Effects of central venous catheter dressing replacement frequency on skin bacterial colonization: A multicenter, randomized, non-inferiority trial

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Statistical Analysis Plan

The Data Management and Statistical Analysis Plan is directed to support the aims of the study

Version 2.0

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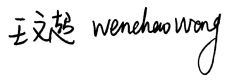
Wenchao Wang (Project Executor)	

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Catalogue

1. Introduction

Central venous catheter (CVC) is one of the most commonly used venous access in critically ill children. Continuous access to the central vascular is desirable for administering fluids, drugs, and blood products. However, the wide application of CVC increases the incidence of complications, such as central venous catheter-related bloodstream infection (CLABSI) and central line-associated thrombosis. Studies have shown that CVC-related bloodstream infection increases mortality by 25% [1]. The occurrence of CVC-related bloodstream infection will prolong the hospitalization time of children, increase the medical expenditure of children's families, and even lead to the death of children [2]. In currently published studies, it was found that skin bacterial colonization is one of the important factors leading to CVC-related bloodstream infection [3]. However, most studies focus on the culture of catheter tips, bacterial colonization on the inner surface of dressings, skin bacterial colonization underdressing when extubation and the growth of bacterial film on the inner surface of catheters [4-9], and few studies focus on skin bacterial colonization during placement of indwelling CVC. This trial aims to evaluate the effects of dressing change frequency of CVC on bacterial colonization in pediatric intensive care unit (PICU) in China.

2. Study Objective and Outcomes

2.1 Study Objective

The primary objective is to compare the occurrence of skin bacterial colonization in patients who change dressing after seven days of CVC catheterization versus those who change dressing after 24 hours. The secondary objectives include comparing the incidence of CLABSI and medical adhesive-related skin injury (MARSI) between the two groups during CVC catheterization.

2.2 Outcomes

2.2.1 Primary outcome

The primary outcome is the occurrence of skin bacterial colonization on the seventh or eighth day after CVC catheterization.

- Description:

  For patients whose dressing is changed after seven days of CVC catheterization, skin samples will be taken on the seventh day after CVC. For patients whose dressing is changed after 24 hours of CVC catheterization, skin samples will be taken on the eighth day after CVC. The detailed sampling method is shown in the protocol. The colony number above 15 colony-forming units / cm^2 will be defined as skin bacterial colonization that occurred.

- Time Frame:

  The experimental group will be detected on the seventh day after CVC catheterization. The control group will be detected on the eighth day after CVC catheterization.

- Type: binary variable: Yes / No.

2.2.2 Secondary outcomes

(1) Incidence of CLABSI

- Description:

  CLABSI will be defined as:

  When removing the CVC, the clinical nurse will collect the patient's venous blood sample and sample at the CVC tip. The sampling method is detailed in the protocol. Laboratory personnel independent of the study will report the type of bacteria from blood culture or CVC tip. The Center for Disease Control uses 'definite', 'probable' and 'possible' to distinguish between CRBSI status. This study uses the 'definite'

definition to diagnose CLABSI. The diagnostic criteria for definite CRBSI are the growth of the same pathogen from blood culture of peripheral vein and from the culture of CVC tip or growth of the same pathogen from blood culture of the peripheral vein and from the culture of CVC. The infection department will make a definite diagnosis for CLABSI.

- Time Frame: Time point for CVC removal or suspected bloodstream infection.
- Type: Binary variable: Yes / No.

(2) Incidence of MARSI

- Description:

  MARSI is defined as persistent erythema and/or other skin abnormalities (including but not limited to blisters, bullae, erosion, or tear) within 30 minutes or more after the nurse changes the dressing. If the bedside nurse finds a suspected MARSI when changing the dressing, inform the specialist nurse to determine MARSI.
- Time Frame: During CVC catheterization.
- Type: time-to-event outcome.

3.Study Design

3.1 Design

The trial is a multicenter, randomized controlled non-inferiority trial. Patients who fulfill the eligibility criteria outlined in the protocol will be invited to participate consecutively and randomized to the experimental or control group. Block randomization (block size of 4) will be applied.

3.2 Trial Sites

The trial will be conducted in four hospitals in China: Children's Hospital of Fudan University, Xiamen Children's Hospital, Shenzhen Children's Hospital, and Anhui Province Children's Hospital.

3.3 Interventions

3.3.1 Control arm:

Active Comparator: Change the dressing 24 hours after CVC catheterization (CD24h treatment)

Patients in this arm will receive standard dressing change operations. The dressing change will be performed 24 hours after CVC catheterization in the operating room or PICU, and then the second dressing change will be completed seven days later (if there are no clinical indications such as fluid oozing and bleeding). Skin flora sampling will be performed on the eighth day after CVC catheterization. The sampling method is detailed in the protocol.

3.3.2 Experimental arm:

Intervention: Change the dressing seven days after the CVC catheterization (CD7d treatment)

Patients in this arm will change the dressing seven days after the CVC catheterization in the operating room or PICU (if there are no clinical indications such as fluid accumulation and bleeding). Skin flora sampling will be performed on the seventh day after CVC catheterization when the dressing is changed. The sampling method is exactly the same as that of the control group.

3.4 Randomization

Central block randomization with a block size of 4 will be used in this trial. Eligible patients will be randomly assigned to the control arm or the experimental arm (allocation ratio 1:1). According to the seed generated by an independent statistician using SAS software (version 9.4), a sequence of study numbers and randomized allocations will be generated. The allocation sequence will be concealed and placed in the non-transparent sealed envelopes by the independent statistical group from the Clinical Trial Unit (CTU) of the Children's Hospital of Fudan University: the four allocations of each block will be placed in the four sealed small envelopes numbered 1 to 4 in order, and then put into the same large envelope marked with the corresponding block number.

Before each site enrolls the first patient of the block, the coordinator will contact the central coordinator of Children's Hospital of Fudan University, and the central coordinator will assign the envelopes to each site. The clinical nurse in each site will assess the eligibility of the patients and obtain signed informed consent, and then contact the coordinator to obtain the allocation. The coordinator will open the envelopes in numbered order according to the enrollment order, inform the nurse of the allocation, and record the assignment of each enrolled patient.

3.5 Blinding

The sample collectors and laboratory personnel will be blinded to the assignment of the patients. The trial statistician will also be blinded regarding the treatment code when developing the statistical analysis plan and writing the statistical programs. The actual allocation will only be provided to the study team after the database lock.

3.6 Sample Size

This study is a non-inferiority design, and the primary outcome is the occurrence of skin bacterial colonization on the seventh or eighth day after CVC catheterization (binary outcome). The sample size is calculated based on the difference between the two groups of the primary outcome.

According to our previous pilot study that included 49 subjects, the occurrence of skin bacterial colonization in the CD7d group and the CD24h group was 56.3% and 55.6%, respectively. A non-inferiority margin of 20% is considered to be clinically acceptable. Based on the assumptions of (i) the occurrence of skin bacterial colonization of 55% in the CD24h group, (ii) the non-inferiority margin of 20%, (iii) power of 80%, and (iv) a one-sided alpha of 0.025, the sample size estimation resulted in 98 subjects per group (calculated with PASS software, version 16.0). Considering a 30% drop-out rate, a total of 280 subjects should be randomized (140 per group).

4.Analysis Populations

4.1 Study population data sets

Two study populations will be considered in the analysis as follows:

- **Intent-to-Treat population**

  Intent-to-treat (ITT) population will be defined at the moment the randomization is performed. For example, if a participant receives the wrong treatment or no treatment at all or is lost for follow-up for outcomes, he/she will be analyzed according to the arm to which they were allocated. This will be the primary analysis for the trial. Participants will be excluded from the ITT analysis if the primary outcome is missing, forming a modified ITT population (mITT).

- **Per-protocol population**

  Per-protocol (PP) population will only include patients who received the treatments according to the protocol. In addition, the patients in the CD7d group completed skin sample collection on the seventh day after CVC catheterization, and the patients in the CD24h group completed it on the eighth day.

  Participants will be excluded from the PP population if they:

  - Did not adhere to per-protocol treatment, including the CD7d group changing the dressing less than seven days after CVC catheterization, or the CD24h group does not change the dressing more than 24 hours after CVC catheterization.
  - Switched treatment.

  This population will be used for the supportive analyses.

4.2 Study Close Date

The data collection close date is when the last patient removed the CVC to achieve outcomes.

4.3 Data Cleaning

The data will then be checked to ensure no erroneous entries and that all missing data is properly coded. Any changes will be made to the database.

4.4 Data Check-up

Once all data have been inputted and checked, the database will be locked and a data download request made. The data will be downloaded into SAS and Stata formats for

statistical analyses.

5. Statistical Analyses

5.1. Primary Outcome Analysis

5.1.1 ITT analysis of the primary outcome - the primary analysis

The primary outcome is a binary outcome: the occurrence of skin bacterial colonization on the seventh or eighth day after CVC catheterization. The primary analysis will be based on the ITT population as defined above.

Hypothesis: Let π_1 denote the occurrence of skin bacterial colonization on the eighth day after CVC catheterization in the CD24h group (control group), and let π_2 denote the occurrence of skin bacterial colonization on the seventh day in the CD7d group (experimental group), the non-inferiority margin Δ=20%. The null hypothesis is H_0: $\pi_2 - \pi_1 > \Delta$ versus the alternative hypothesis is H_A: $\pi_2 - \pi_1 \leq \Delta$.

A generalized linear model (GLM) will be used to test the above hypothesis. In the GLM, the occurrence of skin bacterial colonization will be treated as the dependent variable and the treatment as the fixed effect, following a binomial distribution and identity link function. A point estimate of risk difference between groups in the difference and its 95% confidence interval (CI) will be estimated. CD7d treatment will be considered non-inferior to the CD24h treatment if the upper 95% confidence limit is no greater than Δ, where Δ= 20%, the predetermined non-inferiority margin.

5.1.2 Sensitivity analyses of the primary outcome

- PP analysis with GLM (described in 5.1.1) will be performed.
- An analysis of the primary outcome will be adjusted for age, gender, CVC catheterization site, type of disease, and administration set at baseline in ITT and PP population, respectively. The adjusted difference and 95% one-sided upper limit comparing the two groups will be derived by GLM (described in 5.1.1). If the above identity-binomial GLM does not converge when all covariates are introduced into the model, the adjusted model will be performed by removing a covariate one by one until the model converges.

5.1.3. Subgroup analyses of the primary outcome

Subgroup analyses for the primary outcome will be performed using GLM. We will stratify by gender and disease type. Gender will be divided into male and female. Disease type will be divided into congenital heart disease, congenital biliary atresia, tumor and others. Subgroup analyses will be performed if each subgroup contains enough patients after stratification.

5.2. Secondary Outcome Analysis

All secondary outcomes will be analyzed as a superiority design, and two-sided 95% CIs for the differences in these outcomes between two groups will be calculated. Secondary outcome analyses will be based on the ITT population unless specified.

5.2.1 Analysis of binary outcomes

The incidence of CLABSI will be summarized by the number (%) of patients with event by treatment group and analyzed by GLM (the same method as the primary outcome).

The difference of incidence and its two-sided 95% CIs between the two groups will be estimated. If necessary for analysis, odds ratios or risk differences with two-sided 95% CIs of the two groups will be derived from the GLM with binomial distribution, and logit or identity link functions, respectively.

5.2.2 Analysis of time-to-event outcomes

The incidence of MARSI will be analyzed as a time-to-event outcome and will be summarized by the number (%) of patients with event by treatment group. The log-rank test will be used to compare the incidence of MARSI, the difference and its 95% CI for the comparison between the two groups will be estimated. Cox proportional hazards regression model will derive hazard ratio and its two-sided 95% CI for comparing two groups. In addition, Cox regression model after adjusting for age, disease type, and CVC catheterization site will also be performed.

5.2.3 Analysis of continuous outcomes

The continuous outcome will be summarized using the number of patients (n), mean, standard deviation (SD), minimum, and maximum by treatment group, and will be analyzed by GLM with treatment as a fixed effect and with normal distribution and identity link function. Differences in the mean outcome and mean differences with their two-sided 95% CIs between two groups will be derived.

5.2.4 Handling of Missing data

Different data imputation methods will be used according to the reasons for the missing data. For randomly missing data, such as vital signs, laboratory indicators, auxiliary examinations, etc., multiple imputations (MI) will be used to impute the missing data for analyses of secondary outcomes.

5.2.5 Analysis of other secondary outcomes

Other statistical methods may be used if deemed necessary.

6.General Considerations for Data Analyses

STATA® (version 16.0) will perform all data analyses and generate most data displays. SAS (version 9.4) or R may also be used for some data analyses and generating statistical graphs.

6.1 Data Summaries

Continuous variables will be summarized according to the number of patients (n), mean, standard deviation (SD), median, minimum, maximum, and range interquartile (IQR). Categorical variables will be summarized according to the absolute frequency and percentage of patients (%) by category levels. The denominator for the percentages is the number of subjects in the treatment arm with data available unless noted otherwise.

6.2 Graphical / Table Displays

Figure 1: Patient flow chart. A patient disposition flow chart will be presented showing the number of patients randomized to each treatment arm, reasons for withdrawal, and numbers available for each analysis population.

Table 1. Baseline characteristics of patients

Characteristics	Statistics	CD7d treatment (N=)	CD24h treatment (N=)
Age (year)	Mean(SD)		
Height (cm)	Mean(SD)		
Weight (kg)	Mean(SD)		
Birth weight (kg)	Mean(SD)		
Gender, n (%)	Female		
	Male		
Admission disease diagnosis, n (%)	Congenital heart disease		
	Congenital biliary atresia		
	Tumor		
	Others		
CVC catheterization site, n (%)	Jugular		
	Subclavian		
	femoral		

Table 2. Primary outcome of occurrence of bacterial colonization by treatment

Population	**Occurrence of bacterial colonization (95% CI)**		**Difference (95% CI)**	**Non-inferiority P value**
	CD7d treatment (N=)	CD24h treatment (N=)		
Primary analysis:				
ITT population				
Sensitivity analysis:				
PP population				
Adjusted analysis (ITT)*				
Adjusted analysis (PP)#				

* The analysis will be adjusted for age, gender, CVC catheterization site, type of disease, and administration set in the ITT population.

The analysis will be adjusted for age, gender, CVC catheterization site, type of disease, and administration set in the PP population.

Table 3. Summary of generalized linear model analysis of secondary outcomes

Outcomes	Incidence (95% CI)		Difference (95% CI)	P value
	CD7d treatment (N=)	CD24h treatment (N=)		
Incidence of CLABSI				

Table 4. Proportion hazards models for time-to-event outcomes

Outcomes	Incidence (95% CI)		Hazard ratio (95% CI)	P value
	CD7d treatment (*No. of events / No. of patients*)	CD24h treatment (*No. of events / No. of patients*)		
Incidence of MARSI				
Unadjusted analysis				
Adjusted analysis*				

* The analysis will be adjusted for age, disease type, and CVC catheterization site.

7. Study variable list

Variable	Variable interpretation	Variable Type
center	Name of center	Text
center_no	Number of center	Text
name	Initials of subject	Text
id	Study ID of subject	Number
date_start	Date of enrollment	Date
date_end	Date of end	Date
investigator	Initials of investigator	Text
arm	Intervention allocation	Categorical
date_birth	Date of birth	Date
gender	Male / Female	Binary
height	Height at baseline	Continuous
weight	Body weight at baseline	Continuous
birth_weight	Body weight at birth	Continuous
cathete_site	Jugular/ Subclavian/ femoral	Categorical
cathlum_num	Number of catheter lumen	Categorical
diagnosis	Disease type	Categorical
bact_coloni	Occurrence of bacterial colonization	Binary
clabsi	Occurrence of CLABSI	Binary
marsi	Occurrence of MARSI	Binary

8.Reference

[1] KAUR M, GUPTA V, GOMBAR S, et al. Incidence, risk factors, microbiology of venous catheter associated bloodstream infections--a prospective study from a tertiary care hospital.[J]. INDIAN J MED MICROBI, 2015,33(2): 248-254.

[2] GARCIA-RODRIGUEZ J F, ALVAREZ-DIAZ H, VILARINO-MANEIRO L, et al. Epidemiology and impact of a multifaceted approach in controlling central venous catheter associated blood stream infections outside the intensive care unit.[J]. BMC INFECT DIS, 2013,13: 445.

[3] Safdar N, Maki DG. The pathogenesis of catheter-related bloodstream infection with noncuffed short-term central venous catheters[J]. INTENS CARE MED, 2004(30): 62-67

[4] IELAPI N, NICOLETTI E, LORE C, et al. The Role of Biofilm in Central Venous Catheter Related Bloodstream Infections: Evidence-based Nursing and Review of the Literature.[J]. Reviews on

recent clinical trials, 2020,15(1): 22-27.
[5] NISHIKAWA K, TAKASU A, MORITA K, et al. Deposits on the intraluminal surface and bacterial growth in central venous catheters.[J]. The Journal of hospital infection, 2010,75(1): 19-22.
[6] HE Y, ZHAO H, WEI Y, et al. Retrospective Analysis of Microbial Colonization Patterns in Central Venous Catheters, 2013-2017.[J]. J HEALTHC ENG, 2019,2019: 8632701.
[7] ROSA L, CUTONE A, COLETTI M, et al. Biotimer assay: A reliable and rapid method for the evaluation of central venous catheter microbial colonization.[J]. J MICROBIOL METH, 2017,143: 20-25.
[8] GUIDET B, NICOLA I, BARAKETT V, et al. Skin versus hub cultures to predict colonization and infection of central venous catheter in intensive care patients.[J]. INFECTION, 1994,22(1): 43-48.
[9] LUFT D, SCHMOOR C, WILSON C, et al. Central venous catheter-associated bloodstream infection and colonisation of insertion site and catheter tip. What are the rates and risk factors in haematology patients?.[J]. ANN HEMATOL, 2010,89(12): 1265-1275.