

**Comparison of the Effectiveness of Preurodynamic Single Dose
Levofloxacin with Posturodynamic Levofloxacin for Three Days
on the Incidence of Urinary Tract Infections**

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Research Title

Comparison of the Effectiveness of Preurodynamic Single Dose Levofloxacin with Posturodynamic Levofloxacin for Three Days on the Incidence of Urinary Tract Infections

Abstract

a) Study aims

This study aims to compare the effectiveness of preoperative single dose of levofloxacin with postoperative levofloxacin for three days on the incidence of urinary tract infections (UTI) after urodynamic examination.

b) Research Method

This study uses a randomized single-blind trial design to compare the proportion of posturodynamic UTI in the group receiving preurodynamic single-dose levofloxacin with the group receiving three days posturodynamic levofloxacin. The target population is patients who undergo urodynamic examination at the RSUPN dr. Cipto Mangunkusumo during any given time. The total sample size in this study is determined based on a two-proportion analytical sample calculation formula with type 1 error of 5% and type 2 error of 80%. On the fourth posturodynamic day, urinalysis and urine culture are performed to determine the diagnosis of UTI. To analyze the association between UTI and the treatment group, the chi-square test is used. Results are considered statistically significant if $p < 0.05$.

c) Expected Results

The expected result is data on the comparison of the incidence of UTI after urodynamic examination in the group given a single dose of levofloxacin and levofloxacin for three days after the examination.

d) Outcome

The incidence of UTI in the group receiving a single preurodynamic dose of levofloxacin compared to the group receiving levofloxacin for three days posturodynamics.

e) Benefit

By obtaining data on the comparison of the effectiveness of a single preurodynamic dose of levofloxacin and levofloxacin for three days posturodynamics on the incidence of UTI after a urodynamic examination, it can be used as a basis for selecting a therapeutic regimen to prevent the occurrence of posturodynamic UTI. This can directly contribute to quality improvement, namely the reduction of antibiotic resistance rates and savings in service costs at dr. Cipto Mangunkusumo Hospital

Background

Urodynamic examination is an important examination in the field of urology. Through urodynamic examination, the function of the lower urinary tract can be determined and a diagnosis of the cause of incontinence can be established. However, given the invasive nature of the examination, the patient's risk of urinary tract infection is high. For this reason, prophylactic antibiotics are given so that post-urodynamic infections can be avoided. This statement is also supported by the results of research by Rahardjo, et al. in 2016 where prophylactic antibiotics for 3 days post-urodynamics can reduce the rate of UTI by 55% compared to placebo. And considering the number of urodynamic examinations which is increasing by 15-20% annually, the incidence of infection and the cost aspect in giving prophylactic antibiotics after urodynamics is a burden on health services that need special attention in RSCM.

Data from the Department of Clinical Pathology RSUPD dr. Cipto Mangunkusumo from January – December 2017 showed that 41.3% of 978 isolates of urinary *E. coli* were sensitive to ciprofloxacin and 33% of 973 isolates were sensitive to cotrimoxazole. In the same period, 49.6% of 1097 isolates of *E. coli* urine were sensitive to levofloxacin. The majority of these data were obtained from hospitalized patients. Given the good sensitivity of levofloxacin to UTI, the investigators saw the potential for using levofloxacin as an effective prophylactic antibiotic in patients undergoing urodynamic examination.

Through previous research (Rahardjo, et al. 2016), researchers have identified that giving levofloxacin 3 days has good efficacy in preventing post-urodynamic UTI. However, several other studies have shown that single-dose prophylactic antibiotics also have satisfactory efficacy in preventing post-urodynamic UTI. The results of this study are considered appropriate and in accordance with the theme because they directly support the quality of RSCM services, improve the quality of services in the field of Urology and reduce the use of unnecessary antibiotics so as to reduce antibiotic resistance and reduce service costs.

Study of Literature

Urodynamic Examination

Urodynamics is an examination tool that measures the relationship between abdominal-bladder pressure and urine flow through the urethra so that it can be used to assess the functional status of the lower urinary tract. The main function of urodynamics is to help establish the diagnosis of a lower urinary tract based on the appropriate pathophysiology. Urodynamic examination can examine the function of the bladder and urethra both in the filling phase, storage phase (storage), and voiding phase. In addition, several provocative maneuvers such as coughing, sneezing, laughing can also be used during the examination to see if the symptoms match the clinical complaints of the patient.²

Some of the examinations included in routine urodynamics include: non-invasive uroflowmetry examination, post voiding residual (PVR) measurement, and cystometrography (CMG) measurement. CMG is used to assess the sensation of filling, a sense of fullness, and urgency. Bladder compliance and detrusor contractions (phasic contractions) can also be measured using CMG during the filling phase. Normally, water medium/physiological NaCl solution is used to fill the bladder during urodynamic examination. Multichannel urodynamics is a more complex examination and can be used to measure data that can complement information outside of routine urodynamics such as: abdominal leak-point pressure (ALPP) and electromyography (EMG) of the bladder and abdomen. The most recent form of urodynamics is videourodynamics which is complemented by static cystography and voiding cystourethrography on top of multichannel urodynamic examination. However, the medium used in videourodynamics is radiological contrast.²⁻³

The usefulness of urodynamic examination lies in its ability to assess the pathophysiology of a particular clinical course so that it can lead to the appropriate diagnosis and therapy. Because without proper assessment, treatment such as surgery for incontinence cases can lead to unwanted morbidity and complications. Unfortunately, urodynamic examination is one of the most expensive examinations and requires tools and expertise to operate, thus limiting its widespread use. Therefore, it is very important to use urodynamics in case-specific and clinical cases that have been reviewed using an appropriate history.⁴

Urodynamics is basically a non-physiological examination. Studies show that the normal range of uroflowmetry and cystometry results can vary. Although it can be a valuable examination tool, to be clinically meaningful the results of the urodynamic examination need to be adjusted to the patient's complaints. Especially if the condition of the complaint can be reproduced again during the urodynamic examination. Urodynamic examination that does not cause clinical symptoms according to the patient's complaints can be considered as an inconclusive examination. Likewise, if the urodynamic examination produces abnormal results without accompanying symptoms/complaints. However, by far, urodynamics is the best available examination tool for assessing lower urinary tract function.³⁻⁵

Urodynamic Indication

The history and physical examination often do not provide sufficient accurate information to determine therapy, but these data can be a good basis for determining whether a patient is eligible for more complex and/or invasive examinations.⁶

The following clinical factors are indicative of the need for further urodynamic examination:⁶

- Patients with obstructive complaints of lower urinary tract (LUTS) and neurological disorders
- Young male with LUTS
- All patients with neurological disorders who have neurogenic bladder dysfunction.
- Children with urgency and urgency-type incontinence that occur outside of sleep
- Children with persistent diurnal enuresis
- Children with spinal nervous system disorders
- Neurologically impaired patients with discrepancies between symptoms and clinical findings
- Patients with persistent LUTS under appropriate therapy
- Patients who are at high risk of complications from a therapy that will be carried out
- Conditions where therapeutic decisions are unclear and a more specific diagnosis is needed
- Patients with recurrent incontinence and planned surgery
- Patients with mixed stress and urgency incontinence and those with urinary disorders

Good Urodynamic Practice

According to the standards of the International Continence Society, good urodynamic performance should follow the following criteria:⁷⁻⁸

- causing clinical symptoms according to patient complaints
- checking the recording results to guarantee the quality of inspection
- interpreting of the results in the context of the appropriate clinical problem
- taking into account the existence of physiological variability in the same subject.

UTI Classifications

The most widely used classification of urinary tract infections (UTIs) is the classification developed by the CDC, IDSA, ESCMID, and the US FDA. As adjusted for EAU guidelines, UTI can be classified according to clinical features, anatomic location, severity of infection, categorization of comorbid risk factors and presence of therapy.⁹

The following is a UTI classification adapted from the EAU guidelines:⁹

| UTI Classifications | |
|---------------------|--|
| Non-complicated UTI | Acute, sporadic or recurrent infections of the lower and/or upper urinary tract, affecting nonpregnant women, postmenopausal women without anatomic abnormalities and comorbidities of the urinary tract |
| Complicated UTI | All UTIs that cannot be classified as non-complicated. In other words, UTI is in patients with a higher risk of complications, such as: men, pregnant women, patients with anatomic or functional abnormalities of the urinary tract, and/or with other coexisting immune disorders such as diabetes or HIV. |
| Recurrent UTI | Recurrent non-complicated and/or complicated UTI with a frequency of at least 3 times a year or 2 times in the last 6 months. |

| | |
|----------------------|--|
| Catheter-related UTI | Catheter-related UTI refers to UTI that occurs in patients who use repeated/routine catheters and have used a catheter for at least the last 48 hours. |
| Urosepsis | Urosepsis is defined as life-threatening organ dysfunction resulting from dysregulation of the supervisor's response to infections originating in the urinary tract and/or male reproductive organs. |

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

| Terminologi | Definisi |
|--------------------------|--|
| Pyuria | Presence of >10 white blood cells/mm ³ per large visual field |
| Bacteriuria | >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 symptoms/signs |

Asymptomatic bacteriuria

Asymptomatic bacteriuria is the presence of bacteriuria without accompanying genitourinary symptoms/signs. This condition is common and can be caused by an imbalance of the normal flora of the urinary tract. Clinical studies suggest that this condition may be protective against other symptomatic bacterial infections. Therefore, the treatment of bacteriuria is aimed especially if it is believed that the administration of antibiotics will provide greater benefits than the risks. By giving antibiotics, at least there are commensal bacteria that are eradicated and reduce the protective effect of these normal flora against other pathogens that can cause symptomatic infection.⁹⁻¹⁰

Epidemiology

Asymptomatic bacteriuria occurs in about 1-5% of normal premenopausal women and will increase to 4-19% in elderly women and men. Approximately 0.7-27% occur in diabetic patients and 2-10% in pregnant women and 15-20% in the elderly population living in nursing homes, and 23-89% in patients with spinal disorders. Asymptomatic bacteriuria in younger men is rare but may increase the risk of complications such as chronic bacterial prostatitis. The bacterial spectrum of asymptomatic bacteriuria is often similar to the normal flora found in non-complicated UTI although other risk factors should also be considered.

Diagnostic Evaluation

The diagnosis of asymptomatic bacteriuria can be made using a midstream urine collection technique. If the culture of this sample yields 10⁵ colony forming/mL in 2 consecutive samples in women and a single sample in men, a diagnosis of asymptomatic bacteriuria can be made. If the sample is taken through a catheter, the diagnosis of bacteriuria can be made if the number of bacteria exceeds 10² cfu/mL, including men and women. If urease-producing bacteria such as *Proteus mirabilis* are found, the diagnosis of urinary tract stones should be ruled out. In these patients a distal rectal examination (DRE) should be performed to rule out prostate disease.¹⁰

Epidemiology of UTI on urodynamic examination

Various studies show that a single episode of catheterization can increase the percentage risk of UTI by 2%. Meanwhile, the magnitude of post-procedure UTI infection according to several studies can range from 3-20% despite using good asepsis techniques. Several studies also show that gender is the most influential risk factor for the incidence of urinary tract infections after invasive procedures. With regard to the high rate of urinary tract infections associated with invasive procedures in the urinary tract, several guidelines suggest the use of antibiotics as prophylactic agents to prevent postoperative UTIs.

Levofloxacin as an antibiotic

Levofloxacin is a fluoroquinolone antibiotic with a broad spectrum of activity against Gram-positive and Gram-negative bacteria and atypical pathogens. Levofloxacin has antimicrobial effect against both penicillin-susceptible and penicillin-resistant *Streptococcus pneumoniae*. In America, the prevalence of *S. pneumoniae* resistance to levofloxacin is <1% overall. A number of studies have shown that levofloxacin is effective in treating infections of the respiratory tract, genitourinary tract, skin and integumental system. In one study comparing the administration of antibiotics in patients with nosocomial pneumonia, oral administration of levofloxacin 750 mg orally once daily for 7-14 days was equivalent to that of an intravenous imipenem/cilastatin regimen of 500-1000 mg every 6-8 hours followed by oral ciprofloxacin 750 mg. twice a day. In patients with community pneumonia (CAP), levofloxacin 500 mg intravenously and/or orally once daily for 7-14 days has a similar effect to regimens such as amoxicillin/clavulanic acid, clarithromycin, azithromycin, ceftriaxone and/or cefuroxime axetil and gatifloxacin. Oral levofloxacin is as effective as ofloxacin in uncomplicated urinary tract infections or equivalent to ciprofloxacin in the treatment of complicated urinary tract infections. In men with chronic bacterial prostatitis, levofloxacin 500mg orally once daily achieves levels equivalent to 500 mg orally ciprofloxacin twice daily. Compared with other quinolone antibiotics, levofloxacin is generally well tolerated. Some of the most commonly reported side effects include nausea and diarrhea; while some of the side effects that are often encountered with quinolones such as photosensitivity are also less common with the use of levofloxacin.¹¹

Use of Levofloxacin in the prevention of post-urodynamic UTI

Although the evidence regarding the use of antibiotics after urodynamic examination varies, the experience of researchers in previous studies has shown that giving 3 doses of the antibiotic levofloxacin 500 mg can reduce the magnitude of the risk of post-urodynamic UTI by 55% compared to patients who do not receive prophylactic therapy at all.¹²

Pre-Urodynamic use of Levofloxacin for the prevention of UTI

Although prophylactic administration to prevent UTI after urodynamic examination using levofloxacin has not been studied before, there have been many studies that have tried to use various antibiotics such as augmentin, ciprofloxacin, cotimoxazole, nitrofurantoin, norfloxacin, trimethopim, and cinoxacin as prophylactic therapy that can be given. And through a meta-analysis of these studies showed that the use of post-urodynamic prophylaxis can reduce the risk of infection by 40%.¹ Therefore, prophylaxis using antibiotics is also applied in several guidelines, especially if the conditions under which urodynamics are performed cannot be regulated in such a way as to achieve ideal conditions.¹³

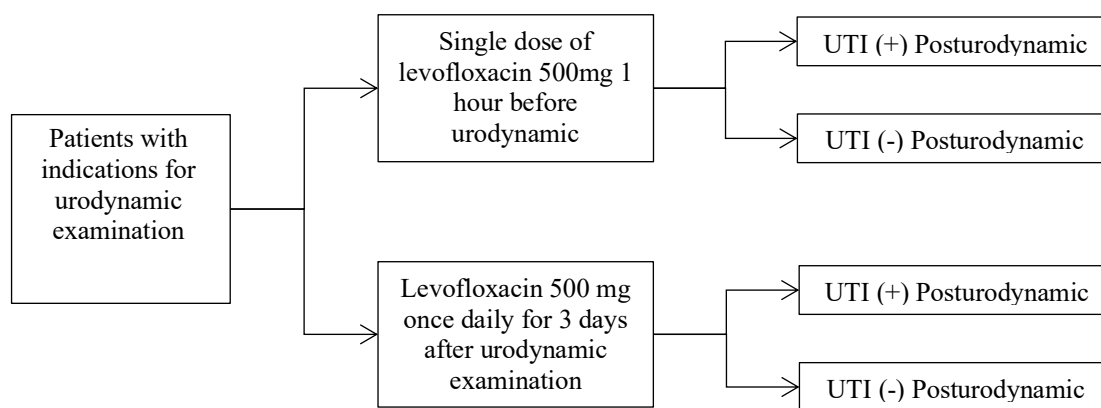
Research methodology

This study is an experimental study with a single-blinded randomized clinical trial design to compare the proportion of UTIs in a group of patients receiving levofloxacin 500 mg single dose one hour before urodynamic examination and patients receiving levofloxacin 500 mg once daily for three days postoperatively-urodynamic examination. To determine the sample treatment group, blocked randomization technique is used in this study.

This study uses a single-blinded design because the outcome assessed in this study is urinalysis which is the objective outcome. The urinalysis evaluator is blinded to the drug regimen obtained by the research subjects.

An additional consideration for the use of a single-blinded design is the limited facility for making placebos.

Conceptual Framework



Definition of work

1. Single dose of Levofloxacin
Single-dose levofloxacin is defined as the administration of 500 mg of levofloxacin one hour prior to urodynamic procedures.
2. Levofloxacin for 3 days
Levofloxacin for 3 days is defined as the administration of levofloxacin 500 mg/day for 3 days post-urodynamic examination.
3. UTI
Urinary tract infection is defined based on the results of urinalysis in which one of the following conditions is present: leukocyturia (found > 5 leukocytes/per field view), positive bacteria, positive nitrite, and/or leukocyte esterase positive.
4. Urodynamic
Urodynamic examination used in this study consist of non-invasive uroflowmetry examination, measurement of post voiding residual (PVR), and measurement of cystometrography (CMG).

Research hypothesis

Preurodynamic single-dose levofloxacin administration is more effective than posturodynamic levofloxacin for three days against UTI events.

Source

The data source of this research is primary data taken from patients who have indications for urodynamic examination at dr. Cipto Mangunkusumo Hospital, Siloam Asri Hospital, and Persahabatan Hospital during any given time.

Number of Samples

Calculation of the sample is made based on “*Dasar-dasar Metodologi Penelitian Klinis*” (Sastroasmoro et al.) regarding the calculation of proportions for 2 independent groups.¹⁴ From the literature, the effectiveness of posturodynamic prophylactic antibiotics in preventing UTI is 0.40 (P1). The effectiveness of levofloxacin 500mg preurodynamic single dose is believed to be 30% different from P1 (P2=0.70).

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

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

$$n_1 = n_2 = \frac{[1,96\sqrt{2 \times 0,55 \times 0,45} + 0,842\sqrt{0,40 \times 0,60 + 0,70 \times 0,30}]^2}{(0,40 - 0,70)^2}$$

$$n_1 = n_2 = 41,6 \sim 42 \text{ pasien}$$

Considering the possibility of drop-out, it is decided that the number of samples taken is 100 patients, which will then be screened for eligibility and will be equally randomized.

Data Collection Technique

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

The inclusion criteria in this study are:

- Male/female patients > 18 years who have indications for urodynamics
- Willing to participate in research

The exclusion criteria of this study are:

- Allergy to levofloxacin
- History of taking antibiotics in 1 month
- pregnant
- Uncontrolled DM
- Using a urinary catheter
- Having a UTI before urodynamics, based on clinical symptoms and urine examination results

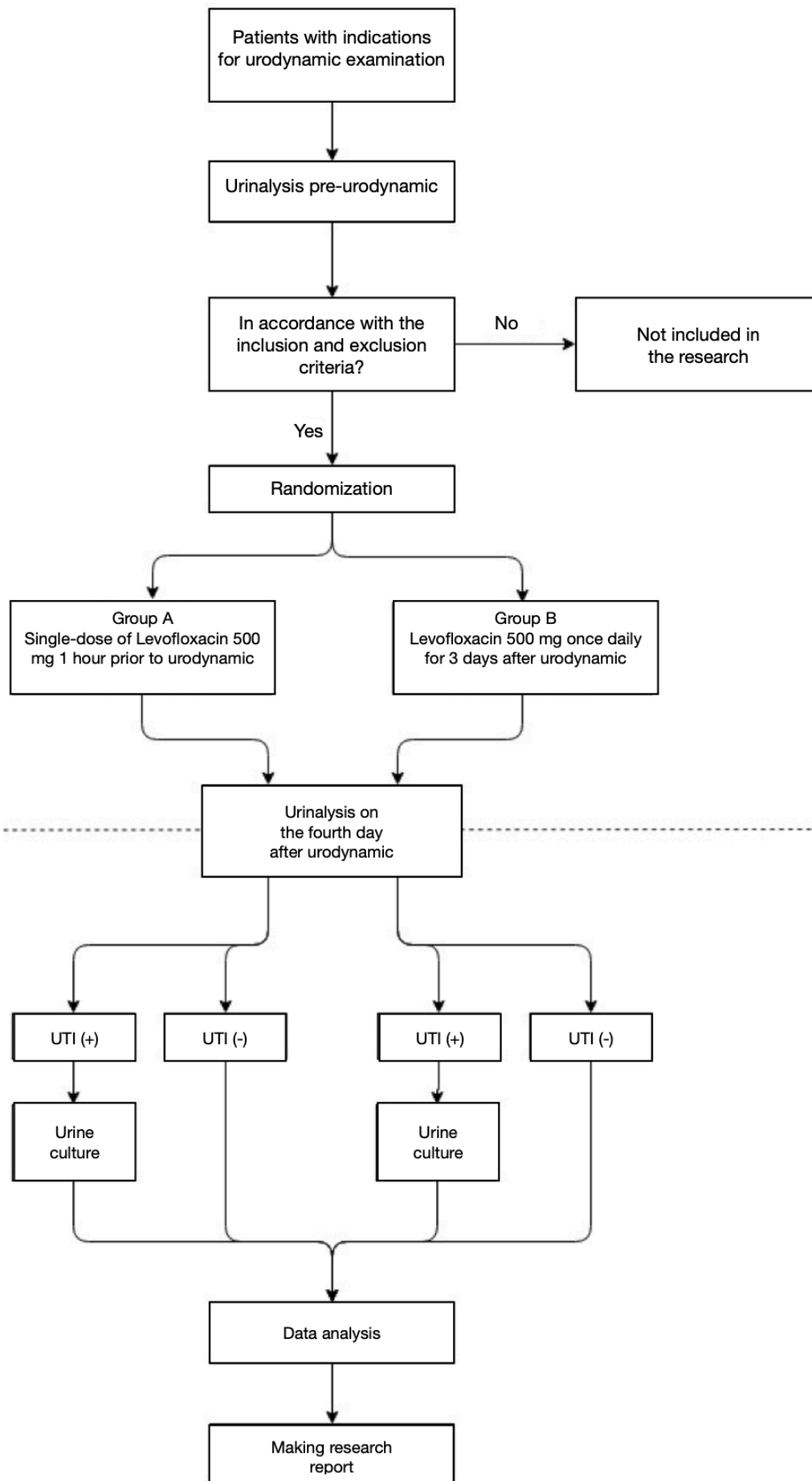
- Refuse to participate in research

Statistical analysis technique

Descriptive exposure is used to assess the characteristics of the subject, such as age, sex, and indications for urodynamics. To assess the relationship between the incidence of UTI with the treatment group, chi-square analysis is used. The data will be processed using SPSS version 24 and is considered significant if $p < 0.05$.

Types of Research Activities

This research activity is experimental with the following research flow chart:
(next page)



Research Places

The research places are the urology outpatient clinic of the Urology Department, dr. Cipto Mangunkusumo Hospital and the Urology Cluster of RSCM Kencana, Siloam Hospitals ASRI, and RSUP Persahabatan. At Siloam Hospitals ASRI, Prof. dr. Harrina Erlianti Rahardjo, Sp.U(K), PhD will be in charge, while at the RSUP Persahabatan, the person in charge is dr. Andika Afriansyah, Sp.U.

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