validity and generalization [13-16]. Many studies published were suboptimum and poorly designed with controversies, resulted in failure of any reliable input in this field. Four recent clinical trials evaluating the effectiveness of continuous antimicrobial prophylaxis showed no significant drop in the incidence of recurrent urinary tract infection [13, 14, 16-18] which led some clinicians to become skeptical about the role of prophylaxis or the need to evaluate children with recurrent urinary tract infection for vesicoureteral reflux. Despite their current widespread use, a growing body of evidence in larger, multicenter studies does not support benefit of prophylactic antibiotics in low-grade (VUR) [14, 18]. A recent systematic review of randomized controlled trials related to the topic found a lack of evidence of a positive benefit for children at risk for developing UTIs [19]. In our review, we focus on the evaluation and actual benefits of prophylactic antibiotics in grade I-III (VUR) after the age of 4 years to reach consensus and recommendations for in hospital protocol on the basis of current best evidence comparing our results to what we found in the latest reports ,we found as other recent reports [20] that there is no strong evidence to the routine continuous use of prophylactic antibiotics in grade I-III (VUR) and normal urinary tract without any health compromise or significant danger in the renal function . We observed that resistant micro-organisms may emerge after long term use of prophylactic antibiotics as reported by other series [21]. In addition, the current National Institute of Clinical Excellence (NICE) guidelines [22] do not advocate the use of prophylactic antibiotics in children with UTIs and may be of no benefit even for younger children [17]. Children with a negligible risk of developing a recurrent febrile UTI are unlikely to benefit from daily antibiotics [23-26].

We conclude from our study and from the available evidence based reports that, routine use of prophylactic antibiotics for low grade I-III (VUR) and normal urinary tract is not indicated after the age of 4 years without any significant health compromise. Certain group of patients with abnormal urinary tract, voiding disorder and high grade IV - V (VUR) may benefit from antibiotic prophylaxis coupled with bowel training to treat constipation, voiding education and rehabilitation, all are helpful measures to prevent long term renal damage.

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