



STUDY PROTOCOL

REVISED Protocol for a comparison study of 1-day (single dose) versus 2-day prophylactic antibiotic administration in Holmium Laser enucleation of the prostate (HoLEP): a randomized controlled trial [version 2; peer review: 2 approved]

Previously titled: Protocol for a comparison study of 1-day versus 2-day prophylactic antibiotic administration in Holmium Laser enucleation of the prostate (HoLEP): a randomized controlled trial

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Abstract

Background: The best method of antimicrobial prophylaxis administration for surgical site infection (SSI) in transurethral holmium laser resection and enucleation of the prostate (HoLEP)/bipolar transurethral enucleation (TUEB) remains controversial. The purpose of this study is to compare one-day and two-day cefazolin in a randomized 2nd-phase study to help establish a protocol with a 95% confidence interval (CI) for SSI prevention.
Methods: Patients undergoing HoLEP/TUEB for benign prostate hyperplasia without preoperative pyuria will be enrolled and randomized to receive prophylactic antibiotic administration for HoLEP/TUEB in two groups, 1-day (single dose) cefazolin and 2-day cefazolin. The primary endpoint is the occurrence rate of postoperative urinary tract infection or urogenital infection within 30 days after HoLEP/TUEB with a statistical 95% CI in comparison between those groups. Secondary outcomes include the kind of infectious disease and evidence of diagnosis, day of diagnosis of infectious disease, performance of urine or blood culture, detection of bacteria, treatments, duration of treatments, AEs other than surgical site infection, and drug-induced AEs.
Discussion: The results of this study will provide evidence for defining the optimal duration of cefazolin prophylactic antibiotic administration for SSI.
Trial registration: This study was registered in the University Hospital Medical Information Network-Clinical Trial Registry (UMIN000027955) based on recommendations from the International Committee of Medical Journal Editors (ICMJE) on July 1st 2017.

Open Peer Review

Reviewer Status

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Any reports and responses or comments on the article can be found at the end of the article.

Keywords

HoLEP, Transurethral resection of the prostate, prophylactic antibiotic administration

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REVISED Amendments from Version 1

We have included those patients with preoperative pyuria, added the related Japanese Urological Association guideline in the 'Discussion' section, and added '(single dose)' after '1-day protocol' throughout the paper.

See referee reports

Abbreviation

SSI: surgical site infection; HoLEP: Holmium laser resection and enucleation of the prostate; TUEB: bipolar transurethral enucleation; CI: confidence interval; TURP: Transurethral resection of the BPH: prostate; benign prostate hyperplasia; UTI: urinary tract infection; PAA: prophylactic antibiotic administration; CEZ: cefazolin

Trial registration

This study is registered in the University Hospital Medical Information Network-Clinical Trial Registry (UMIN000027955) based on recommendations from the International Committee of Medical Journal Editors (ICMJE).

Introduction

Transurethral resection of the prostate (TURP) has been the gold standard for surgical treatment of benign prostate hyperplasia (BPH). However, currently enucleative surgery, such as transurethral holmium laser resection and enucleation of the prostate (HoLEP) or bipolar transurethral enucleation (TUEB), is increasingly performed as a substitution for TURP.

Guidelines for prophylactic antimicrobial administration (PAA) for TURP have been published by the European Association of Urology (EAU), American Urological Association (AUA) and The Japanese Urological Association (JUA)¹⁻³. Prophylaxis guidelines for HoLEP or TUEB are not fully established⁴. A meta-analysis by Ahyia *et al.* showed postoperative urinary tract infection (UTI) occurred in 4.1% (0–22%) of TURP cases and 0.9% (0–4.9%) of HoLEP cases, and concluded that HoLEP had a lower rate of SSI⁵. Similarly, our group presented data from a prospective multi-center study showing that SSI occurred in 8% of TURP cases and 5% of HoLEP cases¹. Importantly, no definitive description of the duration of antibiotic dosing was shown and the optimal duration of prophylactic antibiotic administration (PAA) for SSI need to be established.

Methods*Study sites*

Patients recruitment began on May 1st 2018 and will continue up to April 30th 2021 from the institutions of Kobe University Hospital, Kobe University International Clinical Cancer Research Center, Hara Genitourinary Hospital, Shinko Memorial Hospital, Hyogo prefectural Amagasaki General Medical Center, Kobe City Medical Center West Hospital, Kakogawa Central City Hospital and Hyogo Prefectural Kakogawa Medical Center. Those patients undergoing HoLEP/TUEB for BPH without preoperative pyuria will be enrolled. Preoperative pyuria will be defined as 5 or more white blood cells (WBC)/higher power field

(HPF). Since PAA duration is limited to 72 h or less in TURP and 48h or less in HoLEP or TUEB⁶, we will carry out a randomized study of 1-day (single dose) and 2-day PAA for HoLEP/TUEB using cefazolin (CEZ). This is a feasible randomized 2nd phase study to help design further confirmatory studies evaluating the differences of SSI occurrence rate with a 95% confidential interval.

Eligibility criteria*Selection criteria*

In the period from May 1st 2018 to April 30th 2021, patients 20 years old or older undergoing HoLEP/TUEB without preoperative bacteriuria will be enrolled.

Exclusion criteria

i) Patients who have undergone another procedure such as prostate biopsy or bladder urolithiasis at the time of HoLEP/TUEB. ii) Those with an indwelling urethral catheter. iii) Those with an allergy to CEZ. iv) Hemodialysis patients.

Interventions

Eligible patients will be randomized in equal proportions between 1-day (single dose) and 2-day PAA for HoLEP/TUEB using cefazolin (CEZ).

Outcomes*Primary endpoint*

Primary endpoint is to compare SSI occurrence rate in both 2 groups.

Items of postoperative infection complications:

30-days postoperative infectious complications after HoLEP

In this study, UTI and urogenital infection means prostatitis, epididymitis, pyelonephritis and urosepsis. The occurrence date of these infections and the duration (days) until disappearance of pyuria, in those cases with pyuria, will be recorded.

Secondary endpoints

In cases where perioperative infection requires antibiotic therapies, the following information will be recorded. 1) The kind of infection and reasons for the diagnosis; 2) Occurrence data of such infection; 3) Blood culture and urine culture; 4) Identified bacteria; 5) Methods of therapies; 6) Duration of therapies; 7) Other postoperative complications than infectious ones; 8) Drug-induced adverse events.

Feasible purpose

This is a feasible randomized study to investigate the occurrence rate of postoperative UTI or urogenital infection within 30 days after HoLEP/TUEB with an estimated 95% CI, and will be followed by confirmatory studies.

Participant timeline (See Table 1)**Sample size**

For a feasible randomized comparing study, the target sample size is n=180 (1 day (single dose): n=90 and 2 days: n=90). The

Table 1. Participant timeline.

Items	Preoperative observation period	Day of dosing (surgery day)		Postoperative observation period			
		0 week	1 st day after administration	2nd day after administration	1 week after administration	2 weeks after administration	4 weeks after administration
Term	Hospitalized day During hospitalization	During hospitalization	During hospitalization	During hospitalization	During hospitalization	During hospitalization	Consultation3
Informed consent	○						
Confirmation of patients' background	○						
Antibiotic administration (one-day group)		↔					
Antibiotic administration (2-days group)		↔					
Subjective symptom/objective findings	○	○	●	●	●	●	●
Observation of adverse events including infectious complications ^a		↔					
Blood pressure	○	○	●	●	●	●	
Heart rate	○	○	●	●	●	●	
Body temperature	○	○	●	●	●	●	●
Laboraty tests	○	○	●	●	●	●	●
Hematological examination	○	○	●	●	●	●	●
Biochemical examination	○	○	●	●	●	●	●
Urinalysis ^d	○	○	●	●	●	●	●
Chest X-ray		○					
ECG		○					
Urine culture	○	○					

○: Items to be done before antibiotic administration, ●: Items to be done after antibiotic administration

a: Adverse events are not necessarily associated with antibiotics.

b: Hematological examination consists of hematological laboratory tests, biochemical laboratory tests and urinalysis to check the safety of the tested antibiotics and includes white blood cell (WBC) and differential white blood count as inflammatory markers. The volume for hematological laboratory tests is 8ml.

c: Biochemical laboratory tests use CRP as inflammatory markers, which is performed within the range of daily clinical examination.

d: Urinalysis includes white blood cell (WBC) and bacteriuria as inflammatory markers. These tests are done as a confirmation safety check for this study.

sample calculation was performed as follows: this study is a feasibility study. We referred to the following study which examined their 164 TURP and HoLEP cases, and found the post-operative infectious complications in 7/72 cases (9.7%) and 2/72 cases (2.8%), respectively. Accordingly, if we estimate 3 or 4 cases of UTI or urogenital infectious complication within 30 days after HoLEP, the occurrence frequencies for a 95% confidence interval (CI) are 0.007-0.094 and 0.012-0.111, respectively. The upper limit of a 95% CI is 10% or so, and it may be useful for planning the next study to set them as in Jhanwar *et al.*⁷.

Statistical analysis

Analysis of study participants' background:

The difference between groups will be analyzed by the following methods:

Pearson's chi-square: nominal variables; Fisher's direct probability calculation method is performed where the expected frequency of less than 5 is 20% or higher; T-tests will be done for continuous variables. The Significance standard is set as 5% in two-sided tests.

Recruitment strategy

Recruitment will be performed from the patients with indication of HoLEP in those institutions participated in this study. Randomization will be performed by a table of random numbers as a simple randomized study under the control of the responsible party (Dr. Yuzo Nakano, Department of Urology, Kobe University Hospital).

Allocation

Participants will be randomly assigned to either 1-day or 2-day antibiotic group with a 1:1 allocation as per a computer-generated randomization schedule.

Blinding

Assessments regarding clinical recovery will be conducted by Dr. Yuzo Nakano blind to treatment allocation. Due to the nature of the intervention neither participants nor staff can be blinded to allocation, but are strongly inculcated not to disclose the allocation status of the participant at the follow up assessments. An employee outside the research team will feed data into the computer in separate datasheets so that the researchers can analyse data without having access to information about the allocation

Assignment of intervention

Tested antibiotics

1st generation cephalosporine : Cefazolin Sodium Hydrate (J01DB04)

Method of administration

Patients will be randomly divided into a 1-day (single dose) group (CEZ 1g, once per i.v. just before HoLEP/TUEB) and a 2-day group (CEZ 1g, i.v. just before HoLEP/TUEB with a repeat dose the next morning). Comparison of SSI occurrence in these 2 groups is a feasible randomization study.

Outline of study

i) One-day dosing (single dose): i.v. initiation of CEZ (1g) 30 min prior to surgery, completed in 30–60 min (with no any other antibiotic administration)

ii) Two-day dosing: i.v. initiation of CEZ (1g) 30 min prior to surgery, completed in 30–60 min, repeated every 12 hours for 2 days including the surgery day. Additional dosing is necessary in cases with 3 hours or longer of surgery time. Test items and schedule of this study is shown in [Table 1](#).

Study therapy

To investigate the inhibiting effect of cefazolin (CEZ) 1-day (single dose) and 2-day administration on perioperative infectious complications in HoLEP with a calculated 95% CI.

Combination medicine

Exclusion criteria include use of other antibiotics or cases requiring an additional antibiotic.

Termination of antibiotic administration

Cases exhibiting or suspicious for drug-induced allergy.

Assignment of interventions (for controlled trials)

Management and delivery of study drug

Applicants will be contacted by fax or e-mail and then given either 1-day (single dose) or 2-day CEZ under randomization as described above.

Post-test treatments

In cases where the attending physician diagnoses a perioperative infectious complication, the doctor can treat at discretion, including i.v. for severe cases and oral antibiotics for mild cases.

Evaluating items

We will gather the following data from the medical records.

i) Patients' background factors

Age, Body Mass Index (BMI), Preoperative IPSS/QOL, Qmax, residual urine volume (ml), Estimated prostate volume(ml), Preoperative PSA, ASA-PS, Diabetes mellitus (HbA1c, blood sugar control), Chemotherapy and immune-suppressants

ii) Surgery-related categories

Surgical time (min, including morcellation), Resected prostate weight (g), Catheterized period (days), Post-operative residual urine volume (ml): until 30 days after surgery, Duration of antibiotic administration (1 day (single dose) or 2 days)

iii) Postoperative infectious complications

Investigation for 30 days after surgery (need to record), UTI or urogenital infection (prostatitis, epididymitis or pyelonephritis), Postoperative complication other than infectious ones, Occurrence date, Cases with infectious complications requiring additional antibiotic therapy, Detail of infection and the

diagnosing evidence, Infection occurrence date, Urine culture and blood culture, Detected bacteria, Therapy, Therapeutic duration, and Days needed to reduce pyuria

Screening tests

Screening tests will be done to check the following criteria i) and ii).

i) Enrollment criteria

Those patients who are older than 20 years old undergoing HoLEP for benign prostate hyperplasia (BPH) without bacteriuria preoperatively and with informed consent.

ii) Exclusion criteria: see above

Information on participants

The following information will be recorded at the time of informed consent acquisition and screening tests.

i) Date of informed consent acquisition; ii) Class card number of study participants; iii) Backgrounds of study participants, birth date, age, height, body weight, past history, complication (underlying disease), iv) Present illness: date of definitive diagnosis, risk scoring, family history

Items for observation/ tests/ evaluation

Subjective symptom/ objective findings

Observation of adverse events including infectious complication, blood pressure, heart rate, body weight, hematology examination, blood biochemical examination, urinalysis, chest X-ray, ECG, urine culture

Patients' background

Age, body mass index (BMI), preoperative PSS/QOL, Qmax, residual urine volume (ml) estimated prostate weight (ml), preoperative PSA, ASA-PS, diabetes mellitus (HbA_{1c}, blood sugar control), chemotherapy or immune-suppressants,

Surgery-related items

Surgical time (min; including morcellation time), resected prostate weight (g), duration (days) to removal of urethral catheter postoperatively, Postoperative residual urine volume (ml) till 30-days after surgery, duration of prophylactic antibiotic administration (CEZ) : 1-day (single dose) or 2-days group

Items for postoperative perioperative infection and complications: Examination till 30-days after surgery

UTI and urogenital infection (prostatitis, epididymitis and pyelonephritis), postoperative adverse events including infectious ones, except postoperative infection, occurrence date.

In cases with perioperative infection who need antibiotic therapies, the details include bacterial information (see above).

Cancellation criteria

i) Those cases who are not willing to continue this study and/or wish to withdraw informed consent. ii) Those cases who are found not to be satisfied about their applicability to this study or who cannot continue the study owing to the occurrence of complications and/or exacerbation. iii) Those cases who cannot continue the study owing to study-related adverse events. iv) The study itself is canceled. v) Cases with uncontrollable infectious complications postoperatively. vi) PIs or the members of this research judge that cancellation is needed owing to other reasons.

Study period

May 1st 2018 to April 30th 2021; the follow-up period is 1 year afterwards.

Analysis of efficacy

Main analysis

We will estimate the difference in postoperative infection occurrence rate at the 95% CI and do the 5% two-sided test for Significant for such differences.

Interim analysis

This study needs interim analysis because it is planned as a feasible randomized study.

That is, once 45 cases are completed, the occurrence rate of postoperative infection can be compared in the 2 groups and to determine if there is less than a 5% of difference and then to continue if the difference is 5% or less.

Ethics and dissemination

Ethical consideration and consent

This protocol was approved by the Institutional review board of the Kobe University Graduate School of Medicine (C180043). All procedures were in compliance with the relevant laws and guidelines in accordance with the ethical standards of the Declaration of Helsinki.

This study was registered in the University Hospital Medical Information Network-Clinical Trial Registry ([UMIN000027955](#)) based on recommendations from the International Committee of Medical Journal Editors (ICMJE) on July 1st 2017.

Protocol amendments

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be approved by the Ethics Committee/IRB (institutional review board) prior to implementation and notified to the health authorities in accordance with local regulations. Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be

agreed upon by Ethics Committee/IRB, and will be documented in a memorandum. The Ethics Committee/IRB may be notified of administrative changes at the discretion of Helsinki Declaration.

Consent of assent

A trained research doctor will introduce the trial to patients who will be shown an informed consent form regarding the main aspects of the trial. Research doctors will discuss the trial with patients in light of the information provided in information sheets. Patients will then be able to have an informed discussion with the participating consultant. Research doctors will obtain written consent from patients willing to participate in the trial. Information sheets and consent forms are provided for all patients (Extended data⁶). All information sheets and consent forms transcripts have been translated into Japanese.

Confidentiality

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with limited access. All laboratory specimens, reports, data collection, process, and administrative forms will be identified by a coded ID number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

Access to data

The Data Management Coordinating Center will oversee the intra-study data sharing process, with input from the Data Management Subcommittee.

All Principal Investigators will be given access to the cleaned data sets. Project data sets will be housed on the Project Accept Web site and/or the file transfer protocol site created for the study, and all data sets will be password protected. Project Principal Investigators will have direct access to their own site's data sets, and will have access to other sites data by request. To ensure confidentiality, data dispersed to project team members will be blinded of any identifying participant information.

Ancillary and post-trial care

Patients that are enrolled into the study are covered by national health insurance in all the tests and treatments including the ones performed additionally owing to the adverse events of this study.

Dissemination policy

We plan to disseminate the information of this study through the UMIN and our department homepage.

Study status

The study is now undergoing pre-recruitment for participants (recruitment started May 1st, 2018).

Discussion

This study is designed to address the following issues:

1) AMR: antimicrobial resistance action plan

WHO suggested the AMR action plan in 2015 based on recent trends of emergence of antibiotic resistant bacteria in infectious diseases. Many researchers suggest that inappropriate antibiotics use may cause this problem. Inappropriate antibiotic prescriptions are often seen, for instance in upper respiratory infections which is caused by not only bacteria but also virus⁹. Accordingly, the Japanese government suggested an AMR action plan aiming at a 50% decrease in the use of oral antibiotic such as cephalosporines or macrolides¹⁰. The chief justification for the preventive use of antibiotics is for the purpose of inhibiting postoperative infectious complications. Not only surgery, but interventional examinations such as transrectal prostate biopsy require antibiotics. There are many reports on the efficacy of PAA to inhibit SSI when compared with no use of antibiotics^{11,12}.

2) Duration of PAA

Considering the two contradictory concepts mentioned above, what we should do next is to determine how to safely decrease antibiotic use without affecting or increasing the SSI occurrence rate. Another thing we need to consider is that long term antibiotic use can cause untreatable infections by antibiotic-resistant strains¹³. Therefore, this kind of prospective study is a valuable way to learn how to decrease antibiotic use safely.

3) Semi-contaminated

Many guidelines say that surgeries need to be classified according to the extent of pre-surgical pollution, infection, or bacterial colonization. Especially in urological cases, the concept of clean-contaminated operation exists when opening the urinary tract with the possibility of urine dissemination. Preoperative pyuria or bacteriuria should be checked in advance pre-operatively and treated before surgery, including confirmation of absence of such infection in order to decrease the risk of SSI.

4) HoLEP in Japan

Most of the prospective studies on how to decrease antibiotic use, for instance comparisons between 1-day and 3-day prophylactic antibiotic administration (PAA) for urological surgeries such as TUR-P in prospective 2-group or double-blind studies are from western countries¹⁴. Moreover, there are the debate that most studies select a 3-day regimen as a comparator. Then Japanese Urological Association (JUA) guideline recommend single-dose or dose within 48 hours for TUEB/HoLEP as hospitalized patients¹⁵. Arguably, individual studies need to be designed or undertaken in each country or region with the same or similar medical systems. For

instance, one major difference between most western countries versus Korea and Japan is that high volume surgical centers are more common in the west, and thus the number of surgical cases per surgeons is higher in the west than Japan. High volume centers expect shorter surgical times, which can affect SSI occurrence^{7,16}. These issues support the necessity of our study.

5) Prior studies as evidence for drawing up guidelines

There are several studies regarding the optimal PAA duration period^{17,18}. However, we need to decrease the variation in patients' backgrounds in such studies; How many patients with preoperative UTI cases that need to be controlled before surgery. There is no definitive study for comparison between controlled and uncontrolled preoperative UTI caused by retention¹⁹ and SSI occurrence after HoLEP. Also, case numbers are limited; so, variations in patient criteria and the surgeons' experience cannot be ignored.

6) Sample size

This kind of prospective feasibility study needs a setting with the necessary case numbers for analysis. A similar study referred to above had 164 cases for comparison in 2 groups with TUR-P and HoLEP for SSI occurrence, with SSI occurrence after HoLEP being 2/72 cases (2.8%)⁹. We therefore anticipate 180 cases (90 cases per arm) for a feasibility study with 95% CI for the future design of a prospective double blind non-inferiority study. To our knowledge, no definitive study with one-day PAA for HoLEP has been performed so, we have designed this study as a comparison with 2-days dosing.

7) Study setting

In most retrospective studies, the study period for patients' enrollment may be different. For instance, comparing TUR-P and HoLEP, HoLEP is a comparatively newer technique leading to the possibility of selection bias for HoLEP surgeons with TUR-P experience and this may influence the results of SSI occurrence. To reduce selection bias, prospective studies where not only patients but also surgeons have similar backgrounds, should be undertaken for definitive conclusions with high evidence level.

8) Significance and problems with prospective studies

Many guidelines refer to prospective studies as providing a high evidence level²⁰. However, prospective randomized studies with intervention may be more difficult to perform²¹. In Japan, apart from research by medical doctors, publication of scientific papers in the medical field is decreasing. IRB referees need to be strict about study approval and this can make things more complicated for prospective clinical interventional studies. Protocol papers will help researchers plan, design and perform clinical studies. This study describes a comparison study of PAA for HoLEP with 1-day (single dose) and 2-day dosing and help to establish a protocol for PAA taking into account decreasing unnecessary antimicrobial use to prevent the development of AMR.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required

Extended data

The consent form and information sheet that will be used in this study is available from Harvard Dataverse

Harvard Dataverse: Extended data. Replication data for Protocol for a comparison study of 1-day versus 2-day prophylactic antibiotic administration in Holmium Laser enucleation of the prostate (HoLEP): a randomized controlled trial <https://doi.org/10.7910/DVN/SGTWJN>⁸

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Seung-Ju Lee 

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I have no further comments.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Antimicrobial prophylaxis for urological surgeries

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 02 May 2019

<https://doi.org/10.5256/f1000research.19311.r47977>

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Florian Wagenlehner

Clinic & Policlinic for Urology, Pediatric Urology & Andrology, Justus-Liebig University, Giessen, Germany

The authors submitted a protocol studying two different prophylactic regimens in patients undergoing Holmium Laser enucleation of the prostate. The study is randomized.

The topic of the study is worth while studying, as there are relatively little data especially in laser

enucleation of the prostate.

The study design is well described and set up, including the important in- and exclusion criteria. There is one exclusion criterium leucocyturia, which should be reconsidered, as especially patients with large prostates, might have elevated leucocytes in their urine, and those patients would not be included in the study, although holmium laser enucleation is especially done in patients with large prostates.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: infections of the urogenital tract

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 02 May 2019

Katsumi Shigemura, Kobe University Graduate School of Health Science, Kobe, Japan

Thanks, we added the patients with leucocyturia and reflected on the text (See in Eligibility criteria). We revised as same way in another part (See in Screening test).

Competing Interests: No competing interests were disclosed.

Reviewer Report 29 April 2019

<https://doi.org/10.5256/f1000research.19311.r44091>

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Seung-Ju Lee

Department of Urology, St Vincent's Hospital, The Catholic University of Korea, Paldal-gu, Suwon, South Korea

This study protocol aims to establish optimal duration of cefazolin antibiotic prophylaxis prior to HoLEP procedure. The rationale and objective of the study protocol is clearly defined and the overall study design looks appropriate. Regarding details of the method, I have a couple of queries.

- First, one-day dosing and single-dose dosing should be distinguished. If you look at your protocol, it's single-dose (CEZ 1g, once per i.v. just before HoLEP/TUEB). However, the study title is 1-day vs. 2-day. Cefazolin is a cephalosporin antibiotic and is time-dependent. Therefore, 1-day (two or three doses per a day) and single-dose are different dosages.
- Second, most studies select a 3-day regimen as a comparator. Why did you choose 2-day? The reason for comparing the 2-day regimen in this study should be more clear.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

No

Are the datasets clearly presented in a useable and accessible format?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Antimicrobial prophylaxis for urological surgeries

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 30 Apr 2019

Katsumi Shigemura, Kobe University Graduate School of Health Science, Kobe, Japan

First, one-day dosing and single-dose dosing should be distinguished. If you look at your protocol, it's single-dose (CEZ 1g, once per i.v. just before HoLEP/TUEB). However, the study title is 1-day vs. 2-day. Cefazolin is a cephalosporin antibiotic and is time-dependent. Therefore, 1-day (two or three doses per a day) and single-dose are different dosages.

(Amendment)

Thanks, our 1-day protocol means single-dose protocol.

Second, most studies select a 3-day regimen as a comparator. Why did you choose 2-day? The reason for comparing the 2-day regimen in this study should be more clear.

(Amendment)

Thanks, but JUA guideline recommend single-dose or dose withing 48 hours (ref: [Yamamoto S](#),

Shigemura K, Kiyota H, Wada K, Hayami H, Yasuda M, Takahashi S, Ishikawa K, Hamasuna R, Arakawa S, Matsumoto T; Japanese Research Group for UTI. Essential Japanese guidelines for the prevention of perioperative infections in the urological field: 2015 edition. *Int J Urol*. 2016 Oct;23(10):814-824.).

Competing Interests: No competing interests were disclosed.

Author Response 02 May 2019

Katsumi Shigemura, Kobe University Graduate School of Health Science, Kobe, Japan

And my previous comment (single dose) were reflected in the text (See in many places including title)

Next comment (most studies select a 3-day regimen as a comparator. Why did you choose 2-day? The reason for comparing the 2-day regimen in this study should be more clear.): We reflected on the text (See in 4) HoLEP in Japan in Discussion).

Competing Interests: No competing interests were disclosed.

Author Response 03 May 2019

Katsumi Shigemura, Kobe University Graduate School of Health Science, Kobe, Japan

I have posted new version of manuscript.

Competing Interests: No competing interests were disclosed.

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