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Clinical Study Protocol

A Randomized Phase 2 Trial of Antibiotic Prophylaxis Versus No Intervention for Muscle Biopsy in A Neurology Department

Keiichi Nakahara[a§], Tokunori Ikeda[b§], Koutaro Takamatsu[a], Nozomu Tawara[a], Kentaro Hara[a], Yuki Enokida[c], Naomi Tanoue[c], Sawana Narita[b, c], Akiko Fujii[b], Yoshinori Yamanouchi[b], Jun Morinaga[b], and Satoshi Yamashita[a*]

[a]Department of Neurology, Graduate School of Medical Sciences, Kumamoto University, Departments of [b]Clinical Investigation, [c]Pharmacy, Kumamoto University Hospital, Kumamoto 860-8556, Japan

Muscle biopsy can be used to confirm the diagnosis of neuromuscular diseases. However, it is unclear whether antibiotic prophylaxis prior to muscle biopsy is needed to prevent surgical site infection (SSI). We are conducting a phase 2, single-center, open-labeled, prospective randomized trial to clarify the need for antibiotic prophylaxis in patients at low risk for SSI undergoing muscle biopsy. Patients will be randomized to an antibiotic prophylaxis group or a control group, and the incidence of SSI will be compared between the groups. Our findings will clarify the need for antibiotic prophylaxis in this patient population.

Key words: muscle biopsy, antibiotic prophylaxis

Antibiotic prophylaxis prior to invasive surgical procedures is used to decrease the incidence of surgical site infections (SSIs) [1]. This approach can induce asepsis at the operative site, thereby preventing contamination by bacterial content and ultimately SSIs [1, 2].

In the context of neurological medicine, muscle biopsy is an important but invasive procedure performed to obtain information on, for example, muscle fiber degeneration or the presence of infiltrating inflammatory cells, facilitating a direct understanding of the patient's clinical state and a more definitive diagnosis [3, 4]. Following muscle biopsy, oral antibiotics may be prescribed to prevent the occurrence of SSIs, and to date we have not experienced SSI in this clinical setting. However, there are no guidelines and no evidence regarding the use of antibiotic prophylaxis or whether it is necessary in patients undergoing a muscle biopsy; it is thus unclear whether this treatment strategy is appropriate. Moreover, previous studies reported that antibiotic prophylaxis prior to surgery or less-invasive examinations did not decrease the incidence of SSIs [5-7], and antibiotic prophylaxis has been questioned in some cases. According to the Japanese clinical practice guidelines for antimicrobial prophylaxis in surgery, when performing soft tissue surgery (muscle, tendon, and peripheral nerve), the administration of cefazolin within 24 h is recommended [7]. However, the guidelines include a proviso that consensus was not achieved regarding antibiotic prophylaxis in patients at low risk of SSI or in those undergoing short-duration procedures [7]. The duration of a muscle biopsy is typically < 1 h, and this procedure is less invasive compared to other common surgeries such as orthopedic procedures. Antibiotic prophylaxis may be useful for patients with diabetes who are at high risk of SSIs [8], patients with infected wounds [8], patients undergoing surgical procedures with longer

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*Corresponding author. Phone: +81-96-373-5893; Fax: +81-96-373-5895
E-mail: y-stsh@pg8.so-net.ne.jp (S. Yamashita)
[§]These authors contributed equally to this work.

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durations [8], patients with a body mass index ≥ 25 kg/m^2 [9], and patients who are immunocompromised [10].

We therefore plan to evaluate the incidence of SSI in patients who are immunocompetent, at low risk of SSI, and undergoing a muscle biopsy with or without antibiotic prophylaxis. If the incidences of SSI in the patients with and without antibiotic prophylaxis are comparable, it is possible that the superfluous use of antibiotic prophylaxis can be reduced, thereby decreasing the opportunity for bacteria to acquire antibiotic resistance.

Study Design

This study is a phase 2, single-center, open-labeled, prospective randomized trial to investigate whether the use of antibiotic prophylaxis during a muscle biopsy in low-risk immunocompetent patients is required. An overview of the study design is shown in Fig. 1. This trial is being conducted at Kumamoto University Hospital.

Ethical Considerations

The study has been approved by the Institutional Review Board of Kumamoto University (permit no. 2384).

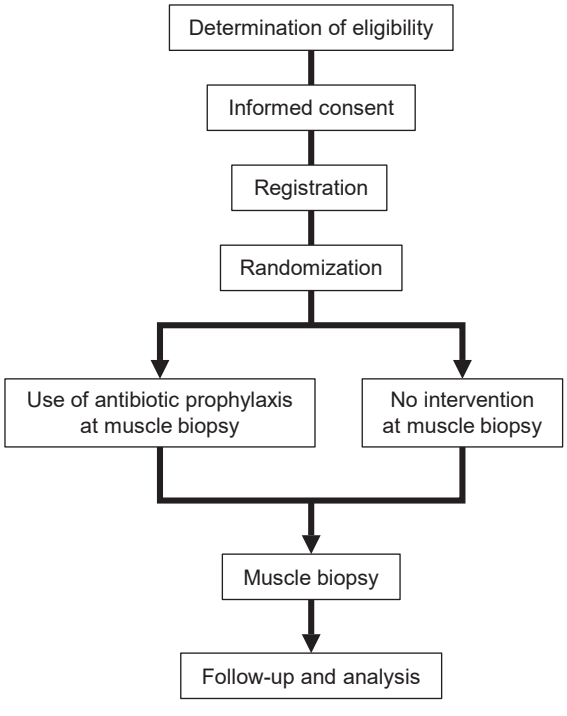

Fig. 1 Overview of the study design.

Written informed consent will be obtained from all patients prior to their participation, and all procedures will be carried out with the adequate understanding of each patient and in accordance with the Declaration of Helsinki. This trial is registered with the University Hospital Medical Information Network Individual Clinical Trials Registry (UMIN 000034535).

Endpoints

The primary endpoint is the rate of SSIs during an observation period defined as the time point of the muscle biopsy to the time point of the suture removal at the site. The incidence of SSI will be judged by either the patient's attending physician or the physician performing the muscle biopsy. SSI is defined as the existence of pus or serous fluid containing pathogenic organisms.

Secondary endpoints include the background characteristics of patients in the 2 groups (with/without antibiotic prophylaxis); adverse events associated with antibiotic treatment; wound scoring [11] at the muscle biopsy region; the relationship between the number of days until suture removal and treatment with or without antibiotics; the relationship between body temperature and treatment with or without antibiotics; and the relationship between treatment with/without antibiotics and longitudinal changes in the following laboratory blood parameters: red blood cells (RBC), white blood cells (WBC) and subsets (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), hemoglobin (Hb), platelets (PLT), blood urea nitrogen (BUN), creatinine (Crea), total protein (TP), albumin (Alb), creatine kinase (CK), aspartate transaminase (AST), alanine transaminase (ALT), and C-reactive protein (CRP).

In addition, the characteristics of the patients with SSI will be examined. Wound scoring with a maximum of 100 points will be used as follows: prolongation of admission to treat an SSI (2 points per day and maximum 20 points), use of wound dressing (1 point per day and maximum 10 points), existence of pus (10 points) and serous fluid (10 points), presence of pathogens (10 points), incidence of cellulitis (moderate or severe: 10 points; mild: 5 points), use of antibiotics to treat SSI infection (10 points) and wound dehiscence (10 points), and need for surgical drainage (10 points).

A subgroup analysis will be performed to validate the relationship between longitudinal changes in laboratory blood data and the disease type (inflammatory

myopathies, inclusion body myositis, and other muscle diseases), the muscle biopsy region, the duration (min) of the muscle biopsy procedure, and the manual muscle testing (MMT) value of the muscle region where the muscle biopsy is performed, as well as the relationship between the duration of the muscle biopsy procedure, the disease type, the muscle biopsy region, and the MMT value.

Eligibility Criteria

The inclusion and exclusion criteria are listed in Table 1. Eligible patients will be enrolled from September 2018 to March 2022.

Randomization

Information on eligible patients who have received verbal and written information on the study and provided written informed consent will be registered in the HOPE eACReSS system (Fujitsu, Japan) at Kumamoto University Hospital. Patients will be randomly assigned to an antibiotic prophylaxis group or a control group within the HOPE eACReSS system using a stratified permuted block method. Patients will be stratified by sex, and no blinding will be applied.

Table 1 Patient eligibility

Inclusion criteria
(1) Scheduled muscle biopsy
(2) Age 20–80 years
(3) Provision of informed consent provided by the patient or his/her proxy
Exclusion criteria
(1) Patients who are not hospitalized at the neurology department
(2) Patients who are pregnant or planning to become pregnant
(3) Immunocompromised patients
(4) History of diabetes
(5) Body mass index (BMI) ≥ 25 kg/m^2
(6) History of cephalosporin allergy
(7) History of anaphylactic shock associated with cephalosporin use
(8) History of hypersensitivity to local anesthetic such as anilide
(9) Serum creatinine level >1.5 mg/dl
(10) Presence of infectious disease
(11) Planned treatment with an immunosuppressive agent immediately after muscle biopsy
(12) Presence of a skin lesion at the planned site of muscle biopsy
(13) Patients who are judged unsuitable for participation in this trial by the attending physician

Treatment Methods

Intervention. For the evaluation of primary or secondary endpoints, all enrolled patients in both groups will be monitored daily during the hospital stay. On the day of the muscle biopsy procedure, patients in the antibiotic prophylaxis group will receive a single intravenous dose of 1 g cefazolin, administered continuously during the 30 min prior to the start of the procedure. After completion of the muscle biopsy procedure, the wound will be covered with an Opsite™ Post-Op Visible dressing, and the presence or absence of SSI without disinfection will be confirmed daily. In the absence of any complications, the dressing will be removed 5 days after the muscle biopsy, and sutures will be removed at 7-10 days after the procedure.

Vital signs will be recorded and a blood sample taken after informed consent is obtained from eligible patients. The disease type and muscle biopsy region will be recorded 1 day prior to the muscle biopsy procedure. Upon completion of the procedure, the duration of the muscle biopsy procedure, the MMT value, and the use of analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) to inhibit muscle biopsy-associated pain will be recorded. Vital signs and analgesic use will be recorded and blood sampling will be performed at days 1 and 3 after the procedure and at the time point of suture removal. All patients will be followed until suture removal, at which point the wound score and the number of days from the muscle biopsy to the suture removal will be recorded. The incidence of SSI infection will be documented throughout the observation period.

Adverse events. Adverse events related to cefazolin use, including allergy or anaphylactic shock, blood disorders such as granulocytopenia, liver failure, kidney failure, pseudomembranous colitis, skin disorders such as Stevens-Johnson syndrome, and interstitial lung disease will be monitored during the hospital stay. Although SSIs are also considered adverse events, the incidence of SSI will be recorded as the primary endpoint.

Statistical Considerations

Sample size. In studies using retrospective data, the incidence probability of SSI has been considered to

be very low [5, 6]. Particularly, in the case of minimally invasive operations such as inguinal hernia repair, the non-incident rate of SSI was > 0.99 with or without antibiotic prophylaxis [6]. Moreover, we typically do not observe SSIs in patients undergoing a muscle biopsy at our hospital when oral antibiotics are administered after the muscle biopsy. Therefore, we estimated the threshold probability of not developing SSI in the group without antibiotic prophylaxis as 0.990-0.995, which was described as π. The probability of developing SSI was thus $1-(\pi)^n$, so we calculated that 6-11 patients would be needed in each group (probability < 0.05). Finally, we selected 11 patients as the size of each group for the analyses of secondary endpoints, and we plan to include 24 patients in total to allow for potential exclusions or withdrawals.

Statistical analysis. For the primary endpoint, Fisher's exact test will be used for comparisons between the 2 groups because accurate comparative verification is expected to be difficult, given that the sample size was estimated independently for the 2 groups. For the secondary endpoints, continuous data will be expressed as medians and interquartile ranges. Categorical variables will be presented as percentages. To ascertain a normal distribution of variables, Shapiro-Wilk's test will be performed. For a univariate analysis, a Wilcoxon rank sum test will be used for continuous variables and Fisher's exact test will be used for categorical variables. A linear mixed model will be used to examine the effects of antibiotic prophylaxis on the time course of laboratory blood data at days 1 and 3 after each muscle biopsy and at suture removal compared with the baseline blood data prior to the procedure. Adverse events associated with antibiotic use will be graded and categorized according to the Common Terminology Criteria for Adverse Events (ver. 5.0).

In the subgroup analysis, the disease type, muscle biopsy region, duration of the muscle biopsy procedure, and MMT value will be analyzed for each group, and changes in laboratory blood data will be used in linear mixed models. To validate the relationship between the duration of the muscle biopsy procedure and the disease type or muscle biopsy region or MMT value, a two-way analysis of variance or multivariate analysis will be performed. The data analyses will be performed using R ver. 3.3.2 (The R Foundation for Statistical Computing, Vienna, Austria) and SAS ver. 9.4 (SAS Institute, Cary, NC, USA) with the level of statistical significance set at $p < 0.05$.

Limitations. It is possible that there is an incidental risk of SSI other than those considered in our exclusion criteria (*i.e.*, hepatic failure or poor nutritional status). In addition, although we narrowed the target age in the inclusion criteria, age is an obvious confounding factor; when we perform the subgroup analysis, we will therefore consider the risk factors.

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