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Clinical Study Protocol

A Clinical Trial Evaluating the Usefulness of Tailored Antimicrobial Prophylaxis Using Rectal-culture Screening Media Prior to Transrectal Prostate Biopsy: A Multicenter, Randomized Controlled Trial

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The aim of this report is to introduce an on-going, multicenter, randomized controlled trial to evaluate whether tailored antimicrobial prophylaxis guided by rectal culture screening prevents acute bacterial prostatitis following transrectal prostate biopsy (TRPB). Patients will be randomized into an intervention or non-intervention group; tazobactam-piperacillin or levofloxacin will be prophylactically administered according to the results of rectal culture prior to TRPB in the intervention group whereas levofloxacin will be routinely given in the non-intervention group. The primary endpoint is the occurrence rate of acute bacterial prostatitis after TRPB. Recruitment begins in April, 2021 and the target total sample size is 5,100 participants.

Key words: antibiotic prophylaxis, selective culture media, prostate biopsy, fluoroquinolone-resistant, extended-spectrum beta-lactamase

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Transrectal prostate biopsy (TRPB) is an essential procedure to diagnose prostate cancer. Although TRPB is usually preferred to transperineal biopsy from the standpoint of limiting post-operative pain and hospitalization stays, acute prostatitis after TRPB is a major concern. Previous reports have noted that urinary tract infection after TRPB occurs in 0.1% to 7% of cases, some of which have been fatal [1, 2]. The role of antibiotic prophylaxis to prevent infectious complications after TRPB is well established. The American Urological Association (AUA), European Association of Urology (EAU), and Japanese Urological Association (JUA) support the use of prophylactic antibiotics before performing a TRPB [3-5]. Fluoroquinolones (FQs) remain the most common agents for TRPB antibiotic prophylaxis, as recommended by worldwide guidelines. However, increasing incidences of rectal colonization by FQ-resistant *Escherichia coli* (*E. coli*) and extended spectrum β-lactamase (ESBL)-producing *E. coli* have been reported; these are the bacteria most commonly responsible for acute bacterial prostatitis after TRPB [5, 6].

As acute bacterial prostatitis is caused by rectal flora, several reports have demonstrated that antibiotic prophylaxis based on rectal swab cultures may be the most reasonable approach to reduce infections [7-9]. We previously reported that the use of selective media for detecting FQ-resistant and ESBL-producing pathogens from the rectum was a logical and rapid approach to prevent urinary infection after TRPB [7]. In addition, our results indicated that pre-TRPB screening of rectal flora using selective media could meaningfully guide prophylactic antibiotic treatment, and potentially reduce acute bacterial prostatitis after TRPB [7]. However, a larger trial is necessary to evaluate the efficacy of rectal culture screening using selective media to reduce acute bacterial prostatitis and sepsis after TRPB. The aim of this multicenter, randomized controlled clinical trial is to investigate the usefulness of a tailored use of prophylactic antimicrobials according to results of screening for FQ-resistant or ESBL-producing *E. coli* colonies on selective media.

Endpoints

The primary endpoint in this trial is the incidence of acute bacterial prostatitis. Prostatitis consists of pyuria and systemic symptoms such as a high fever over 38°C, urinary frequency/urgency, and dysuria without evidence of other infections. Our diagnostic criteria do not include an elevated inflammatory response, as evidenced by such measures as white blood cell (WBC), c-reactive protein (CRP), and serum PSA levels, bacteriological tests, or imaging results. Pyuria is defined as ≥ 10 WBCs/μL as determined by flow cytometric analysis, ≥ 10 WBCs/mm^3 as counted using a counting chamber, a positive leucocyte esterase result from a urine test strip with uncentrifuged urine, or > 5 WBCs/high-power field (hpf) in the sediment of centrifuged urine. The incidence of acute prostatitis will be compared among the non-cultured, positive-culture, and negative-culture groups.

Secondary endpoints are the accuracy of the selective media and the severity at the onset of acute prostatitis. The severity of prostatitis will be assessed using serum WBC, CRP, procalcitonin, or a quick Sequential Organ Failure Assessment score (qSOFA).

Eligibility Criteria

In this study, patients at participating facilities will be recruited starting April, 2021 and continuing for five years or until our target enrollment is met. Adult (> 20 years old) male patients who schedule a transrectal prostate biopsy with suspected prostate cancer during the period are eligible for enrollment. All patients will be provided with written informed consent to participate in this study with full understanding. There are four exclusion criteria. *I*: Cases at high risk of infection, defined as a prostate volume ≥ 75 mL, diabetes mellitus, systemic steroid use, high-grade obstruction of the lower urinary tract (IPSS ≥ 20, $Q_{max} \leq 12$ mL/s, or residual urine ≥ 100 mL), or an immunocompromised status; in such cases two doses of PIPC/TAZ (pre- and post-operatively) are recommended, regardless of rectal culture results [10]. *II*: Transperineal prostate biopsy. *III*: Presence of pyuria at enrollment, as pyuria indicates asymptomatic bacteriuria, which increases the risk of postoperative acute bacterial prostatitis independent of rectal microbiota. *IV*: A recent history of antibacterial medication, as such would affect the results of rectal culture; thus, all patients receiving antibacterial medication less than four weeks before the rectal culture or prostate biopsy will be excluded.

Treatment Methods

This study is a multicenter, open-label, randomized controlled trial comparing the efficacy of tailored antibiotic prophylaxis based on rectal cultures using selective media versus standard levofloxacin prophylaxis to prevent acute prostatitis. The trial will be conducted at 16 sites in Japan (Table 1). After eligibility is confirmed, participants will be randomized 1 : 1 to an intervention group or non-intervention group (rectal-culture group and non-rectal-culture group, respectively) (Fig. 1). Participants will be matched in pairs according to the institution of participant registration, age, prostate volume and history of antibacterial drug use for the past 6 months. Randomization will be conducted by the central registration system at the office of the Japanese Research Group for Urinary Tract Infection (JRGU) located at the Department of Urology, Hyogo College of Medicine. Cases will be assigned based on a random assignment sheet prepared in advance. Participant blinding is not possible due to the nature of the investigation.

Selective screening media. We will use two kinds of CHROMagar Orientation media, developed to detect FQ-resistant and ESBL-producing *E. coli* (Kanto Chemical, Tokyo Japan), respectively. *E. coli* forms purple colonies on CHROMagar Orientation medium. Levofloxacin is added to the medium to detect FQ-resistant *E. coli*, and CHROMagar Orientation/ESBL is available to detect ESBL-producing *E. coli* [7, 11]. Feces from the glove used for the rectal examination of patients with suspected prostate cancer will be applied to both selective screening media and incubated for 24 h before results are interpreted.

Protocol. Participants will be randomly divided into a rectal-culture group and non-rectal-culture group (Fig. 1). Patients in the rectal-culture group will be further divided into a positive-culture and negative-culture

Table 1 Participating medical institutions and doctors in charge

Institutions	Investigators
Fujita Health University Hospital, Aichi	Kiyohito Ishikawa
Hakodate Goryoukaku Hospital, Hokkaido	Yoshiki Hiyama
Hiroshima University Hospital, Hiroshima	Hiroyuki Kitano, Jun Teishima
Hyogo College of Medicine College Hospital, Hyogo	Shingo Yamamoto
Internationla University of Health and Welfare Hospital, Tochigi	Jun Miyazaki, Ei-Ichiro Takaoka
Internationla University of Health and Welfare Narita Hospital, Chiba	Jun Miyazaki
Japanese Red Cross Okayama Hospital, Okayama	Tadasu Takenaka
Jikei University Katsushika Medical Center, Tokyo	Hiroki Yamada, Hiroshi Kiyota
Kobe University Hospital, Hyogo	Katsumi Shigemura, Masato Fujisawa
Kyoto University Hospital, Kyoto	Takayuki Goto
Nagasaki University Hospital, Nagasaki	Tsubasa Kondo, Yasuyoshi Miyata
Okayama City General Medical Center, Okayama	Masaya Tsugawa
Okayama Medical Center, Okayama	Takafumi Sakuma, Norihiro Kusumi, Takaharu Ichikawa
Okayama Rosai Hospital, Okayama	Yoshitsugu Nasu
Okayama University Hospital, Okayama	Takuya Sadahira (Principal Investigator), Yuki Maruyama, Kohei Edamura, Takehiro Iwata, Motoo Araki, Masami Watanabe, Toyohiko Watanabe, Yasutomo Nasu, Koichiro Wada
Sapporo Medical University Hospital, Hokkaido	Satoshi Takahashi, Naoya Masumori

group, depending on the results of their selective media cultures. For the positive-culture group, piperacillin/tazobactam 4.5 g will be administered 30 min before the biopsy and 4 h after the biopsy [10]. For the negative-culture group, one 500-mg dose of levofloxacin will be administered orally 2 h before the biopsy [12]. Patients in the non-rectal-culture group will also receive 500 mg of levofloxacin orally 2 h before the biopsy. After the biopsy, there will be a one-month observation period to detect the incidence of acute bacterial prostatitis and its severity. If there is evidence of acute prostatitis, participants will be provided the appropriate treatment depending on the results of a urinalysis, urine culture, and blood tests.

Statistical Consideration

Data management. In this trial, data will be collected during the observation period by the local research staff. Participating centers will send their case report forms as Excel files to the central research center (Okayama University), where data entry into the database will be completed and monitored by the central data manager. Data on the case report form include: institution of participant registration, age, body mass index, prostate volume, history of antimicrobial exposure for the past 6 months, preoperative prostate-specific antigen level, serum creatinine, and the results of the rectal culture on selective media. If patients develop prostatitis, researchers will complete an additional data sheet.

Sample size calculation. The required sample size was calculated under the primary endpoint assumption that the pre-biopsy rectal culture reduces acute prostatitis from 2% to 1%, with a statistical power of 80% and an alpha error of 5%. Using a two-sided Fisher's exact test, it was calculated that 5,038 patients (2,519 per group) would be needed to detect a standardized difference between the rectal-culture and non-rectal-culture groups. Assuming some attrition, a sample size of 5,100 participants is thus required, and the study will continue until that number is reached.

Statistical analysis. Depending on data normality, continuous data will be presented as either the means and standard deviations or medians and interquartile intervals. The statistical analysis will be performed with either the Mann-Whitney *U*-test or Student's *t*-test. For categorical variables, the data will be presented as counts and percentages then analyzed using Fisher's exact test. To confirm the efficacy of the rectal culture using selective media, a univariate and multivariate logistic regression analysis will be performed. Statistical significance will be confirmed at

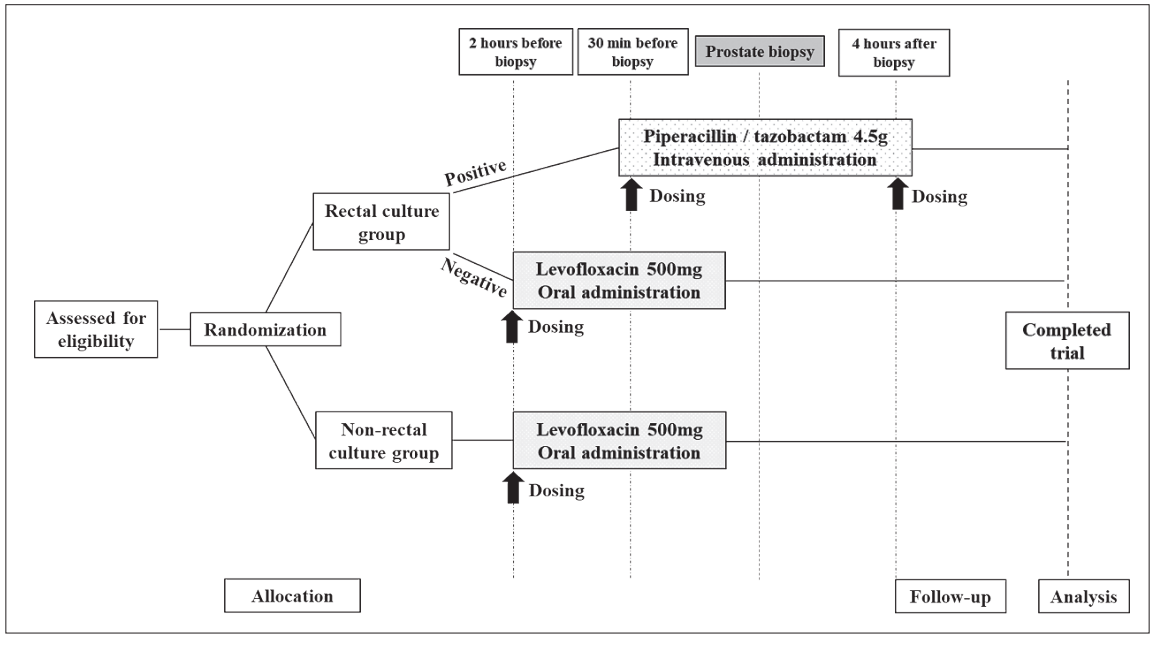

Fig. 1 Trial protocol of the present study.

$p < 0.05$ for all analyses. Statistical analyses will be performed using JMP software (ver. 11; SAS, Cary, NC, USA).

Ethics

This clinical study was approved by the Okayama University Institutional Review Board prior to study initiation (approval number; 2003-003). The study was registered with the UMIN Clinical Trials Registry, Japan (UMINI000039478). The patient participants will be given an opportunity to review the documents regarding the study's purposes, methods and risks and to receive individual counseling before providing written consent.

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