Sapporo Medical Journal
Volume 55, Issue 07, July 2021

The Use Of Antibiotic Prophylaxis In Transurethral Resection Of The Prostate: A Meta-Analysis Studies

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Abstract—Transurethral resection of the prostate (TURP) is currently the gold standard procedure for benign prostate hyperplasia (BPH). It may lead to various complications, such as urinary tract infection (UTI). Antibiotic prophylaxis use for TURP in the world has been studied, especially in high-risk case.We aimed to evaluate the effectivity of antibiotic prophylaxis in reducing bacteriuria and sepsis incidences on post-TURP patients. A systematic search was conducted in PUBMED, SCIENCE-DIRECT databases. The eligible analysis and article selection followed The Preferred Reporting Items for Systematic Reviews and Meta-Analysis(PRISMA) protocol, analysis of bias used Cochrane Risk of Bias Tools, each was done by 2 independent reviewers.Five RCT articles are declared eligible and involved 872 patients. The forest plot shows data heterogeneity from post-TURP bacteriuria incidence, and there is significant difference between antibiotic prophylaxis and placebo/no therapy (OR=0.38, 95% CI=0.17 – 0.88; p = 0.02). Forest plot shows data homogeneity from post-TURP sepsis incidence, and there is no significant difference between antibiotic prophylaxis and placebo/no therapy (OR=0.64, 95% CI=0.09 – 4.53; p = 0.66). Post-TURP bacteriuria incidence in patients administered with antibiotic prophylaxis is lower than placebo/no therapy, but post-TURP sepsis incidence in patients administered with antibiotic prophylaxis is the same as placebo/no therapy.

Keywords: antibiotic prophylaxis, bacteriuria, sepsis, TURP

1. Introduction

Urethral stricture is one of the most commonly found urological problems, in which there is a narrowing of the urethra caused by fibrosis and scar tissue.[1] It can occur in many patients with various etiologies. It can be caused by trauma, infection, ischemia, inflammation, instrumentation, or other unknown causes.[2] Studies reported that it occurs in 200 in 100,000 people, with an increasing incidence rate in the last 50 years.[3] The treatments recommended to urethral stricture patients include urethrotomy, dilatation, and urethroplasty.[4] Internal urethrotomy is routinely used amidst the development of urethroplasty technique.[5]

Internal urethrotomy is used for urethral stricture with a length of less than 1.5cm. However, the efficacy of internal urethrotomy is still being questioned because of its high stricture recurrence rate.[6] A case control study regarding urethral stricture in Indonesia by Gede et al.[7] in 2017 stated that the urethral stricture recurrence after internal urethrotomy was as high as 92.5%. Many treatment alternatives after internal urethrotomy have been widely studied to reduce the urethral stricture recurrence rate. Corticosteroid is one of the commonly used drugs studied. It has been widely used in centers to reduce scar formation. It is able to decrease collagen, glycosaminoglycan synthesis, and the expression of inflammatory mediators.[8] Among those regularly reported is triamcinolone.[9] However, results surrounding the subject vary. As of the conduction of this review, many studies investigating the role of corticosteroids have been published.[10–13] Therefore, we aimed to evaluate several studies reporting on the effects of triamcinolone after internal urethrotomy to reduce urethral stricture recurrence.

2. MATERIAL AND METHODS

Type of Studies

This MA study was done by searching all randomized controlled trials (RCT) studying TURP patients who

had received antibiotic prophylaxis versus placebo/no therapy during peri-operative period. The A systematic searching was done on published studies by using PUBMED and SCIENCE-DIRECT search-engine database, and relevant lists of articles' references, reviews, research, and books' chapters, also all main urological conference proceedings.

Type of Participants

Inclusion Criteria

All studies with complete manuscripts enrolling patients undergoing TURP with pre-operative sterile urinary culture without history of catheterization were included. Also, studies with 2 arms or more directly comparing administration of antibiotic prophylaxis versus placebo/no therapy were included, which were given once at the latest 24 hours post-operation.

Exclusion Criteria

All studies with 2 arms or more comparing 2 antibiotics without control group were excluded. Also, studies enrolling TURP patients with pre-operative positive urinary culture or UTI and systemic infection; patients who had been administered with antibiotic therapy more than one time and or more than 24 hours post-operation; patients with pre-operative indwelling catheter; malignancy (prostate or bladder); diabetes mellitus (DM); renal failure; hypersensitivity to antibiotics; immunocompromised patients prone to infection; intra-corporeal implants (e.g., hip and knee replacement, artificial cardiac valves); and congenital heart diseases were excluded. Studies which did not distinguish TURP with open prostatectomy, trans-urethral resection of the bladder tumor (TURBT), or other endo-urological procedures were also excluded. Studies with incomplete manuscripts were also excluded.

Type of Outcome Measures

1. Bacteriuria: the finding of bacteria within urine in asymptomatic patients. It is defined as a single bacterial growth 10^5 colony forming unit (cfu) per ml in urinary culture on a clean-catch urine or 10^3 cfu/ml in in-out catheter specimen or any bacterial growth in suprapubic catheter. Urinary specimen was taken before TURP and there was no post-operative maximal time for urinary collection.
2. Sepsis: a life-threatening organ dysfunction caused by dysregulation of host response on infection, marked by either persistent temperature above 38.3^{o}C, finding of bacteria in blood culture, or increased C-reactive protein/procalcitonin.

Data Collection and Analysis

Selection of Study

A systematic search was done on various scientific database, such as PUBMED, SCIENCE-DIRECT, and relevant lists of articles' reference, reviews, studies, and book chapters, accompanied by all conference proceedings. Additional search would manually be done by means of related studies' references. The search was performed using the terms prophylactic antibiotic, trans-urethral resection (of the prostate), chemoprophylaxis, and similar/related keywords. The study search and selection were done according to The Preferred Reporting Items for Systematic Reviews and Meta-Analysis(PRISMA) protocol.

Risk of Bias Assessment

Assessment of research bias and quality of every selected journal article were conducted in this study. For RCT, this study utilized method from CochraneRisk of Bias Tools (ROB) for Randomized Trials. If the number of the study was sufficient, a funnel-plot test would be performed to assess risk of publication bias. The test was made to minimalize bias publication potential by performing a very sensitive, broad, and comprehensive search strategy.

Data Analysis and Statistical Test Techniques

In this study, data from each selected article would descriptively be presented and analysis of intervariable comparison would be done. The baseline data were the name of researcher, year of study, criteria of exclusion/bacteriuria/sepsis, time of post-operative urinary collection, total sample, study design, antibiotic name, and clinical symptoms would be reported as descriptive data.

Statistical analysis was used to observe the difference between the examined variables. In this study, forest plot was used to observe inter-variable differences on each study. In continuous data, the analysis used mean and standard of deviation (SD) to find mean difference. On dichotomous data, total proportion and sample

were used to observe the difference of risk ratio (RR) from each study.This study used Review Manager (RevMan) version 5.4 for Windowsas a software for processing data analysis. All obtained data would be pooled in a tabulation integrated with a single data system. In case where an MA of the data was not possible, the result would be presented in a descriptive form.
Heterogeneity was initially analyzed with eye-balling, and then used X^2 statistic with significant level of 0,05; and I^2 test. When significant heterogeneity was still detected (I^2>50%), a possible explanation would be pursued, and analysis of sensitivity would be done. If it was still heterogenous and there was a plausible reason, a separate analysis would be done. If the cause of unclear heterogeneity was due to divergent data in terms of result direction, the data would not be pooled.

3. Results

Search results and study characteristics
Systematic search using PRISMA flowchart in PUBMED and SCIENCE-DIRECT databases resulted in 274 articles match with keywords, as seen in Figure 1. From the articles obtained from the 2 databases, there were 12 duplications. Screening based on title and abstract of the 262 articles resulted in 71 articles. Evaluation of eligibility from the article resulted in 5 studies match with the criteria for quantitative analysis or MA.

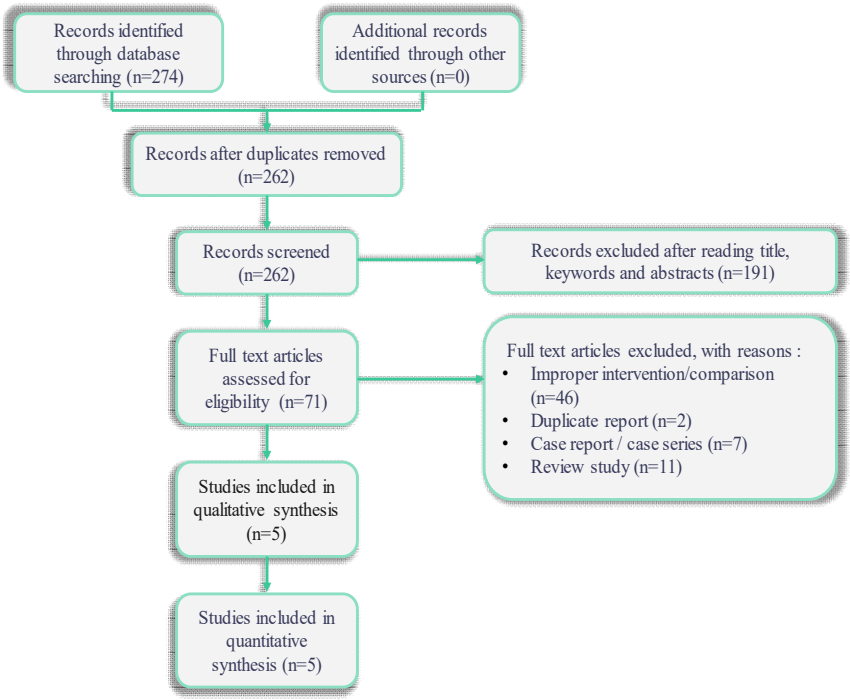

Figure 1. Flowchart of article searching and screening

There were 872 samples included from the 5 studies. Antibiotic prophylaxis used in the trials were cephradine, cefazolin, cefonicid, cefuroxime, cefotaxime, ceftazidime, levofloxacine, ciprofloxacin, and amikacin. In control group, the patients might be administered with placebo or without any therapy. The characteristics of the samples are explained in Table 1, which include the name of researcher, year of study, criteria of exclusion/bacteriuria/sepsis, time of post-operative urinary collection, total sample, study design, antibiotic name, and clinical symptoms.

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Table1. Characteristics and sample sizes of trials of TURP patients in pre-operatively sterile culture.

Criteria of exclusion	Criteria of bacteriuria	Criteria of sepsis	Time of intra-/post-operative urinary collection	Type of treatment
Pre-operative bacteriuria, comorbidity (DM and neurogenic bladder), and history of antibiotic or steroid therapy.	$>10^5$ cfu/ml	Not studied	On catheter removal, discharge from hospital, and 3 months post-operation.	Cefotaxime 2 g and NaCl 0.9%
Pre-operative bacteriuria, catheterization, and history of antibiotic therapy/allergy.	$>10^4$ cfu/ml	Not studied	Introduction of resectoscope, during hospitalization (daily), 2-4 weeks post-operation.	Cefonicid 1 g and placebo
Pyuria, pre-operative catheterization, prostate cancer/urolithiasis/comorbidities (hepatic/kidney failure), history of antibiotic/immunosuppresant therapy.	$>10^5$ cfu/ml	Not explained	During cystoscopy, 3 days, 2 weeks, and 3-month post-operation.	Cephradine 1 g and NaCl 0.9%-soaked gauze
Pre-operative bacteriuria, catheterization, history of antibiotic therapy/allergy, malignancy (prostate and bladder)/comorbidities (renal/hepatic failure, immunodeficiency, urolithiasis)	$>10^5$ cfu/ml	Not studied	2 and 10 days post-operation.	Cefazolin 1 g, cefuroxime 750 mg, ceftazidime 1 g, and placebo
Pyuria and pre-operative catheterization.	Not studied	Fever, hypotension, increased serum lactate	Not performed.	Levofloxacine 500 mg/ciprofloxacine 400 mg/cephazolin 2 g/amikacin 1 g and placebo

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Risk of bias analysis

This MA used Cochrane Risk of Bias (ROB) Tools for Randomized Trials instrument to evaluate bias level from each included study. Analyses of bias from the 5 RCTs were presented in Figure 2 and 3. All studies had been randomized in dividing allocation of antibiotic arm. Baten and Öztürk studies explained that the allocation result was blinded from samples, while other studies did not explain the blinding.

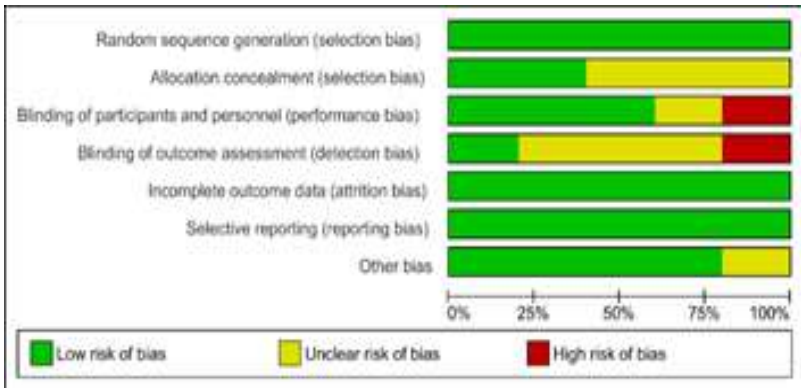

Figure 2. Risk of bias graph from the 5 RCTs.

Ibrahim study had a high risk of bias on blinding process because the method of treatment and evaluation of the result on the samples in the study were conducted openly. Baten study was conducted on 5 different centers with different randomization methods. The difference might lead to bias from the reported results.

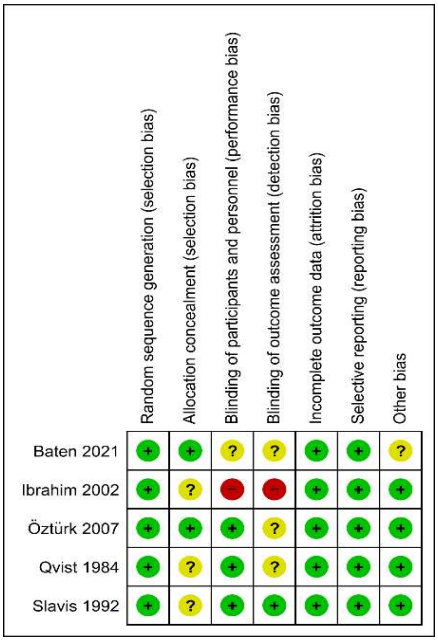

Figure 3. Summary of the risks of bias in the study. The green circle indicates low bias level, the yellow circle indicates unclear bias level, and the red circle indicates high bias level.

Effects of intervention

As shown in Figure 4, the mean comparison of bacteriuria incidence between antibiotic prophylaxis and placebo/no therapy arms shows significantly different results (OR=0.38, 95% CI=0.17 – 0.88, p=0.02), indicating that post-TURP bacteriuria incidence in patients administered with antibiotic prophylaxis is lower than placebo/no therapy. The utilized analysis model is random-effects because of interstudy heterogeneity ($I^2 = 62\%$).

	Prophylactic antibiotic		Control			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Ibrahim 2002	14	37	29	66	29.3%	0.78 [0.34, 1.77]
Ozturk 2007	15	88	14	30	27.6%	0.23 [0.09, 0.58]
Qvist 1984	6	43	8	45	22.9%	0.75 [0.24, 2.37]
Slavis 1992	3	43	17	46	20.2%	0.13 [0.03, 0.48]
Total (95% CI)		211		187	100.0%	0.38 [0.17, 0.88]

Figure 4. Antibiotic treated group vs. control: risk differences for incidence of bacteriuria after TURP.

The mean comparison of sepsis incidence between antibiotic prophylaxis and placebo/no therapy arms did not show significantly different results (OR=0.64, 95% CI=0.09 – 4.53, p=0.66; Figure 5), indicating that post-TURP sepsis incidence in patients administered with antibiotic prophylaxis is the same as placebo/no therapy. The analysis model utilized fixed-effect due to interstudy homogeneity ($I^2 = 0\%$).

	Prophylactic antibiotic		Control			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Baten 2021	1	211	1	263	33.2%	1.25 [0.08, 20.07]
Ibrahim 2002	0	37	2	66	66.8%	0.34 [0.02, 7.36]
Total (95% CI)		248		329	100.0%	0.64 [0.09, 4.53]
Total events	1		3			

Figure 5. Antibiotic treated group vs. control: risk differences for incidence of sepsis after TURP.

4. Discussion

This study is to provide an assessment related with antibiotic prophylaxis in BPH patients undergoing TURP whose pre-operative urinary cultures are sterile and are not catheterized pre-operatively. The results of the study indicate that the administration of antibiotic prophylaxis may reduce bacteriuria incidence. The samples will experience bacteriuria if there is bacterial growth $>10^4$ cfu/ml in an RCT and 10^5 cfu/ml in 3 RCTs.

The result shows that the incidence of bacteriuria is lower in antibiotic prophylaxis group, which is statistically significant (OR=0.38; 95% CI=0.17 – 0.88; p=0.02) and nearly constant in the entire included studies. From Figure 4 and 5, we can see that the total population on intervention arm that experiences bacteriuria is lower than the total population on control arm that experience bacteriuria. This result is the same as the last MA (2013), which shows a significant difference in TURP patients administered with antibiotic prophylaxis vs. placebo/no therapy.[19]

Althouth most bacteriuria incidences are transient and may resolve over time, in some cases it may develop fever and sepsis events. The data of sepsis incidence in post-TURP patients can only be obtained from 2 studies, with 577 assessed patients because only the 2 studies meet the inclusion and exclusion criteria of this study, thus lead to insignificant difference on sepsis incidence data between antibiotic and control arms. Besides, our MA has more homogenous population characteristics and fewer total sample than previous MA, where our MA only includes studies which only administered single-dose antibiotic prophylaxis. Due to the exclusion of patients with comorbidities, post-TURP bacteriuria incidence will not lead to significant incidence on sepsis. On the contrary, many patients with comorbidities such as geriatrics, anatomical disorders, malnutrition, smoking, chronic corticosteroid therapy, immunodeficiency, chronic intra-corporeal

implant usage, infected endogenous or exogenous materials, distant secondary infection, and prolonged hospitalization also influence the susceptibility for infection and sepsis.[20]

Total bacteriuria and clinical sepsis act as outcome measures for efficacy of antibiotic prophylaxis. Relationship between bacteriuria and UTI varies. In 24 hours after TURP, there are many transient asymptomatic bacteriuria cases, while bacteriuria at later period is closely related with clinical symptom of infection. Despite of the limitations, bacteriuria still becomes the accepted proxy for UTI incidence, especially 2 days after operation[21], and its presence, along with pyuria, is laboratorically needed for UTI diagnosis.[22]

Post-TURP UTI symptoms are usually manifested as bladder irritative symptoms, eg. frequency, urgency, and dysuria.[23] According to Bruyère *et al* (2018), UTI symptoms may be accompanied with febris, and sometimes severe sepsis in 5-10% patients.[24]

From the 5 studies, there were only 71 patients reporting the incidence of adverse event (hipersensitivity), forcing them to replace the antibiotics. All patients came from Baten study.[18]

The choice for antimicrobial prophylaxis is still important. The appropriate antibiotic has to be effective against common uropathogens, gives minimal influence on microbial resistence, has minimal adverse effect, reaches appropriate tissue concentration, and is easy to administer. Bacteriological examination indicates that most of baterial isolates are Gram-positive species, while more serious systemic infection is caused by Gram-negative species. Any chosen agent must have broad coverage with special acitivity against Gram-negative pathogens.[18]

This study has some limitations, such as variation in antibiotic posology and dosage, leading to heterogenous data distribution, except on the analysis of sepsis. It is important to conduct a more standardized clinical experiment in the future. A more homogenous data is expected to make the next MA study producing more conclusively evidence-based results

5. Conclusion

In summary, post-TURP bacteriuria incidence in low-risk patients administered with antibiotic prophylaxis is lower than placebo/no therapy, but post-TURP sepsis incidence in patients administered with antibiotic prophylaxis is the same as placebo/no therapy group. Further investigation is needed with larger population, more uniform parameter criteria, and longer period with additional parameters such as cost-effectiveness, long term adverse events, duration of catheterization and hospitalization to anticipate the difference of long-term efficacy on diverse antibiotic usage.

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