Antibiotic prophylaxis in infants with Grade III, IV, or V vesicoureteral reflux

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This trial from the PREDICT group, aimed to evaluate if continuous antibiotic prophylaxis (CAP) can prevent urinary tract infections (UTIs) in infants with dilating (Grade III-V) vesicoureteral reflux (VUR) without a prior history of UTI. This was a multinational, open-labelled randomized controlled trial (RCT) performed at 39 European centres from October 2013 to January 2020.

A total of 292 infants, aged 1–5 months, with Grade III-V VUR without a prior history of UTI were included. Participants were randomized in a 1:1 fashion into prophylaxis or control (no-treatment) arms and no crossover between the groups was allowed. The calculated sample size was 146 per arm to achieve an 80% power, 0.05 alpha error, and assuming a 25% dropout rate. All the patients underwent a baseline evaluation with serum creatinine, urinalysis, ultrasound abdomen, and Dimercaptosuccinic acid renogram. The imaging was repeated at the end of the follow-up at 24 months and was reviewed centrally by three blinded assessors. The choice of the antibiotics depended on the local sensitivity patterns and Amoxicillin, Trimethoprim-Sulfamethoxazole, Nitrofurantoin, or Cefixime were prescribed. Clinical progression and adherence to the medication were assessed every 6 months with diaries. The primary outcome was the first symptomatic UTI and the secondary outcomes included number of UTIs, admissions, new renal scars, estimated glomerular filtration rate (eGFR), causative organisms, and resistance patterns. Symptomatic UTI was defined as fever >38 C, along with symptoms such as irritability and loss of appetite. A positive urine culture was defined as any growth on the suprapubic aspirate, $>10^4$ colony forming units (CFU)/mL of one organism on the catheterized sample, and $>10^5$ CFU/mL on a mid-stream sample.

The majority (75%) of the patients were males and the mean age was 3 months. Most (80.5%) of the patients had Grade IV/V reflux and 48.3% had bilateral reflux. Five (2.2%) of the male infants were circumcised previously. The first symptomatic UTI was reported in 31/146 (21.2%) of the patients in the CAP arm as compared to 52/146 (35.6%) among the controls, by the intention-to-treat analysis. This risk reduction of 45%, was statistically significant (hazard ratio [HR] 0.55, 95% confidence interval [CI] 0.35–0.86, $P = 0.008$) and the number needed to treat to prevent one UTI was 7. The time to first UTI (6.4 months CAP, 5.2 months control), number of UTIs (60-CAP, 79-control [relative risk (RR) 0.76, CI: 0.59–0.97]), new renal scars (21-CAP, 17-control [RR 1.22, 95% CI 0.69–2.18]), adverse events (6.2%-CAP, 4.1%-control [$P = 0.43$]) and the eGFR, were similar between the two groups. CAP did not reduce the need of hospitalizations for UTI (16 [27%]-CAP, 27 [30%]-control [RR 0.88, 95% CI 0.51–1.5]). Interestingly, the development of renal scarring was found to be independent of UTI (19% with and 18.8% without UTI) and the incidence of UTIs was lower in males (HR 0.46, 95% CI 0.29–0.73). Also, the authors found a three fold higher incidence of resistance to antibiotics in the CAP arm (52%-CAP vs. 17%-control [RR 2.98, 95% CI 1.5–5.92]).[1]

COMMENT

Traditionally, CAP after the diagnosis of dilating VUR, was considered as the standard of care in all children. Currently, a risk-stratified approach is suggested as asymptomatic reflux has a low to moderate risk of UTI. Most level 1 evidence on the subject comes from studies performed on children with VUR diagnosed after a prior UTI, which is only a subset of the total population with VUR.[2] This was the first RCT that proved the efficacy of CAP in infants with high-grade VUR without a prior UTI and it is known that preventing UTIs does decrease the overall morbidity. Other strengths of the trial were its multicentre, randomized design with adequate, representative sample. However, the heterogeneity of the prophylaxis prescribed, lack of a placebo, lack of non-Caucasian population, and short follow-up were its drawbacks.[1]

The existing evidence in the pediatric population with VUR without a prior UTI is limited to retrospective series which are marred by heterogeneous inclusion criteria and the lack of controls. A systematic review showed an increased rate of UTI in girls (OR 2.3, 95% CI 1.1–4.7) but was unable to draw conclusions on whether antibiotic prophylaxis

protected the infection-naive population due to inadequacy of the data.[3]

Though the previous placebo-controlled randomized trials in children with VUR and prior UTIs such as RIVUR and PRIVENT[4] showed a marginal benefit of prophylaxis vis-à-vis a reduction in the episodes of UTI, these trials included older children with absent/low-grade VUR in whom the impact of a febrile UTI is likely to be minimal. A systematic review by Cochrane reported a similar rate of UTI (HR 0.77 [0.54, 1.07]), febrile UTI (HR 0.73 [0.5, 1.08]) and renal scarring (HR 0.73 [0.33, 1.61]) in the prophylaxis and the control arms, however, the antibiotic resistance was threefold higher in the prophylaxis arm (HR 2.72 [1.85, 4], $P < 0.0001$).[5] Therefore, there is an unmet need for further RCTs to aid in risk stratification of the VUR to identify those children who are most vulnerable to UTI and renal scarring so as to balance the benefits of CAP against emergence of antibiotic resistance. The results on the long-term impact of CAP, through possible changes in the urinary and faecal microbiome, their effects on the UTI susceptibility, and the antibiotic resistance, are awaited and these may add clarity to this contentious issue in the future.

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