BMJ Open Efficacy and safety of 1.5% aqueous olanexidine gluconate antiseptic solution compared to 1% alcoholic chlorhexidine for the prevention of intravenous catheter-related infections (Apollo study): a protocol for a randomised controlled trial

Hideto Yasuda ,¹ Masahiro Kashiura ,¹ Yuki Kishihara,¹ Toru Hifumi,² Takayuki Abe,³ Junichi Sasaki,⁴ Takashi Moriya,¹ Keita Morikane,⁵ Nobuaki Shime⁶

To cite: Yasuda H, Kashiura M, Kishihara Y, *et al.* Efficacy and safety of 1.5% aqueous olanexidine gluconate antiseptic solution compared to 1% alcoholic chlorhexidine for the prevention of intravenous catheter-related infections (Apollo study): a protocol for a randomised controlled trial. *BMJ Open* 2021;**11**:e053925. doi:10.1136/bmjopen-2021-053925

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-053925>).

Received 31 May 2021
Accepted 10 December 2021

© Author(s) (or their employer(s)) 2021. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Dr Hideto Yasuda;
yasudahideto@me.com

ABSTRACT

Introduction Chlorhexidine alcohol (1.0%–2.0%) is currently recommended as a skin disinfectant to be used prior to catheterisation for preventing catheter-related infections. However, chlorhexidine alcohol has various side effects and has little antibacterial effect on methicillin-resistant *Staphylococcus aureus* (MRSA). Therefore, MRSA remains a concern for catheter-related bloodstream infection (CRBSI) prevention. Olanexidine, containing 1.5% olanexidine gluconate in aqueous solution, was developed in Japan in 2015 and is structurally similar to chlorhexidine. Olanexidine has been used as a disinfectant against various gram-positive and gram-negative bacteria and MRSA. This study aims to compare the efficacy of 1.5% aqueous olanexidine gluconate and 1% chlorhexidine alcohol as skin antiseptics for the prevention of catheter-related infections.

Methods and analysis This Apollo study is an open-label, multicentre, non-inferiority, two-arm, parallel-group, randomised controlled trial conducted at 21 intensive care units (ICUs) and high-care units (HCUs) in Japan. All patients scheduled to be admitted to the ICU or HCU of a facility participating in this study, who require central venous catheter insertion are eligible. Eligible patients will be assigned to either the 1.5% aqueous olanexidine gluconate or 1% chlorhexidine alcohol group by randomisation in a ratio of 1:1 with stratification by centres. The antibacterial agents are to be used as a skin disinfectant before and during catheter placement. The primary endpoint is the proportion of catheter-related infections, defined as a composite of catheter-related sepsis without bacteraemia and CRBSI. A total of 1980 patients will be included in this study.

Ethics and dissemination This clinical trial was approved by the Institutional Review Board of Jichi Medical University and the ethics committees of the participating institutions. The study results will be disseminated through conferences, peer-reviewed publications and meetings with interested parties.

Strengths and limitations of this study

- This study is the first randomised controlled trial to evaluate the efficacy of olanexidine gluconate as a skin antiseptic before catheter insertion with a large sample size.
- The outcome of this study is catheter-related infection, which is considered a clinically important outcome, and this study may provide clinically relevant results.
- The concentration of chlorhexidine alcohol used in this study is 1%, which is the maximum concentration available in Japan, rather than the 2% formulation used as the standard in other countries.

Trial registration number University hospital Medical Information Network (registration ID: UMIN000042343). This registration includes all items in the WHO Trial Registration Data Set.

Protocol version This protocol corresponds to the original protocol version 5.

INTRODUCTION

Catheter-related bloodstream infections (CRBSIs) are common nosocomial infections occurring in critically ill patients.¹ CRBSIs prolong hospitalisation and significantly impact health economics.² The prevention of CRBSI is crucial, even more so than its treatment. Recently, various clinical trials analysing the prevention of CRBSIs have been conducted.^{3,4} Catheters coated with and dressings containing antimicrobials are reportedly effective in the prevention of CRBSIs; however, cost-effectiveness remains a major concern.³ Therefore, a recent guideline has

advocated for the use of skin disinfectants at the time of catheter insertion as a simple and inexpensive option to prevent intravascular catheter-related infections.⁵

Chlorhexidine alcohol (0.5%–2.0%) is the main drug used for skin disinfection prior to catheterisation.⁶ In 2011, the Centers for Disease Control and Prevention (CDC) recommended that chlorhexidine alcohol be used at concentrations >0.5% before inserting central venous catheters.⁷ The validity of this recommendation was examined in a subsequent clinical study⁸ and in a network meta-analysis.⁶ However, chlorhexidine alcohol has various side effects. It is an alcoholic solution, and therefore cannot be used in patients who are hypersensitive to alcohol. Further, exposure to resistant bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA), in the intensive care unit (ICU) or the emergency department is the leading cause of CRBSIs.^{9 10} Unfortunately, chlorhexidine alcohol has little antibacterial effect on MRSA, and this remains a concern for the prevention of CRBSIs.^{11 12}

Olanedine (Otsuka Pharmaceutical Factory, Tokushima, Japan), containing 1.5% olanexidine gluconate in aqueous solution, was developed in Japan in 2015 as a new biguanide disinfectant with structural similarity to chlorhexidine. It has been used as a disinfectant against various gram-positive and gram-negative bacteria, such as MRSA, vancomycin-resistant enterococci (VRE), *Pseudomonas aeruginosa*, and *Serratia monocytogenes*,¹² and against other bacteria resistant to conventional topical disinfectants.^{11 12} These two studies showed that 1.5% aqueous olanexidine gluconate was more effective in disinfection than 0.5% chlorhexidine alcohol and 10% aqueous povidone-iodine. Therefore, olanexidine gluconate may be effective in preventing MRSA infections.

However, no studies have compared a 1.5% olanexidine gluconate solution with other skin disinfectants used before catheterisation. As discussed previously, a 1.5% olanexidine gluconate solution may be more effective than 1.0% chlorhexidine alcohol as a precatheter skin disinfectant against MRSA. However, the efficacy against other microorganisms may be comparable between the two skin antiseptics; thus, the non-inferiority of 1.5% olanexidine gluconate solution to 1.0% chlorhexidine alcohol may impact future practices for the prevention of CRBSI. Therefore, this study aims to compare the efficacy of a 1.5% olanexidine gluconate solution to a 1% chlorhexidine alcohol solution in preventing catheter-related infections.

METHODS AND ANALYSIS

Trial design and setting

This Apollo study is an open-label, multicentre, non-inferiority, two-arm, parallel group, randomised controlled trial conducted at 21 ICUs and high-care units (HCUs) in Japan. ICUs and HCUs are defined by the number of patients per nurse; ICUs have two patients per nurse, and HCUs have four. Patients scheduled to be admitted to the

ICU or HCU who require a central venous catheter will be randomised to either the olanexidine gluconate group or the chlorhexidine alcohol group. The inclusion period is planned to be roughly 1 year from July 2021; inclusion will be terminated when the target number of patients is reached.

Participant eligibility and consent

All patients scheduled to be admitted to the ICU or HCU of a facility participating in the study who require insertion of a central venous catheter are eligible, regardless of where the catheter is inserted (in the emergency department, operating room, general ward, ICU or HCU). Consecutively admitted patients who meet all inclusion criteria and none of the exclusion criteria are candidates for this study. Eligible patients will be enrolled after they are provided verbal and written information and after obtaining written informed consent from either the patient or the next of kin.

Inclusion and exclusion criteria

The inclusion criteria are adult patients (aged ≥18 years) scheduled to be admitted to either the ICU or HCU who require insertion of a central venous catheter. The exclusion criteria are as follows: patients with a disinfectant allergy, systemic skin diseases, a skin ulcer wound, antimicrobial catheters or antimicrobial-containing dressings; patients participating in intervention trials related to CRBSI prevention (eg, trials including dressings, skin disinfectants, antibacterial catheters, antibacterial medications, etc); if the catheter is replaced by guide-wire; patients who do not provide informed consent; and patients in whom it is difficult to obtain consent, for instance, due to an emergency.

Interventions

Eligible patients will be randomly assigned to either the olanexidine gluconate group (OLG group: 10 mL of 1.5% Olanedine disinfectant solution using a swab-type applicator; Otsuka Pharmaceutical Factory, Tokushima, Japan) or the chlorhexidine alcohol group (CHG group: 1% chlorhexidine gluconate ethanol disinfectant solution; Toho Yakuhin Co., Tokyo, Japan) in a 1:1 randomisation scheme only once with stratification by centres. The antimicrobial agents will be used as a skin disinfectant before catheter insertion (once for 30 s in the OLG group; twice for 30 s in the CHG group) and during catheter maintenance. In Japan, it is generally recommended that disinfection with 1% chlorhexidine alcohol be performed twice. In contrast, olanexidine is proposed by the manufacturer to be effective with a single application. After disinfection, the catheters will be inserted by the physicians of participating institutions with maximum barrier precautions, including the use of a cap, mask, sterile gown, sterile gloves and a sterile full body drape, as recommended by CDC guideline.⁷ Any physician who is authorised to insert central venous catheters according to the standards of each facility can do so, and no specific

Figure 1 Timeline of the study. HCU, high-care unit; ICU, intensive care unit.

rules have been set for the inserters. The selection of the site of catheter insertion and the healthcare provider is left to the individual facility, while the first choice of puncture site is the internal jugular vein. The insertion site of the catheter will be dressed with sterile polyurethane film dressing not containing antimicrobials, such as 3M Tegaderm Transparent Dressing, to be changed every 7 d if cleanliness is maintained. If the dressing site is not clean, the dressing will be changed, and gauze dressings will be used in cases with heavy exudate. A dressing that is not completely adherent will also be changed immediately. The management protocols during and after catheter insertion will be standardised in advance throughout the study (see online supplemental file 1). The timeline for this study is shown in figure 1.

Study outcomes

Primary endpoint

The primary endpoint is the proportion of catheter-related infections, defined as a composite of catheter-related sepsis without bacteraemia and CRBSI. This definition is a modified version of the definition commonly used in previously reported articles, such as the CLEAN study.¹³ Catheter-related sepsis without bacteraemia is defined as a combination of (1) a fever of 38.5°C or higher or hypothermia of 36.5°C or lower, (2) improvement in fever or hypothermia within 48 hours of catheter removal or purulent exudates from the catheter site and (3) no other source of infection identified. CRBSIs are defined as a combination of (1) a fever of 38.5°C or higher or hypothermia of 36.5°C or lower, (2) at least one strain identified in blood cultures taken around 48 hours after catheter removal (more than one positive blood culture is required for coagulase-negative Staphylococci bacteraemia) and (3) no other source of infection identified.

Secondary endpoints

The secondary endpoints of this study are as follows:

- ▶ Incidence of catheter-related infections (rate per 1000 catheters per day).

- ▶ In-hospital mortality.
- ▶ ICU mortality.
- ▶ Number of outbreaks of antibiotic-resistant bacteria (MRSA, multidrug-resistant *P. aeruginosa*, or VRE).
- ▶ Number of adverse events (redness, urticaria, anaphylaxis, contact dermatitis, etc). Contact dermatitis is defined according to the International Contact Dermatitis Research Group.¹⁴

Sample size calculation

The proportion of catheter-related infections in previous studies was approximately 6.3% with 1% chlorhexidine alcohol¹⁵; no such data have been reported with OLG. However, the proportion of CRBSIs with 1% chlorhexidine alcohol is comparable to that with OLG in previous studies (unpublished data; 1% vs 0.9%). Therefore, we assumed the proportion of catheter-related infections to be 5% in both groups. The non-inferiority margin Δ was set at 2.5%. Under these assumptions, 940 patients per arm (total, 1880 patients) are required to have 80% power with one-tailed 5% alpha. Considering a dropout rate of 5%, a total of 1980 patients (990 patients in each group) are needed. The rationale for setting the non-inferiority margin Δ at 2.5% was considering the maximum range that clinicians involved in infectious diseases, infection control and intensive care consider reasonable.

Assignment of interventions and randomisation

Allocation

A block randomisation sequence will be generated on a central computer by the final statistician using REDCap (Vanderbilt University Medical Center, Nashville, Tennessee). The statistician will not be involved in screening patients or assessing outcomes. Patients will be assigned to either the OLG group or the CHG group in a 1:1 randomisation scheme only once. The allocation will be stratified and assigned by the clinical research institute.

Blinding

As this study aims to use an applicator-type OLG solution, patients and healthcare providers will not be blinded to the drugs. However, the drugs will be blinded to outcome assessors and statistical analysts. The outcome assessors will be blinded to the allocation groups and will independently judge the outcomes of this study based on the patient data registered on REDCap by each institution.

Data collection

Data will be entered into a web-based electric case report form using REDCap and stored electronically on two password-protected computers. Hard copies of the data (clinical research files) will be stored in a locked and secure office. The following data will be recorded:

- ▶ Baseline patient characteristics
 - Age
 - Sex
 - Date of admission
 - Admission ward (ICU, HCU, other)
 - Height and weight

- Simplified Acute Physiology Score II
- Sequential Organ Failure Assessment Score
- Charlson Comorbidity Index
- Presence of hypertension and dyslipidaemia
- Route of admission (general outpatient, emergency department, ward, operating room/catheter, transfer, etc)
- Hospitalisation category (internal medicine, scheduled postoperative, emergency postoperative or other)
- Reasons for admission (nervous system, respiratory system, cardiovascular system, digestive system, nephrology, metabolic endocrinology, trauma, haematology, obstetrics and gynaecology, skin and soft tissue, orthopaedics or other)
- Presence of sepsis at admission (none, sepsis or septic shock)
- Ventilator use (none, conventional oxygen therapy, non-invasive positive pressure ventilation, high flow nasal cannula or invasive ventilation)
- Characteristics of catheters
 - Date of catheter insertion
 - Catheter insertion site (femoral vein, jugular vein, etc)
 - Location of catheter insertion (ICU, emergency department, etc)
 - Presence of infection at the time of catheter insertion
 - Type of antimicrobial agent used at the time of catheter insertion
 - Presence of infection during catheter insertion
 - Type of antimicrobial agent used during catheter insertion
 - Type of dressing
 - How the catheter was secured
- Outcome data
 - Date of catheter removal
 - Catheter removal and reason for removal
 - Presence of CRBSI, date of diagnosis (body temperature at the time of and within 48 hours after catheter removal, presence or absence of blood culture collection, positive blood culture, and name and species of bacteria)
 - Date of ICU discharge
 - ICU death
 - Date of hospital discharge
 - Death at the hospital
 - Presence of adverse events (contact dermatitis as per the International Contact Dermatitis Research Group criteria, redness, urticaria, anaphylaxis, purulent exudates and others)
 - Presence of protocol deviation (randomised but not admitted to ICU/HCU, used wrong disinfectant at 'insertion', failed to disinfect as prescribed at 'insertion', failed to disinfect as prescribed at 'administration', failed to dress as prescribed at 'administration', or failed to disinfect as prescribed at 'removal, death, or transfer to a hospital with central venous catheter in place')

Only objective information necessary for determining the outcome of catheter-related infections will be collected by the researchers at each institution. The data management centre will blind the assigned disinfectant, and the Outcome Evaluation Committee will determine catheter-related infections. Three members of the Outcome Judging Committee are listed from this research group. The outcome judgement method will be conducted according to the following procedure: (1) outcome judgement will be conducted automatically based on the data items required for outcome judgement. (2) If the outcome is found to be positive by the automatic judgement, three members of the committee will independently evaluate the validity of the judgement. (3) If all three members make the same judgement, the outcome will be judged as positive or negative. If even one member makes a different judgement, the judgement will be made through consultation among the three members. [Table 1](#) shows the trial measures to be collected and their purpose.

Data monitoring and auditing

The monitoring manager will consistently monitor the study to ensure the reliability of the research; that participant human rights, safety and welfare are protected; that the research is conducted in compliance with the research protocol; and that the data are collected accurately. The monitoring manager will designate one person to oversee and ensure monitoring is conducted appropriately in accordance with the procedures prepared in advance (see online supplemental file 2, written in Japanese). As this study is a clinical trial with a minor invasion, only central monitoring will be conducted; on-site monitoring will not be conducted unless problems are identified during central monitoring.

- *Items for central monitoring:* documents related to the ethical review, explanatory documents and consent forms, drug management, eligibility, accuracy of reported data and adverse event reporting.
- *Items for on-site monitoring:* enrolment status, eligibility, data entry status and a confirmation of data error values and presence of protocol deviation.

Procedures for central and on-site monitoring

On the first day of each month, the above items will be monitored on the registered data at the central institution, and the reports will be submitted to the president and principal investigator via the designated report form.

Auditing

The drugs used in this study are skin disinfectants already widely used in general hospitals, and as the drugs are not administered directly into the body, they are considered a minor invasion. Therefore, the incidence of serious adverse events is expected to be small and insignificant. Additionally, this study will improve data quality assurance by collecting data using electronic data capture. The quality of the research and safety of the participants

Table 1 Data collection items and collection timing

Timing	At admission to ICU/HCU	At insertion of the catheter	At removal of the catheter	At discharge from hospital
Baseline patient characteristics				
Age	☐			
Sex	☐			
Date of admission	☐			
Admission ward	☐			
Height and weight	☐			
SAPS II	☐			
SOFA score	☐			
Charlson comorbidity index, presence of hypertension and dyslipidaemia	☐			
Route of admission	☐			
Hospitalisation category	☐			
Reasons for admission	☐			
Presence of sepsis at the time of admission	☐			
Ventilator use	☐			
Characteristics of catheters				
Date of catheter insertion		☐		
Catheter insertion site		☐		
Location of catheter insertion		☐		
Presence of infection at the time of catheter insertion		☐		
Type of antimicrobial agent used at the time of catheter insertion		☐		
Presence of infection during catheter insertion		☐		
Type of antimicrobial agent used during catheter insertion		☐		
Type of dressing		☐		
How the catheter was secured		☐		
Catheter outcomes				
Date of catheter removal			☐	
Catheter removal and reason for removal			☐	
Presence of CRBSI, date of diagnosis			☐	
Presence of adverse events			☐	
Presence of protocol deviation			☐	
Patient outcomes				
Date of ICU discharge				☐
ICU death				☐
Date of hospital discharge				☐
Death at the hospital				☐

CRBSI, catheter-related bloodstream infection; HCU, high-care unit; ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; SOFA, sequential organ failure assessment.

will be maintained, and no audit will be conducted in this study.

Statistical analysis

Statistical analysis will be performed after the required number of participants is reached. There is no plan for interim analysis.

Regarding demographic data, continuous variables will be presented as means with SD or medians with

interquartile ranges and categorical variables as percentages, as appropriate. Student's t-test and χ^2 or Fisher's exact t-test, as appropriate, will be used for comparison.

The primary analysis population is the full analysis set, based on the intention-to-treat principle, and excludes patients with no efficacy data after randomisation. The primary endpoint is the proportion of patients with catheter-related infections, wherein the one-tailed 90%

CI for the between-group difference (OLG and CHG groups) will be estimated using the normal approximation method. If the upper limit of the 90% CI is less than or equal to the non-inferiority margin (Δ 2.5 %), it will demonstrate that OLG is non-inferior to 1% chlorhexidine alcohol. For the secondary endpoint of time-to-catheter-related infection, the non-inferiority of OLG to 1% chlorhexidine alcohol will be tested in terms of the estimated HR with the Cox regression model and $\Delta=2.0$ for HR. For other secondary endpoints, proportions will be compared between the two groups using Fisher's exact t-test; time-to-event data will be summarised for each group using the Kaplan-Meier method and compared using the log-rank test. As mortality before catheter removal is considered a competing risk, the Fine and Gray subdistribution hazard regression model will be conducted to compare the effects of 1.5% aqueous olanexidine and 1% chlorhexidine alcohol under the competing risk. The significance level for the non-inferiority analyses will be one-tailed at 5%, and that for other analyses will be two tailed at 5%. Statistical analyses will be performed using SAS V.9.4 (SAS Institute).

Subgroup analyses

1. Route of admission (medical, surgical).
2. Severity of disease (Simplified Acute Physiology Score II score >51 , ≤ 51).
3. Insertion site (femoral, internal jugular or subclavian).
4. Antimicrobial use before and during catheter insertion.

Sensitivity analysis

1. This will exclude clinical research institutions with poor quality catheter management practices (to be determined at monitoring).
2. We will evaluate the incidence of catheter-related infections using a marginal Cox model adjusted for covariates (including study groups) that will be significantly imbalanced between the groups ($p<0.20$ on univariate analysis).

Patient and public involvement

There was no patient, public, or community involvement in this study design.

ETHICS AND DISSEMINATION

Ethical approval was obtained from the Institutional Review Board of Jichi Medical University and the ethics committees of the participating institutions. The names of the review boards of all participating institutions and approval reference numbers are provided in online supplemental file 3.

Consent

The physician in charge of the study will properly explain the following items to the patient or his/her next of kin (spouse, adult children, parents, grandparents, relatives, etc) using the consent and explanation documents approved by the study Ethics Review Committee of the clinical research organisation before the start of the

study. After confirming that the patient or his/her family has fully understood the contents of the document, the free and voluntary consent of the patient to participate in the study will be obtained in writing.

Both the physician in charge of the study and the patient to whom the study is explained must sign and date the consent/explanation document. If supplementary explanations are provided by a study collaborator, the collaborator will also sign and date the document.

After consent is obtained, the physician in charge of the study will deliver a copy of the consent form and explanatory document with the name, seal or signature and the date before the patient participates in the study. The original will be kept in the electronic medical record by the physician in charge of the study. The storage period will be 5 years after the completion of the study or 3 years after the final publication, whichever is later.

If information on the efficacy or safety of the antiseptic that may affect patient consent is obtained after signing the informed consent or if the protocol is revised in a way that may affect patient consent, information will be provided to patients as soon as possible and their willingness to continue to participate in the study will be confirmed in advance. The consent and explanation documents will also be revised with prior approval from the Ethics Review Committee, and consent will be obtained from the patient. The consent form is provided as online supplemental file 4, written in Japanese. The patient may withdraw their consent at any time; the reason for withdrawal will be inquired, and the patient will be asked if data collected up to the time of withdrawal can be used. If consent is withdrawn, it must be mentioned in the consent withdrawal form (online supplemental file 5, written in Japanese).

Confidentiality

Data will be handled in a consolidated and anonymised manner, and no information (name, address, telephone number, etc) will be used to identify the patient outside the clinical research institution. When this study is presented or published at a conference or in a paper, sufficient care will be taken to ensure that the study participant is not identified. If it is necessary to refer data to a clinical research institution, this will be done through the data management centre, and the research patterns will be identified using a correspondence chart maintained by the participating physicians within the clinical research institution. Patient enrolment from each institution will be done through REDCap to keep individual patient information confidential. When the final registration data are shared with each institution, the electronic file containing the patient data will be stored in a password-protected file by the person in charge at each clinical research institution and the data management centre in charge of data analysis. Each patient and clinical research institution will be assigned an patient identification number for this study, and patient data will be consolidated and anonymized. Only the patient identification

number and the identification number of the clinical research institution will be retained in the patient database, and no data that can identify the patient will be retained. Patient identification number will be used when communicating with clinical research institutions. At the end of the study, investigators at each institution will only have access to the data from their institution. The data management officer and statistical analyst will have access to all enrollment data.

Dissemination policy

The results obtained in this study will be presented at domestic and international conferences related to intensive care, infectious diseases or infection control and will be published as papers in appropriate journals. The results to be published will only be statistically processed, and no personal information of the participants will be disclosed. The authors of this study will follow the International Committee of Medical Journal Editors guidelines.

Data availability statement

Data will be shared with those who apply for data sharing if all study members agree with sharing this study data.

- ▶ Will individual participant data be available?
Yes
- ▶ What data in particular will be shared?
All individual participant data collected during the trial, after deidentification.
- ▶ What other documents will be available?
Study Protocol, Statistical Analysis Plan, Informed Consent Form, Clinical Study Report, Analytic Code.
- ▶ When will data be available?
Immediately following publication. No end date.
- ▶ With whom?
Anyone who wishes to access the data.
- ▶ For what types of analyses?
Any purpose.
- ▶ By what mechanism will data be made available?
Proposals should be directed to yasudahideto@me.com.

DISCUSSION

Although the frequency of CRBSIs has decreased in recent years, there remains a high possibility of infections caused by indwelling intravascular catheters, even if they do not lead to CRBSI,¹³ and prevention of such infections is clinically and medico-economically important.

Catheter-related infections caused by multidrug-resistant bacteria affect patient prognosis, and prevention of such infections is crucial in medical practice.^{9 10} Olanexidine is a new skin disinfectant developed in Japan and is expected to be effective against multidrug-resistant bacteria.¹² Since its development in 2015, a large clinical trial for the prevention of surgical site infections has shown its efficacy versus 10% povidone-iodine solution.¹⁶ However, no randomized controlled studies (RCTs) have examined its efficacy in preventing catheter-associated infections; this is the first study worldwide to examine the

efficacy of olanexidine for prevention of catheter-related infections. This is the greatest strength of our study. The results of this study may provide a new approach to catheter infection prevention.

The primary outcome of this study is catheter-related infection that includes not only CRBSI but also local infection and improvement of clinical symptoms after catheter removal. Although CRBSI is an important outcome, fevers and localised infections are also outcomes that may necessitate the removal of catheters, and may result in increased healthcare costs. Examining the composite outcomes, which include fever, local findings at the catheter insertion site, improvement in clinical findings after removal, and CRBSI, may be meaningful for clinical practice. In this study, we will set such composite outcomes as primary outcomes, and this examination of more clinically important outcomes may be another strength of our study.

However, this study has several limitations. First, the definition of CRBSI used in the composite outcome does not include catheter colonisation. It is generally believed that a positive correlation exists between catheter colonisation and CRBSI,¹⁷ and it is common to include catheter colonisation in the definition of CRBSI. However, in a previous RCT conducted by our study group, 30% of patients were excluded due to missing catheter colonisation outcomes, resulting in incomplete intention-to-treat analysis.⁸ We will not include catheter colonisation in the definition of CRBSI to prevent missing outcomes in this study because we anticipate that the medical situation in Japan may make it difficult to properly perform catheter tip culture after patients are discharged from the ICU or HCU. The impact is both underestimation and overestimation of the number of outcome occurrences; this may make it difficult to compare our results with those of previous studies. Second, the chlorhexidine alcohol formulation used in this study is a 1% formulation, not the 2% formulation commonly used globally. The maximum concentration of chlorhexidine alcohol that can be used clinically for the prevention of catheter-related infection in Japan is 1 %, and it is difficult to compare 2% chlorhexidine alcohol with 1.5% aqueous olanexidine. Therefore, the external validity of this study may be reduced in countries where 2% chlorhexidine alcohol is used clinically. Finally, in this study, randomisation is not conducted with stratification by catheter insertion site or location of catheter insertion, which may lead to confounding results. Many of the facilities participating in this study are Level 3 emergency centres, and we expect that many of the catheters will be inserted in the emergency department. In addition, the first choice of the central venous catheter insertion site in Japan is the internal jugular vein, and many of the catheters in the previous RCT conducted by our research group were inserted through the internal jugular vein.⁸ Based on these facts, we judged that the difference in catheter insertion site or location of catheter insertion would have little impact on the results of this study. However, we will

be planning to conduct a multivariate analysis including potential confounders in a sensitivity analysis.

This study may provide new insights into the prevention of catheter-related infections in patients with central venous catheters. In this study, 1% chlorhexidine alcohol will be used as a control group, which may reduce the external validity of the study, but it is expected that the results of this study will lead to further clinical trials outside Japan.

Research administrative office

Department of Emergency and Critical Care Medicine, Jichi Medical University Saitama Medical Center. 1-847, Amanuma-cho, Omiya-ku, Saitama-shi, Saitama 330-8503, Japan.

Committee

The Apollo study research group.

Author affiliations

- ¹Department of Emergency and Critical Care Medicine, Jichi Medical University Saitama Medical Center, Saitama, Japan
- ²Department of Emergency Medicine, St Luke's International Hospital, Tokyo, Japan
- ³Department of School of Data Science, Yokohama City University, Kanagawa, Japan
- ⁴Department of Emergency and Critical Care Medicine, Keio University School of Medicine, Tokyo, Japan
- ⁵Division of Clinical Laboratory and Infection Control, Yamagata University Hospital, Yamagata, Japan
- ⁶Department of Emergency and Critical Care Medicine, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan

Twitter Masahiro Kashiura @MKashiura

Contributors HY, MK, YK, TH, JS, TM, KM, and NS participated in the design of the study and drafted the manuscript. TA participated in the design of the study, the plan for statistical analysis, and drafted the manuscript.

Funding This work is supported by Grants-in-Aid for Scientific Research, the Japan Society for the Promotion of Science (JAPAN) [grant number 21K09080] and the Japanese Association for Acute Medicine [grant number 2020-02].

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Hideto Yasuda <http://orcid.org/0000-0003-3153-1595>
Masahiro Kashiura <http://orcid.org/0000-0002-1989-656X>

REFERENCES

- 1 Vincent JL, Rello J, Marshall J, Sakr Y RKEIG of I. and outcomes of infection in intensive care units. *JAMA* 2009;302:2323–9.
- 2 Frasca D, Dahyot-Fizelier C, Mimoz O. Prevention of central venous catheter-related infection in the intensive care unit. *Crit Care* 2010;14:212.
- 3 Timsit J-F, Mimoz O, Mourvillier B, et al. Randomized controlled trial of chlorhexidine dressing and highly adhesive dressing for preventing catheter-related infections in critically ill adults. *Am J Respir Crit Care Med* 2012;186:1272–8.
- 4 Timsit J-F, Schwebel C, Bouadma L, et al. Chlorhexidine-impregnated sponges and less frequent dressing changes for prevention of catheter-related infections in critically ill adults: a randomized controlled trial. *JAMA* 2009;301:1231–41.
- 5 Centers for Disease Control and Prevention. Intravascular catheter-related infection (BSI). Available: <https://www.cdc.gov/infectioncontrol/guidelines/bsi/index.html>
- 6 Masuyama T, Yasuda H, Sanui M, et al. Effect of skin antiseptic solutions on the incidence of catheter-related bloodstream infection: a systematic review and network meta-analysis. *J Hosp Infect* 2021;110:156–64.
- 7 O'Grady NP, Alexander M, Burns LA. Guidelines for the prevention of intravascular catheter-related infections. *Am J Infect Control* 2011;39.
- 8 Yasuda H, Sanui M, Abe T, et al. Comparison of the efficacy of three topical antiseptic solutions for the prevention of catheter colonization: a multicenter randomized controlled study. *Crit Care* 2017;21:320.
- 9 Kajihara T, Yahara K, Stelling J. Comparison of de-duplication methods used by who global antimicrobial resistance surveillance system (GLASS) and Japan nosocomial infections surveillance (JANIS) in the surveillance of antimicrobial resistance. *PLoS One* 2020;15:e0228234.
- 10 World Health Organization. Antimicrobial resistance: global report on surveillance, 2016. Available: <http://www.who.int/drugresistance/en/> [Accessed 29 Oct 2021].
- 11 Nishioka H, Nagahama A, Inoue Y, et al. Evaluation of fast-acting bactericidal activity and substantivity of an antiseptic agent, olanexidine gluconate, using an ex vivo skin model. *J Med Microbiol* 2018;67:1796–803.
- 12 Inoue Y, Hagi A, Nii T, et al. Novel antiseptic compound OPB-2045G shows potent bactericidal activity against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* both in vitro and in vivo: a pilot study in animals. *J Med Microbiol* 2015;64:32–6.
- 13 Mimoz O, Lucet J-C, Kerforne T, et al. Skin antisepsis with chlorhexidine-alcohol versus povidone iodine-alcohol, with and without skin scrubbing, for prevention of intravascular-catheter-related infection (CLEAN): an open-label, multicentre, randomised, controlled, two-by-two factorial trial. *Lancet* 2015;386:2069–77.
- 14 Johansen JD, Aalto-Korte K, Agner T, et al. European Society of Contact Dermatitis guideline for diagnostic patch testing - recommendations on best practice. *Contact Dermatitis* 2015;73:195–221.
- 15 Hanyu R, Fujimoto K, Ikeda A, et al. Evaluation of the preventive effect of skin disinfection using an alcohol preparation containing 1% chlorhexidine gluconate against dialysis catheter-related infections. *Nihon Toseki Igakkai Zasshi* 2018;51:299–304.
- 16 Obara H, Takeuchi M, Kawakubo H, et al. Aqueous olanexidine versus aqueous povidone-iodine for surgical skin antisepsis on the incidence of surgical site infections after clean-contaminated surgery: a multicentre, prospective, blinded-endpoint, randomised controlled trial. *Lancet Infect Dis* 2020;20:1281–9.
- 17 Rijnders BJA, Van Wijngaerden E, Peetermans WE. Catheter-tip colonization as a surrogate end point in clinical studies on catheter-related bloodstream infection: how strong is the evidence? *Clin Infect Dis* 2002;35:1053–8.