The Effectiveness of a Three Day Course Antibiotic Post-urodynamic Study in Preventing Lower Urinary Tract Infection

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ABSTRAK

Tujuan: *menilai efektivitas pemberian antibiotik selama tiga hari pasca-pemeriksaan urodinamik untuk mencegah infeksi saluran kemih (ISK).* ***Metode:*** *uji klinis acak tersamar ganda membandingkan proporsi ISK pada kelompok pasien yang mendapatkan levofloxacin 500 mg satu kali sehari selama tiga hari dan kelompok tanpa antibiotika pasca-pemeriksaan urodinamik. Hasil luaran studi ini adalah insidens ISK bawah pada kelompok levofloxacin dan kelompok plasebo. ISK bawah didefinisikan sebagai pasien dengan gejala klinis satu atau lebih yang mengarah ke ISK bawah dan satu atau lebih kriteria ISK berdasarkan parameter urinalisis. Uji chi square digunakan untuk mengetahui hubungan dengan ISK antara kedua grup.* ***Hasil:*** *total 126 pasien yang mengikuti studi ini dari 2 poliklinik urologi di Jakarta yaitu RS Cipto Mangunkusumo dan RS Asri. Didapatkan 26 pasien (20,6%) mengalami ISK pasca-urodinamik (8 dari 63 pasien pada kelompok levofloxacin (12,7%) dan 18 dari 63 pasien pada kelompok plasebo (28,6%); p=0,028). Isolat kuman terbanyak adalah E. coli (n=18 pasien; 69,2%). Diagnosis klinis sebagai alasan dilakukan urodinamik adalah lower urinary tract symptoms (LUTS) gagal terapi (n=43 pasien; 25%), LUTS pasca-terapi invasif (n=29 pasien; 16,9%), dan overactive bladder gagal terapi (n=22 pasien; 12,7%).* ***Kesimpulan:*** *penggunaan antibiotik pasca-urodinamik dapat mencegah terjadinya ISK.*

Kata kunci: *antibiotik, infeksi saluran kemih, profilaksis, urodinamik.*

ABSTRACT

Aim: *to evaluate the effect of a 3-day course antibiotic post-urodynamic study (UDS) to prevent urinary tract infection (UTI).* ***Methods:*** *this was a randomized double blind clinical trial on the proportion of UTI in patients who received levofloxacin 500 mg once a day for 3 days after UDS compared to nontreated patients. The outcome of this study was the incidence of lower UTI in levofloxacin group and placebo group. Lower UTI was defined as patient with one or more clinical symptoms of lower UTI and one or more urinalysis parameter of UTI. Chi-square was used to evaluate the association between the lower UTI and treatment group.* ***Results:*** *a total of 126 patients were enrolled in this study from two outpatient urology clinics in Jakarta: Cipto Mangunkusumo Hospital and Asri Hospital. Overall, 26 patients (20.6%) had UTI post UDS (8 out of 63 patients from levofloxacin arm (12.7%) and 18 out of 63 patients from placebo arm (28.6%); p=0.028). The most common isolate found was E. coli (n=18 patients; 69.2%). The most common indications to perform UDS were Lower Urinary Tract Symptoms (LUTS) with failure of therapy (n=43 patients; 25%), LUTS after invasive treatment (n=29 patients;*

16.9%), and overactive bladder with failure of therapy (n=22 patients; 12.7%). ***Conclusion:*** *the use of antibiotic post-UDS can prevent incidence of lower UTI.*

Keywords: *antibiotic, prophylaxis, urinary tract infection, urodynamic.*

INTRODUCTION

Antibiotics as prophylactic agents are often used in several urologic invasive treatments with local anaesthetic such as catheter insertion and urodynamic study (UDS) to prevent urinary tract infection (UTI) post treatment. On the other hand, we have to choose wisely when to use prophylactic antibiotic. Considering that with the proper aseptic protocol, UTI could be prevented.

Previous studies regarding the use of prophylactic antibiotic post-UDS came up with inconsistent results.[1-7] Irrational prescription of prophylactic antibiotic could lead to high cost and risks for the patients. Some concerns may also be raised to the fact that there will be a multidrug bacterial resistance once irrational use of antibiotic is continued.

Until recently in our institution (Departement of Urology, Cipto Mangunkusumo Hospital), we are still using antibiotic for patients to prevent UTI. The commonly used regimens include oral quinolone for 3 days post-UDS. However, until now, no study has assessed the benefit of prescribing antibiotic (levofloxacin) post-UDS to prevent UTI. In several previous studies, once daily oral administration of levofloxacin was proven to have good efficacy and tolerability in treating patient with UTI.[8-10]

The aim of this study was to evaluate the effectiveness of antibiotic post-UDS to prevent UTI compared to placebo. We hope that the effective, safe, and rational use of antibiotic could be achieved.

METHODS

A double-blind randomized clinical trial was performed to compare a three day course of levofloxacin post UDS to placebo. Study was peformed and reported according to CONSORT guidelines. The outcome of this study was the incidence of patient with lower UTI. The Faculty of Medicine, Universitas Indonesia Ethics Committee has approved the study protocol with Ethical Clearance number 94/H.2F1/ETIK/2014. The target population was patients who underwent UDS at two outpatient urology clinics in Jakarta: Cipto Mangunkusumo Hospital and Asri Hospital, starting from 5th February, 2004 until 1st July, 2015. The total sample of the study was determined by the analytic sample formula of two proportion with type 1 error 5% and type 2 error 80%.

Baseline Data and UTI Measurement

Men and women above 18 year-old who underwent UDS and were willing to give their consent were eligible for inclusion. The exclusion criteria were allergy to levofloxacin, antibiotic consumption within the foregoing month, pregnancy, uncontrolled diabetes mellitus, use of urinary catheter, proven UTI prior UDS by clinical symptom and urine examination, and those who refused to participate. Urine sample was obtained from all patients prior to UDS. Patients were given the step by step instructions on how to collect urine properly and urine sample was sent to the laboratory for urinalysis. Patients were excluded if there was UTI based on urinalysis.

All patients underwent standard aseptic protocols for catheterization before UDS. The UDS examination used two catheters, each was introduced into the urethra and rectum. At the completion of UDS examination, each patient was either assigned to three days course of levofloxacin tablets 500 mg once daily or placebo tablets once daily by random fashion according to computer generated lists. Placebo tablets resembled the antibiotics in size, shape, and color. The physician and patient were blinded as to which assignment the patient received and the randomization code was not opened until the end of the study.

Urine sample was obtained 4 days after UDS as well as clinical symptoms for lower UTI. Furthermore, urine culture and sensitivity testing were done if the patient met the criteria

of lower UTI using urine analysis and clinical symptom. Lower UTI was defined as patient with one or more clinical symptom of lower UTI (e.g dysuria, frequency, urgency or suprapubic pain) and one or more urinalysis parameter of UTI (e.g leucocyturia, which defined as leucocyte >5 cells/high power field, positive for bacteria, nitrite, and leucocyte esterase).

Statistical Analysis

Descriptive report was used to characterize each subject such as their age, gender and the indication to perform UDS while the comparison of lower UTI between the antibiotic group and placebo group used analytic studies. We used chi square to analyze the association between the lower UTI and treatment group. SPSS for Windows version 17.0 was used for statistical analysis and p-value <0.05 was considered significant.

RESULTS

A flow diagram of the randomized trial is shown in **Figure 1**. One hundred thirty-three patients were screened and 126 patients were enrolled in this study. Seven patients were excluded, two for use of urinary catheter, one for proven UTI pre-UDS study, two had uncontrolled diabetes mellitus, and two patients declined to enroll in this study. Sixty-three patients were assigned to levofloxacin group or placebo group post-UDS, respectively. All of the patients allocated either in levofloxacin or placebo arm were completed for follow-up for four days and a total of 126 of patients were included in final analysis. The characteristics of the patients who underwent UDS on each group are shown in **Table 1** and the clinical diagnosis for performing UDS from all patients can be seen in **Figure 2**.

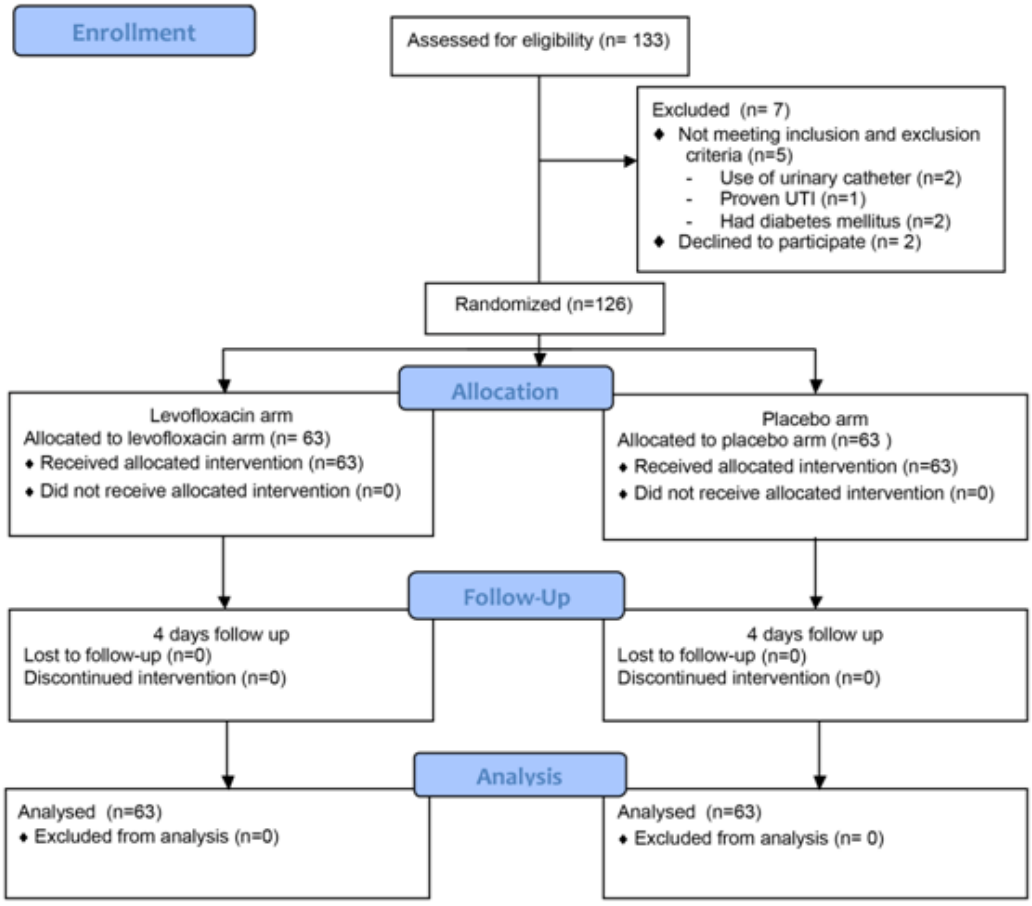

Figure 1. CONSORT diagram of the randomized double blind study of the antibiotic vs. placebo post-urodynamic study

Table 1. Subjects' characteristics

	Treatment (n=63)	Control (n=63)
Age (years), mean (SD)	57.2 (17.0)	53.3 (14.6)
Gender (male), n (%)	34 (54.00)	29 (46.00)
Clinical diagnosis for performing UDS, n (%)		
- LUTS with failure of therapy	26 (41.30)	17 (27.00)
- LUTS after invasive treatment	17 (27.00)	12 (19.00)
- OAB with failure of therapy	5 (7.90)	17 (27.00)
- Stress incontinence with failure of therapy	3 (4.80)	9 (14.30)
- Others	12 (19.00)	8 (12.7.00)

UDS = urodynamic study; LUTS = lower urinary tract symptom; OAB = overactive bladder

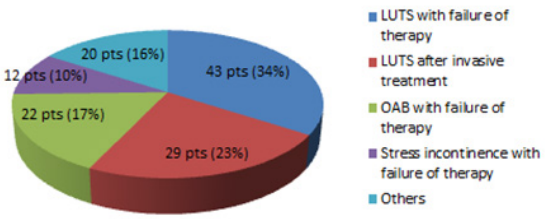

Figure 2. Clinical diagnosis for performing urodynamic study (n=126)

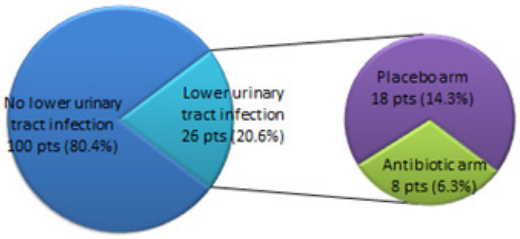

Figure 3. Lower urinary tract infection post-urodynamic study

During filling phase, fifty-four patients (42.9%) had low bladder compliance, 44 patients (34.9%) had detrusor overactivity, 43 patients (34.1%) had small bladder capacity, 17 patients (13.5%) had stress urodynamic incontinence, 14 patients (11.1%) had detrusor overactivity incontinence, and 10 patients (7.9%) had large bladder capacity. Patient could have more than one diagnosis during filling phase.

In voiding phase, fifty patients (39.7%) had detrusor underactivity, 48 patients (38.1%) had bladder outlet obstruction, 13 patients (10.3%) were equivocally obstructed, 12 patients (9.5%) had bladder atonia, and 2 patients (1.6%) had detrusor sphincter dyssynergia. Patient also could have more than one diagnosis during this phase. Normal urodynamic finding was found in 3 patients (2.4%) either in filling phase or voiding phase.

Lower UTI was found in 26 cases out of 126 patients post-UDS (**Figure 3**). Overall, twenty six patients (20.6%) had UTI post-UDS (8 of 63 patients from levofloxacin arm (12.7%) and 18 of 63 patients from placebo arm (28.6%); p = 0.028). Type of bacteria found in urine culture

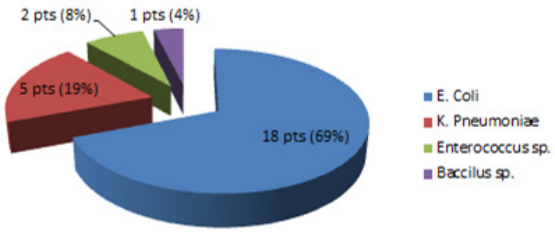

Figure 4. Type of bacteria in urine culture (n=26)

isolate from these 26 cases is shown in **Figure 4**. *E.coli* was the most common bacteria found from the urine culture. The comparison of lower UTI cases on both groups is shown in **Table 2**.

From eighteen *E. coli* species found in the isolate, seven were sensitive to levofloxacin (two from antibiotic arm and five from placebo arm) and eleven were resistant to levofloxacin (three from antibiotic arm and eight from placebo arm). Furthermore, three cases had resistance (two from antibiotic arm and one from placebo arm) to levofloxacin, ciprofloxacin, nitrofurantoin and cotrimoxazole but sensitive to fosfomycin.

Of the five isolate of *K. Pneumoniae*, 3 were sensitive to levofloxacin (all from placebo arm) and 2 were resistant to levofloxacin (each

Table 2. Lower urinary tract infection post-urodynamic study (n=26) on both groups

	Treatment	Control	p value
Cases of lower urinary tract infection post UDS, n/total cases (%)	8/26 (30.80)	18/26 (69.20)	0.028
Type of bacteria in urine culture, n (%)			
- *E. Coli*	5 (62.50)	13 (72.20)	0.152
- *K. Pneumoniae*	1 (12.50)	4 (22.20)	
- *Enterococcus sp.*	2 (25.00)	0 (0.00)	
- *Bacillus sp.*	0 (0.00)	1 (5.60)	

from antibiotic arm and placebo arm). There was one case with resistance to levofloxacin, ciprofloxacin, nitrofurantoin, and cotrimoxazole but sensitive to fosfomycin. All isolates of *Enterococcus sp*. and *Bacillus sp*. were sensitive to levofloxacin.

DISCUSSION

This study reported that the incidence of UTI post UDS was 20.6%. Compared to the previous studies, the incidence of UTI in our study was relatively high. Several previous studies found that incidence of UTI after UDS was 1.1% - 20.6%.[1-7,11-19] Urodynamic procedure is an invasive examination and despite the aseptic protocol before examination, patients still suffer from UTI.[5,12]

Several literatures have already reported the efficacy of antibiotic prophylaxis in preventing UTI post UDS with inconsistent results.[1-7] Some of them used antibiotic before UDS and the others used antibiotic after UDS. Many of them showed lower rate of UTI post UDS compared with placebo even though some of them experienced insignificant results.[1,2,6,7,14] This study found that the UTI in antibiotic treatment group was significantly lower than placebo arm (12.7% vs 28.6%; p = 0.028). This finding was in line with the study done by Kartal, et al.[5]

Some studies have concluded that UTI post UDS is not affected by administration of antibiotic prophylaxis although they reported lower incidence of UTI post UDS in the antibiotic arm versus placebo arm.[1,2,4,7,20] Another study reported that UTI after UDS was significantly decreased by the use of antibiotic prophylaxis and the authors recommend antibiotic prophylaxis for patients undergoing UDS.[3] Additionally, a meta-analysis study from 8 randomized controlled trials came up with the conclusion that the use of prophylaxis antibiotic in UDS reduces the risk of significant bacteriuria.[21] On the other hand, some studies reported higher incidence of UTI post UDS in the antibiotic arm than those in placebo arm.[3,4] Two studies reported the efficacy of antibiotics post UDS study to prevent lower UTI and found that there were no statistically significant difference of incidence of UTI in placebo and antibiotic group.[1,6]

This finding may confirm that infection can occur at the insertion of catheter and minor trauma inflicted during this procedure could make the patient more vulnerable to later infection caused by inflammation formed in the bladder.[5,7] Previous study and guideline showed that they could not give a strict indication whether to use antibiotic prophylaxis for UDS or not.[22] Previous studies and guideline cited that antimicrobial prophylaxis is justified in special circumstances such as advanced age, anatomic anomalies of urinary tract, poor nutritional status, smoking, chronic corticosteroid use, immunodeficiency, externalized catheters, colonized endogenous/exogenous material, distant coexistent infection, and prolonged hospitalization.[12,13,15,23] Based on our findings in this study, all patients with UTI grew microorganism in their urine isolate. In fact, some of them have multiple resistance to primary antibiotics of choice. By putting this into consideration, we believe that it is necessary for us to use antibiotic prophylaxis for patients undergoing UDS in our institution.

According to previous studies, the most common bacteria found in urine sample post

UDS was *E. Coli*.[2,4-6,12,17] This was also consistent with our findings that *E.coli* was found in 69% of urine culture.

American Urological Association (AUA) guideline recommends fluoroquinolone and cotrimoxazole as prophylactic antimicrobials of choice. Alternative antimicrobials include aminoglycoside (aztreonam), ampicillin, cephalosporin, and amoxicillin/clavulanate.[24] Several studies also used fosfomycin and nitrofurantoin as their prophylactic antibiotic for UDS.[1,3,4] In this study, we used levofloxacin 500 mg daily since this is the first drug of choice for UDS as mentioned by the guideline. Resistance of levofloxacin varied among study across the world. Study in Korea found that the rate of levofloxacin resistant *E.coli* was 30% in 2005 and increased up to 31.7% in 2009.[25] Other study in US found that the resistance of levofloxacin for *E.coli* was 9% in 2009.[23] In our study, we found relatively high resistance of levofloxacin. Eleven of *E.coli* isolate (61%) and two of *K. pneumoniae* isolate (40%) were resistent to levofloxacin.

The inconsistent findings with previous studies may be also due to the duration of the prophylactic antibiotic regimen. Many studies showed the superiority of antibiotic arm compared to placebo arm but no significant values were found. Two previous studies using single dose prophylactic antibiotic several hours before examination and the other two using antibiotic just covering one day post UDS.[1,2,6,7] In the recent study, we used antibiotic covering for 3 days post UDS. It could be one of the factors that made inconsistent findings among studies.

CONCLUSION

Patients could exhibit lower UTI after UDS despite the proper implementation of aseptic procedure. A three days course of levofloxacin 500 mg daily could decrease the incidence of lower UTI from 28.6% to 12.7%. This study showed us that the use of antibiotic post-UDS can prevent incidence of lower UTI. Therefore, we recommend the use of antibiotic post UDS. Choice of antibiotic clearly depends on the pattern of microorganisms and their sensitivity-resistance data in each center.

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