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GUIDELINES

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Guidelines for implementation of clinical studies on surgical antimicrobial prophylaxis (2007)

Key words Guideline · Clinical study · Antimicrobial prophylaxis · Surgery · Surgical site infection

Introduction

The objectives of preparing the guidelines are to describe how to implement clinical studies of antimicrobial prophylaxis (AMP) for postoperative infections. The guidelines focus specifically not only on the evaluation of antimicrobial drugs themselves but also on the preparation of protocols regarding usage (e.g., duration of use and timing of administration). The guidelines also include information for physician-led clinical studies, not those managed by pharmaceutical companies, as subjects. They scientifically describe the statistical methods that can be used in clinical settings, including the numbers of patients for whom data are calculated and the methods of allocation to groups. The guidelines are based on clinical evidence in the present situation, and therefore, in the future, revision of the guidelines may need to be considered if new clinical evidence accumulates in Japan.

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Statistical methods necessary for clinical studies

Clinical comparative studies require randomization and masking. On clinically studying administration methods, it is difficult to perform a double-masked randomized trial. If double-masked testing is rarely adopted, it is desirable to have patients randomly allotted to groups by a controller. In studies to evaluate prophylactic antimicrobial drugs for postoperative infections, multicenter trials may be necessary for the registration of the statistically necessary number of patients as subjects. In such situations, it is desirable to conduct randomized allocations at each center as a unit (for example, block allocation, stratified allocation). Multiinstitutional studies also have the advantage that the results allow general evaluation without center-specific findings. On the other hand, because marked differences among centers in factors other than antimicrobial drugs,, including surgical procedures and perioperative management, can affect the results of a study, special attention should be paid to the implementation of multicenter trials.

Meta-analyses have also been performed. Metaanalysis requires the use of procedures such as the Mantel-Haenszel technique to consolidate results from a number of studies, taking into consideration differences in protocols.[1] Because meta-analyses are greatly influenced by bias (for example, selection bias), attention should be paid to the selection of the study results that are used in the analysis.

There are two comparative study patterns, one for indicating superiority and the other for indicating equality or noninferiority. Usually, the latter type is used for the clinical evaluation of AMP agents. The results are analyzed in all patients who are allocated to a study group (intention-to-treat [ITT] analysis), regardless of whether or not the patients meet the criteria for registration as subjects (that is, their treatment is in accordance with the study protocol). It is important, for the evaluation of study quality, to compare the results of the analysis of only those patients who meet the criteria for registration as subjects, and the results of ITT analysis of all the patients allocated to a study group.

Number of patients required for a noninferiority study

When a noninferiority study is planned, the number of patients required for the study depends mainly on the prospective incidence of surgical-site infection (SSI) and on the permissible difference in the incidence (%) that is not considered to be clinically problematic. When the incidence of SSI is 12% in each group and the upper limit of the 90% confidence interval of the between-groups difference (based on the SSI of the control group) is less than 5% (which is regarded as noninferiority), and the power of the test is 80%, then it is assumed that 515 patients would be required in each group for evaluation by the statistical noninferiority test (one-sided significance level, 5%). Figure 1 shows the number of patients required for a study when the incidence of SSI in each group varies from 5% to 30%.

In the present situation, it is difficult to perform clinical studies involving such numbers of patients in Japan. Supposing a practicable number is between 100 and 150, when the incidence of SSI is 6%, and the noninferiority detection level is 7%, then, according to the assumption described above, each group should consist of 141 patients. Furthermore, according to the same assumption, when the noninferiority detection level is 8%, each group should consist of 109 patients. For reference only, the relation of each group's rate of SSI, with the assumption that the permissible difference is 5%, the power of the test is 80%, and the one sided significance level is 5%, with the supposition that the practicable number of patients is 100 or 150, is shown in Fig. 2. This Fig. indicates that rate of SSI in the new-treatment group has to be less than the SSI rate in the control group if the study is performed in Japan. Thus, it is necessary to assess the number of the patients required for each protocol, but, in practice, for a noninferiority study, it is desirable for the number of patients in each group to be at least 100. We used Sample Power Release 2.0, 2000, by Michael Borenstein, Hanna Rothstein, Jacob Cohen, David Schoenfeld, and Jesse Berlin (SPSS, Chicago, IL, USA), to calculate the number of patients required. For the implementation of clinical studies, clinicians are encouraged to seek advice from epidemiologists or statisticians.

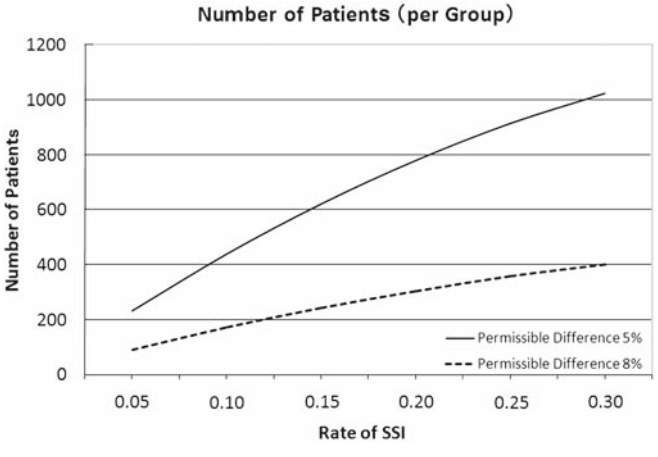

Fig. 1. Number of patients required for a study when the surgical-site infection (SSI) rates in the groups vary from 5% to 30%

Points to note in the preparation of protocols

When performing clinical studies of prophylactic antimicrobial drugs for postoperative infections, those items that have already been recommended on the basis of evidence must be given consideration. However, this rule does not apply if the study is designed to investigate one of these items.

(1) Ethically, clinical studies that compare an AMP with no antibiotic cover at all should not be performed for any operation or class of operation in which the use of that AMP has been shown to reduce SSI rates, based on evidence from clinical trials, nor should such a comparative study be performed for those operations after which an SSI would represent a catastrophe. Such comparative studies may be performed for clean operations[2] (except for cardiovascular surgery, neurosurgery, and laparoscopic cholecystectomy,[3,4] in which the incidence of SSI is extremely low.[5]

(2) As AMP agents to be selected as control drugs in comparative studies, first-generation and second-generation cephems[6–10] and penicillins (see "Selection of AMP agents" below) are recommended.

(3) Antimicrobial drugs for injection are generally used.[6] This rule does not, however, apply if the usefulness of antimicrobial drugs for oral use is being assessed in the study.

(4) When β-lactams are used as the AMP, the initial dose is administered within 2 h (within 30 min, if possible) before the operation.[11,12]

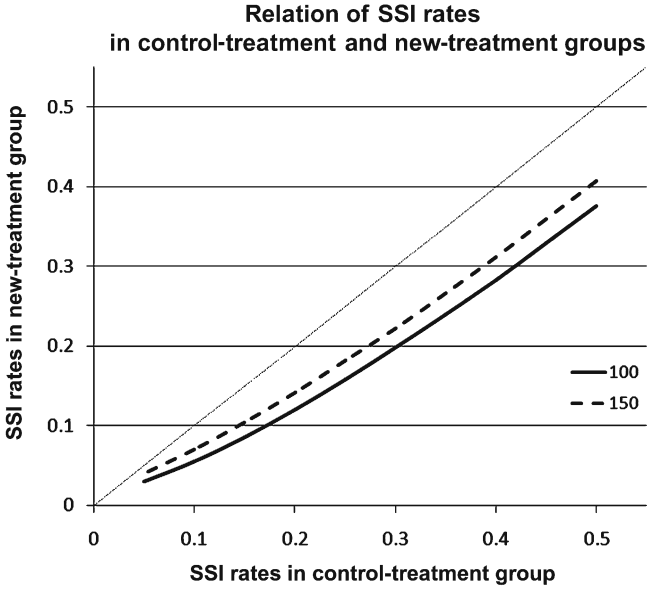

Fig. 2. The relation of SSI rates in two groups, with the supposition that the practicable number of patients is 100 or 150