Probiotics prophylaxis in pyelonephritis infants with normal urinary tracts

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Background: **Pyelonephritis in infants is considered as a major factor for the formation of renal scar. To prevent recurrent pyelonephritis and renal damage, prophylaxis is extremely important. The aim of this study was to compare the effectiveness of probiotic and antibiotic prophylaxis or no-prophylaxis in infants with pyelonephritis and normal urinary tract.**

Methods: **Altogether 191 infants, who were diagnosed with acute pyelonephritis, proven to have normal urinary tracts and followed up for 6 months on prophylaxis, were retrospectively evaluated. According to the types of prophylaxis, the infants were divided into three groups [probiotics (Lactobacillus species), antibiotics (trimethoprim/sulfamethoxazole, TMP/SMX), and no-prophylaxis]. The incidence of recurrent urinary tract infection (UTI) during 6 months after the development of pyelonephritis, main causative uropathogens, and its antimicrobial sensitivities were compared.**

Results: **The incidence of recurrent UTI in the probiotic group was 8.2%, which was significantly lower than 20.6% in the no-prophylaxis group (*P*=0.035) and was not significantly different from 10.0% of the antibiotic group (*P*=0.532). The significant difference between the probiotic and no-prophylaxis groups was seen only in male infants (*P*=0.032). The main causative organism of recurrent UTI was Escherichia coli (*E.coli*), which was not different among the three groups (*P*=0.305). The resistance rate of *E. coli* to TMP/SMX was 100% in the antibiotic group, which was significantly higher than 25.0% in the probiotic group and 41.7% in the no-prophylaxis group (*P*=0.008).**

Conclusions: **Probiotic prophylaxis was more effective in infants with pyelonephritis and normal urinary tract than in those with no-prophylaxis. It could be used as a natural alternative to antibiotic prophylaxis.**

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Key words: **antibiotic prophylaxis; antibiotic resistance; probiotic prophylaxis; pyelonephritis**

Original article

Introduction

Urinary tract infection (UTI) is the most common bacterial infection in children and develops most frequently in infants.[1] Acute pyelonephritis (APN), young age and vesicoureteral reflux (VUR) are recognized as main risk factors for the formation of renal scar, and recurrent pyelonephritis further increases renal damage.[2-4] To prevent recurrent UTI, antibiotic prophylaxis has been used during the past decades in children with primary VUR.[5,6] Frequently seen in children without VUR, however, pyelonephritis per se rather than VUR has been elucidated as the major risk factor for renal scar formation.[7,8] Therefore, antibiotic prophylaxis has been used even in children without VUR.[9] But the effect of this prophylaxis against recurrent UTI has been questioned in Cochrane reviews and meta-analyses,[10-12] although a recent prospective trial showed a 50% reduction of recurrent UTI.[13] The emergence of resistant bacteria has been another concern about the long-term use of prophylactic antibiotics.[14,15]

Probiotics, developed from the concept of normal flora, refer to beneficial live microorganisms that promote the health of the host.[15] They have been widely used for health maintenance and recently have received more attention for the prevention of UTI.[16,17] Probiotics containing lactobacillus strains, the most dominant urogenital microflora, were proved to improve urogenital ecology and prevent recurrent UTI in women.[17-19] A meta-analysis of the published data about women[20] concluded that lactobacillus probiotics are promising as a natural immunomodulating approach in preventing

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recurrent UTI, although the evidence is not enough.[21,22] Clinical data in children are few, but probiotic treatment seems to be equivalent to antibiotic prophylaxis.[23-25]

The present study was to compare the effectiveness of probiotic or antibiotic prophylaxis or no-prophylaxis in infants with pyelonephritis and normal urinary tract.

Methods

We performed a retrospective study of infants with febrile UTI treated at two hospitals affiliated to Ewha Woman's University and Hallym University respectively. A total of 191 infants aged 1-24 months were enrolled. Patients with APN and normal urinary tract were included in the study, and those with UTI and congenital urinary tract anomalies were excluded.

APN was associated with fever (body temperature ≥38°C), pyuria [≥5 white blood cells (WBC)/high power field], significant bacteriuria [positive urine culture with pure growth 103 colony forming unit (CFU)/mL in suprapubic aspirated urine culture or over 10^5 CFU/mL in catheterized urine culture], and photon defect with 99m-Technetium-dimercatosuccinic acid (99mTc-DMSA) renal scan in acute stage. Normal urinary tracts were confirmed by renal ultrasonography and voiding cystourethrography (VCUG). Renal ultrasonography and 99mTc-DMSA renal scan were performed within 5 days after admission of the infant. VCUG was performed after confirmation of negative urine culture, usually within 7 days after the admission. 99mTc-DMSA renal scan and VCUG were interpreted by an experienced nuclear medicine physician and a pediatric radiologist blinded to the patients' clinical and laboratory characteristics. Recurrent UTI was diagnosed by significant bacteriuria in symptomatic infants, characterized by fever, dysuria or pus in a diaper.

The sample size in this study was less than that calculated originally (n=146) for testing equivalency at α=0.05 and β=0.2 (power 80%). Thus, the calculated statistical power of 78% was slightly lower than the expected power, which would have some limitations to this study.

According to the types of prophylaxis, eligible infants were divided into three groups (probiotic group, antibiotic group, and no-prophylaxis group). For the probiotic group (n=73), Lactobacillus species [*Lactobacillus* (*L.*) *acidophilus* (Antibio300®, 1×10^8 CFU/g bid, Hanwha Co.) or *L. acidophilus*+*L. rhamnosus* (Lacidofil®, 2×10^9 CFU/g bid, Phambio Co.) was prescribed. For the antibiotic group (n=50), low-dose trimethoprim/sulfamethoxazole (TMP/SMX, Septrin® 2/10 mg/kg, qhs) was prescribed. The no-prophylaxis group was regarded as a control group (n=68).

During 6 months after the appearance of APN, the incidence of recurrent UTI and major causative uropathogens as well as its antimicrobial sensitivities were compared. There was no patients lost to follow-up.

The study protocol was approved by the ethics committee of the hospital, and informed consent was obtained from the parents of the infants.

The SPSS statistics package (SPSS 11.0, SPSS Inc., USA) was used for analysis. The Chi-square test and Fisher's exact test were used to compare the recurrence rate of UTI and resistance rate of the uropathogens among the three groups. A P value of less than 0.05 was considered statistically significant.

Results

Of the 191 infants, 143 were male and 48 female. The differences in age, male-to-female ratio and clinical characteristics were not significant among the probiotic group, antibiotic group, and no-prophylaxis group (P>0.05) (Table 1).

The incidence of recurrent UTI in the probiotic group was 8.2% (6/73), which was significantly lower than 20.6% (14/68) in the no-prophylaxis group (P=0.035) but not significantly different from 10.0% (5/50) of the antibiotic group (P=0.532). However, the incidence of recurrent UTI in the antibiotic group was low but was not significantly different from the no-prophylaxis group (P=0.415) (Table 2). When stratified by the risk factors such as gender, age, feeding types, physiologic phimosis, vaginal reflux and degree of

Table 1. Clinical characteristics in infants with acute pyelonephritis divided by prophylaxis

Variables	Probiotic prophylaxis (n=73)	Antibiotic prophylaxis (n=50)	No-prophylaxis (n=68)	P value
Male:female	50:23	39:11	54:14	0.293
Age (mon)	4.5±2.4	4.6±2.8	4.2±2.5	0.318
Fever duration (d)	1.6±1.3	2.2±1.8	1.9±1.4	0.523
WBC (/mm^3)	23 920±8660	21 680±8970	19 820±6580	0.225
ESR (mm/h)	24.58±11.95	21.76±28.68	23.96±11.28	0.294
CRP (mg/L)	52.67±23.90	36.02±22.40	59.25±28.50	0.120

WBC: white blood cell; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Table 2. Recurrence rate of urinary tract infection (UTI) in a 6-month follow-up after appearance of acute pyelonephritis

UTI	Probiotic prophylaxis n (%)	Antibiotic prophylaxis n (%)	No-prophylaxis n (%)
Recurrent (+)	6 (8.2)*	5 (10.0)†	14 (20.6)
Recurrent (-)	67 (91.8)	45 (90.0)	54 (79.4)
Total	73 (100)	50 (100)	68 (100)

*: P=0.035, *vs.* no-prophylaxis; †: P=0.415, *vs.* no-prophylaxis.

pyelonephritis, the significant difference between the probiotic and no-prophylaxis groups was present only in male infants (P=0.032) (Table 3).

In recurrent UTI, *E. coli* was the main causative uropathogen (84%), which was not significantly different among the three groups (P=0.305) (Table 4). In one infant of the antibiotic group, extended spectrum beta lactamase (ESBL) positive *E. coli* was cultured. In recurrent UTI, the resistance rate of *E. coli* to TMP/SMX was 100% in the antibiotic group, and it was significantly higher than 25.0% in the probiotic group and 41.7% in the no-prophylaxis group (P=0.008). The resistance rate of *E. coli* to ampicillin was also 100% in the antibiotic group, and it was higher than 50.0% in the probiotic group and 58.3% in the no-prophylaxis group (P=0.006). The resistance rate of *E. coli* to gentamicin was 80% in the antibiotic group, and it was higher than 0.0% in the probiotic group and 8.3% in the no-prophylaxis group (P=0.003) (Table 5).

Table 3. Incidence of recurrent urinary tract infection after stratification by risk factors

Variables	Probiotic prophylaxis (%)	Antibiotic prophylaxis (%)	No-prophylaxis (%)
Gender (male)	6.0*	7.7	20.4
Age (≤6 mon)	10.2	11.9	21.1
Formular feeding	14.9	16.7	22.2
Physiologic phimosis	10.3	11.1	16.6
Vaginal reflux (+)	9.1	20.0	20.0
APN (multifocal)	7.7	11.1	13.3

*: P=0.032 *vs.* no-prophylaxis. APN: acute pyelonephritis.

Table 4. Causative organisms of recurrent urinary tract infection

Organisms	Probiotic prophylaxis *n* (%)	Antibiotic prophylaxis *n* (%)	No-prophylaxis *n* (%)
*Escherichia coli**	4 (66.6)	5 (100)	12 (85.7)
Enterococcus fecalis	-	-	2 (14.3)
Citrobacter freundii	1(16.7)	-	-
Enterobacter cloaca	1 (16.7)	-	-
Total	6 (100)	5 (100)	14 (100)

*: P=0.305. "-": none.

Table 5. Antibiotic resistance rate of *Escherichia coli* in recurrent urinary tract infection

Variables	Probiotic prophylaxis (n=73)	Antibiotic prophylaxis (n=50)	No-prophylaxis (n=68)	P value
TMP/SMX	1 (25.0)	5 (100)	5 (41.7)	0.008
PIP/TAZ	1 (25.0)	1 (20.0)	3 (25.0)	0.432
Cefazolin	1 (25.0)	1 (20.0)	5 (41.7)	0.808
Tobramycin	0 (0)	2 (40.0)	6 (50.0)	0.198
Ampicillin	2 (50.0)	5 (100)	7 (58.3)	0.006
Ciprofloxacin	1 (25.0)	0 (0)	2 (16.7)	1.000
Gentamicin	0 (0)	4 (80.0)	1 (8.3)	0.003

TMP/SMX: trimethoprim/sulfamethoxazole; PIP/TAZ: piperacillin/tazobactam.

Discussion

In this study, probiotic prophylaxis was more effective than no-prophylaxis, but not inferior to antibiotic prophylaxis in pyelonephritis infants with normal urinary tract. The preventive effect was higher especially in male infants, which might be due to the higher male prevalence of UTI in infants. Moreover, probiotic prophylaxis in this study did not increase the resistance rate of *E. coli*, compared with antibiotic prophylaxis.

Antibiotic prophylaxis was described in the controlled trials in the 1970s. The effect of prophylactic antibiotics could decrease the episodes of recurrent UTI[26,27] and antibiotic prophylaxis has been used as a major treatment option for children with primary VUR or recurrent UTI.[5,6] But a recent Cochrane review concluded that it is uncertain whether severe renal scarring can be prevented by antibiotic prophylaxis because of its low efficacy in children with VUR.[11] Moreover, a systematic review of randomized controlled trials showed a small reduction (6% absolute risk reduction, risk ratio 0.65) in the risk of symptomatic UTI over 12 months of antibiotic prophylaxis.[12] Most recently, a RIVUR study demonstrated that antibiotic prophylaxis was associated with a reduced risk of UTI recurrence but not with renal scarring.[13] And the resistance rate of *E. coli* to TMP/SMX was significantly increased compared with that of the placebo group (63% *vs.* 19%). Long-term antibiotic prophylaxis is the main driving force in the emergence of resistant strains of uropathogens and commensal microflora.[14] Compared with no-prophylaxis, antibiotic prophylaxis was associated with the reduction of recurrent UTI, but bacterial resistance to TMP/SMX was significantly increased. The increasing antimicrobial resistance has stimulated interest of researchers in non-antibiotic prophylaxis including probiotic prophylaxis in preventing recurrent UTI.[22]

Probiotic prophylaxis showed the significant deficits of urogenital lactobacilli or the inverse association of vaginal lactobacilli and uropathogens in women with recurrent UTIs and in infants with febrile UTI.[28-30] Lactobacilli given exogenously would replete the deficient urogenital lactobacilli and provide the bacterial barrier like indigenous lactobacilli.[17,18] Various lactobacillus strains were tested and proved to have antimicrobial activities, i.e., the maintenance of acidic pH, interference of bacterial adhesiveness, secretion of bacteriocin, hydrogen peroxide, lactate and biosurfactant, and also stimulation and up-

regulation of the host immunity.[21,31-35] The preventive effect of lactobacillus probiotics was confirmed in animal models of UTI,[36,37] and clinical application of lactobacillus probiotics showed some beneficial effects in adult women. A meta-analysis including two studies using the effective probiotic strain (*L. rhamnosus* GR-1 and *L. fermentum* B-54)[20] showed significant effects of lactobacillus probiotics compared with no-prophylaxis.. A recent trial[38] compared *lactobacilli* with antibiotics in postmenopausal women, which did not meet the non-inferiority criteria in prevention of UTIs, but did not increase the antibiotic resistance.

There were few clinical trials about the use of lactobacillus probiotics in children. In a 6-year-old girl, UTI was successfully prevented with *Lactobacillus acidophilus* DDS-1 from frequently relapsed UTI.[24] Probiotic prophylaxis was as effective as low-dose antibiotic prophylaxis in preventing recurrent UTI in children with persistent primary VUR.[25] In premature infants (<33 weeks or <1500 g) treated with probiotics, the incidence of UTI was reduced,[23] but the difference was not statistically significant. In our study, lactobacillus probiotics decreased the recurrence rate of UTI in infants compared with no-prophylaxis. In infants, postnatal development of lactobacilli may be important in preventing UTI.[39] Human breast milk proven to be a major source of postnatal acquisition of lactobacilli[40,41] is called as a natural probiotic, which may decrease the UTI prevalence in infants on breast feeding.[42]

There are many uncertainties about the effect of probiotics, appropriate strains and effective dosages.[32] But probiotic prophylaxis can be a novel promising approach to prevent UTI in this era of increasing antibiotic resistance.[19,20] There are some limitations in the present study. First, our study design was retrospective; second, doctor's counseling could influence the decision for patient treatment; third, even the results stratified by gender showed difference between the probiotic and no-prophylaxis groups, the number of patients was not large enough.

In conclusion, this retrospective study showed evidence for the effectiveness of probiotic prophylaxis in infants with pyelonephritis and normal urinary tract. Randomized controlled trials comparing antibiotic prophylaxis, a standard of care, and probiotic prophylaxis should be conducted to optimally inform physicians in clinical decision-making.

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