Effectiveness of Single Dose Fosfomycin and Single Dose Levofloxacin as Pre-Urodynamic Antibiotic Prophylaxis for Urinary Tract Infection Prevention in Post-Urodynamic Examination

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Research Title

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Abstract

a) Study aims

This study aims to compare the effectiveness of administering single doses of fosfomycin and levofloxacin pre-procedure on the incidence of urinary tract infections (UTIs) following urodynamic examination.

b) Research Method

This study utilized a single-blinded randomized clinical trial design to compare the proportion of post-urodynamic UTIs in the group receiving single-dose levofloxacin pre-urodynamic versus the group receiving levofloxacin post-urodynamic for three days. The target population consisted of patients undergoing urodynamic examination at RSUPN dr. Cipto Mangunkusumo from November 2022 to August 2023. The total sample size in this study was 100 patients. On the fourth day post-urodynamic, urinalysis and urine culture were performed to determine the diagnosis of UTI. Chi-square test was used to analyze the association between UTI and treatment group. Results were considered statistically significant if $p < 0.05$.

c) Expected Results

The expected results are data regarding the comparison of UTI incidence post-urodynamic examination in the group given single-dose levofloxacin and single-dose fosfomycin prior to urodynamic examination.

d) Outcome

The incidence of UTI in the group receiving single-dose levofloxacin pre-urodynamic compared to the group receiving single-dose fosfomycin pre-urodynamic.

e) Benefits

By obtaining data comparing the effectiveness of single-dose pre-urodynamic levofloxacin and fosfomycin on the incidence of UTIs following urodynamic examination, it can serve as a basis for selecting therapy regimens to prevent post-urodynamic UTIs. This can directly contribute to quality improvement, such as reducing antibiotic resistance rates and cost-saving in service delivery at dr. Cipto Mangunkusumo Hospital

Background

In the field of Urology, urodynamic examination is a functional assessment of the lower urinary tract that is useful for diagnosing the causes of incontinence. The number of these examinations increases by 15-20% annually. Aspects of bladder and urethral function assessed include the filling phase, storage phase, and voiding phase. This examination is invasive and carries a high risk of urinary tract infection (UTI) in patients, hence the need for prophylactic antibiotic use to prevent infection. Previous research by Rahardjo et al. in 2016 stated that the administration of prophylactic antibiotics for 3 days post-urodynamic examination could reduce the incidence of secondary urinary tract infections by 55% compared to placebo. The occurrence of infections and the cost aspect of post-urodynamic prophylactic antibiotic administration are concerns in healthcare provision at Dr. Cipto Mangunkusumo General Hospital (RSCM).

Data from the Clinical Pathology Department of RSUPD Dr. Cipto Mangunkusumo from July to December 2021 showed that 33% of 415 E. coli urine isolates were sensitive to levofloxacin. During the same period, 84% of 219 E. coli urine isolates were sensitive to fosfomycin. The majority of this data was obtained from inpatients. Considering the good sensitivity of fosfomycin to UTIs, researchers intend to compare the use of fosfomycin with levofloxacin as effective prophylactic antibiotics in patients undergoing urodynamic examination.

Study of Literature

Urodynamic Examination

Urodynamic examination is a functional assessment of the lower urinary tract that objectively demonstrates functional capacity and pathological conditions, thus determining the appropriate treatment according to the type of incontinence.[3] Bladder and urethral function is assessed during the filling phase, storage phase, and voiding phase, with several provocative maneuvers such as coughing, sneezing, and laughing used to assess correlation with the patient's clinical symptoms.[4]

Urodynamic examination includes uroflowmetry and measurement of post-void residual urine volume, cystometry, ambulatory urodynamics, videocystometry, and urethral pressure measurement. Uroflowmetry is used as an initial examination to assess urinary dysfunction. Parameters assessed in uroflowmetry include flow rate, maximum flow rate, voided volume, time to maximum flow, flow time, and average flow rate.[5]

Urodynamic Indication

Indications for performing urodynamic examination include patients with obstructive complaints in the lower urinary tract (LUTS) and neurological abnormalities, young men with LUTS complaints, patients with neurological disorders who have neurogenic bladder dysfunction conditions, children with urgency and urgency incontinence occurring outside of sleep, children with persistent diurnal enuresis, children with spinal nerve disorders, patients with neurological disorders with incongruity between symptoms and clinical findings, patients with persistent LUTS under appropriate/correct therapy, patients at high risk of complications from a planned therapy, situations where therapy decisions are unclear and require more specific diagnosis confirmation, patients with recurrent incontinence and planned surgery, patients with mixed incontinence of stress and urgency types and those with urinary disorders.[6]

Generally, urodynamic examinations use water/saline solution as a medium to fill the bladder. Multichannel urodynamic examinations are more complex and can be used to measure data that can complement information beyond routine urodynamic assessments of the bladder and abdomen, such as abdominal leak-point pressure (ALPP) and electromyography (EMG). The most advanced form of urodynamic examination is videourodynamics, which is equipped with static cystography and voiding cystourethrography using radiological contrast.[4,7]

UTI Classifications

Urinary tract infection (UTI) is an infection that occurs in the urinary tract, including the kidneys, ureters, bladder, and urethra. According to the EAU guidelines, UTIs are classified into uncomplicated UTIs, complicated UTIs, recurrent UTIs, catheter-associated UTIs, and urosepsis (Table 1)[8]. Based on location, urinary tract infections can be divided into two categories: upper

UTIs, which involve the kidneys and ureters, and lower UTIs, which involve the bladder and urethra.[9]

Table 1. UTI Classifications[8]

UTI Classifications	
Non-complicated UTI	Acute, sporadic, or recurrent infections in the upper and/or lower urinary tract affecting non-pregnant women, postmenopausal women without anatomical abnormalities and comorbidities in the urinary tract.
Complicated UTI	All UTIs that cannot be classified as uncomplicated. In other words, UTIs in patients with a higher risk of complications, such as: men, pregnant women, patients with anatomical or functional abnormalities in the urinary tract, and/or with other underlying immune disorders such as diabetes or HIV.
Recurrent UTI	Uncomplicated and/or complicated recurrent UTIs with a frequency of at least 3 times per year or 2 times in the last 6 months.
Catheter-related UI	Catheter-associated UTIs refer to UTIs that occur in patients who use catheters regularly and have used a catheter for at least the past 48 hours.
Urosepsis	Urosepsis is defined as life-threatening organ dysfunction resulting from dysregulation of the host response to infection originating from the urinary tract and/or male reproductive organs.

And these followings are the common terminology used to describe UTI clinically.[10]

Terminology	**Definition**
Pyuria	Presence of more than 10 white blood cells/mm^3 per large visual field
Bacteriuria	More than 10^5 colony-forming of urinary pathogens units per mL
Confirmed UTI	Pyuria accompanied by bacteriuria
Asymptomatic bacteriuria	Presence of bacteriuria in the absence of genitourinary symptomps or sings

Diagnostic Evaluation

Diagnosing UTIs can be established through a focused assessment of lower urinary tract symptoms such as dysuria, frequency, and urgency. Diagnostic tests for UTIs consist of three main examinations: dipstick urinalysis, microscopic urinalysis, and urine culture. Urine culture is utilized for patients suspected of acute pyelonephritis, patients whose symptoms do not improve or have recurrent symptoms within 2-4 weeks after completion of treatment, women with atypical symptoms, pregnant women, and male patients suspected of UTI.[10]

Urinary Tract Infections after Urodynamic Testing

Previous studies have reported that the incidence of UTIs following urodynamic examination ranges from 1% to 30%. Another study mentioned that urodynamic testing without prophylactic antibiotic use has a bacteriuria incidence of 4-9%.[11] In previous research, prophylactic antibiotics were administered 1 hour before urodynamic examination.

Levofloxacin for Pre-Urodynamic UTI Prevention

Levofloxacin is a fluoroquinolone antibiotic with broad-spectrum activity against both Gram-positive and Gram-negative bacteria, as well as atypical pathogens. Levofloxacin exhibits antimicrobial effects against Streptococcus pneumoniae, both penicillin-susceptible and penicillin-resistant strains.[12] Previous studies have noted an increasing resistance of Gram-negative bacilli to quinolones.[11]

Fosfomycin for Pre-Urodynamic UTI Prevention

Fosfomycin is a bactericidal antibiotic with activity against several Gram-positive and Gram-negative bacteria, including vancomycin-resistant enterococci, methicillin-resistant Staphylococcus aureus, and carbapenem-resistant Enterobacteriaceae.[13] Research indicates that Escherichia coli and Enterococcus faecalis have high susceptibility to fosfomycin.[14] Single-dose oral fosfomycin 3 grams shows peak urine concentration within 4 hours and remains high (>128 mg/L) for 24 to 48 hours, sufficient to prevent pathogens in the urinary tract.[11]

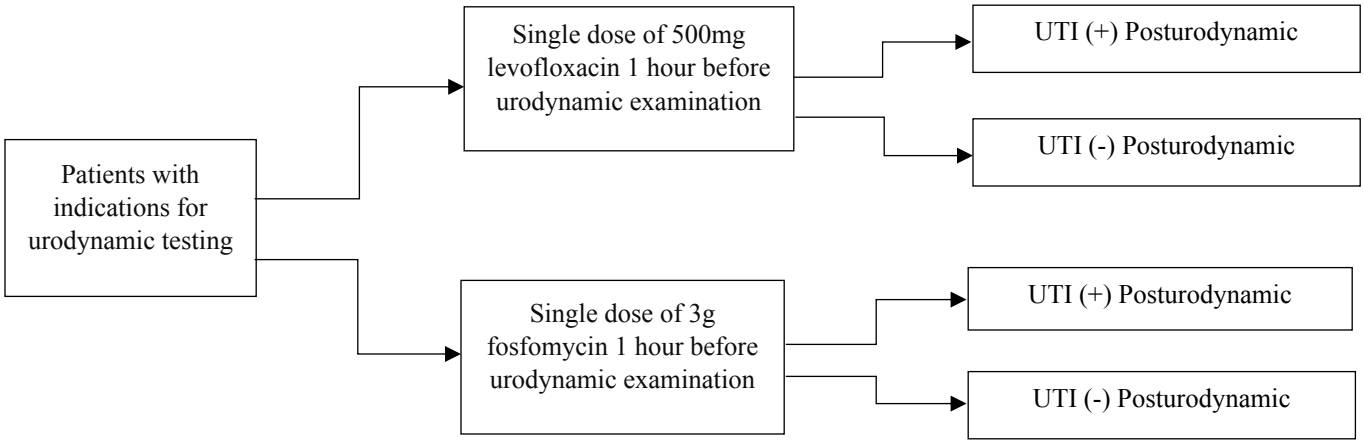
Research Methodology

This study is an experimental research with a single-blinded randomized clinical trial design to compare the proportion of UTIs in patients receiving a single dose of 500 mg levofloxacin and patients receiving a single dose of 3 grams fosfomycin one hour before urodynamic examination. Treatment group allocation was determined using block randomization technique.

This study utilizes a single-blinded design because the outcome assessed in this study is objective urinalysis. The urinalysis evaluator is unaware of the drug regimen received by the research subjects.

UTIs will be assessed based on bacteriuria conditions evaluated within 4 days post-urodynamic using urinalysis examination.

Conceptual Framework



Picture 1. Conceptual Framework

Definition of Work

1. Single Dose of Levofloxacin
   A single dose of levofloxacin is defined as the administration of 500 mg of levofloxacin one hour before urodynamic examination.
2. Single Dose of Fosfomycin
   A single dose of fosfomycin is defined as the administration of 3 g of fosfomycin one hour before urodynamic examination.
3. Urinary Tract Infection (UTI)
   Urinary tract infection is defined based on urinalysis results showing any of the following conditions: leukocyturia (presence of >5 leukocytes/HPF), positive bacteria, positive nitrites, and/or positive leukocyte esterase.
4. Urodynamic
   Urodynamic examination in this study consists of non-invasive uroflowmetry, post-void residual volume (PVR) measurement, and cystometrography (CMG) measurement.

Research Hypothesis

The administration of single-dose fosfomycin pre-urodynamic examination is more effective than single-dose levofloxacin pre-urodynamic examination in preventing UTIs.

Source

The data source for this research is primary data collected from patients with indications for urodynamic examination at the urology clinics of RSUPN Dr. Cipto Mangunkusumo, RS Persahabatan, and RS Siloam Asri from November 2022 to August 2023.

Number of Samples

The sample size calculation is based on the 'Fundamentals of Clinical Research Methodology' regarding proportion calculation for 2 independent groups. Based on literature, the effectiveness of levofloxacin antibiotic against post-urodynamic bacteriuria incidence is believed to have a 20% difference from P2 (P1=0.7) because the effectiveness of fosfomycin against post-urodynamic bacteriuria incidence is 0.9 (P2).[11]

$$n_1 = n_2 = \frac{[Z\alpha\sqrt{2PQ} + Z_\beta\sqrt{P_1Q_1 + P_2Q_2}]^2}{(P_1 - P_2)^2}$$

where $P = \frac{1}{2}(P_1 + P_2)$ and Q = 1-P

$$n_1 = n_2 = \frac{[1{,}96\sqrt{2x0{,}8x0{,}20} + 0{,}842\sqrt{0{,}7x0{,}3 + 0{,}9x0{,}1}]^2}{(0{,}7 - 0{,}9)^2} =$$

$$n_{1=}n_2 = 61{,}5 \sim 62\ patients\ for\ each\ group$$

Considering the possibility of drop-out, it was decided to take a total sample of 126 patients, with 63 patients in each group, who will then undergo screening for eligibility and will be randomized equally.

Data Collection Technique

The data collection technique employs consecutive sampling method until the required number of subjects is reached.

Inclusion and Exclusion Criteria

The inclusion criteria for this study are:

- Male/female patients aged >18 years who have indications for urodynamic testing
- Willing to participate in the study

The exclusion criteria for this study are:

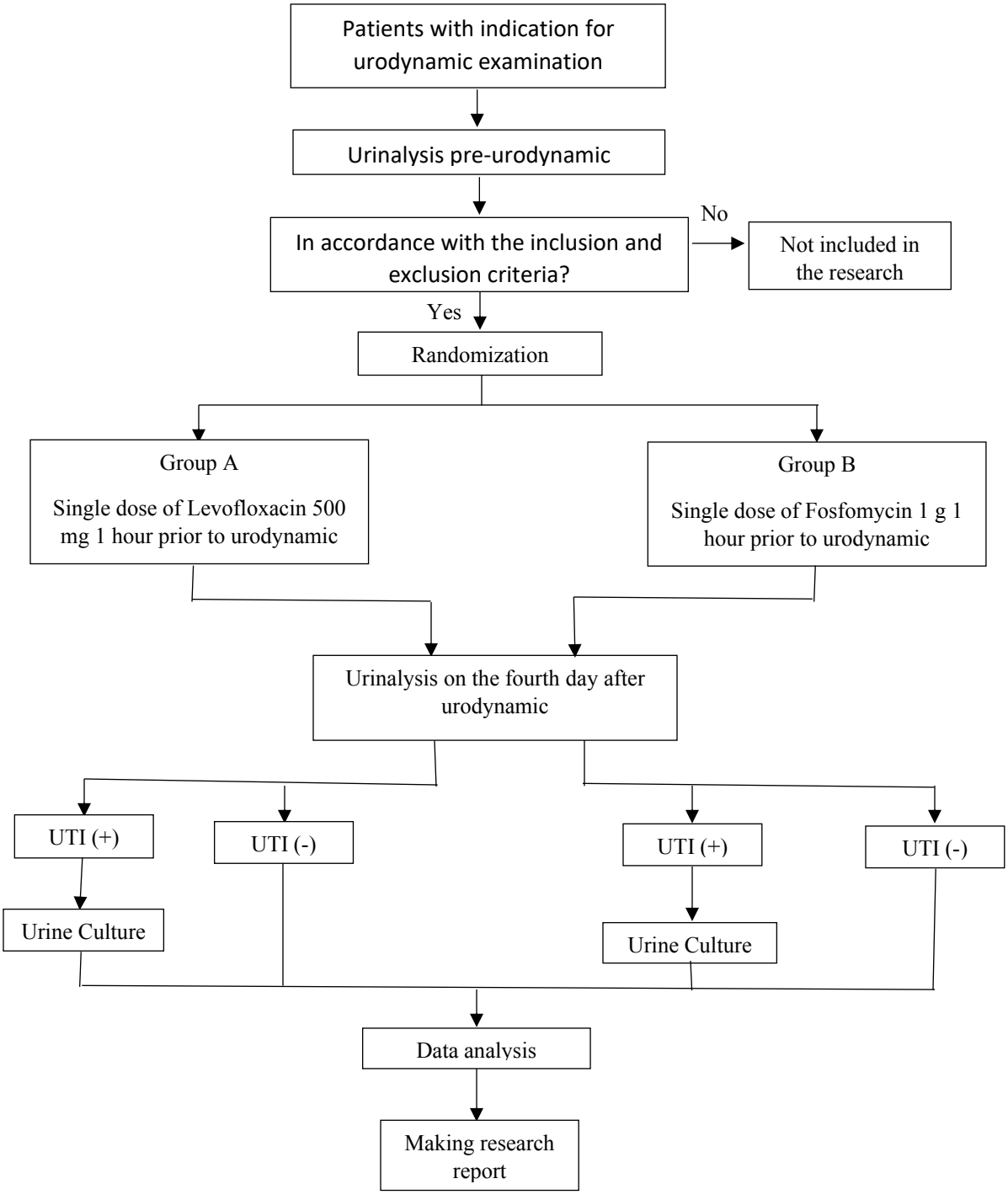
- Allergy to levofloxacin
- Allergy to Fosfomycin
- Pregnancy
- Uncontrolled diabetes mellitus
- Urinary catheterization
- History of UTI prior to urodynamic testing, based on clinical symptoms and urine examination results
- Refusal to participate in the study

Statistical Analysis Technique

Descriptive presentation is used to assess subject characteristics, such as age, gender, and indications for urodynamic testing. The relationship between UTI occurrence and treatment groups is assessed using chi-square analysis. Data will be processed using SPSS version 24 and considered significant if $p<0.05$.

Type of Research Activity

This research activity is experimental with the following research flowchart:



Picture 2. Research Flowchart

Research Places

The study will be conducted at the urology outpatient clinic of the Department of Urology, RSUPN dr. Cipto Mangunkusumo, Uronephrology Cluster of RSCM Kencana, RSUP Persahabatan, and RS Siloam Asri.

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