RESEARCH PROTOCOL

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RESEARCH PROPOSAL

RESEARCH TITLE

Efficacy and Health Economics of Antimicrobial-impregnated Central Venous Catheters (CVCs) compared to Non-impregnated CVCs in Central Line-associated Bloodstream Infection (CLABSI) Prevention in a Malaysia University Hospital Adult Intensive Care Unit (ICU)

Keywords: Antimicrobial-impregnated Central Venous Catheters (CVCs), Central Line-associated Bloodstream Infection (CLABSI), Intensive Care Unit (ICU)

1. INTRODUCTION

Central venous catheters (CVCs) are indispensable in modern critical care as they are highly reliable as intravenous access for administration of vasopressors, inotropes, irritant solutions, total parenteral nutrition and for haemodynamic monitoring. The average central line utilisation ratios in the ICUs across 45 countries were reported at 0.525 (Rosenthal et al., 2021). CVC usage is associated with complications, including central line-associated bloodstream infections (CLABSIs).

The rate of CLABSI is reported at 4.45 per 1000 central line days in ICUs across 45 countries from 2013 – 2018 (Rosenthal et al., 2021). This in turn, is translated to increased healthcare costs and mortality. One of the strategies to reduce the incidence of CLABSI is the use of antimicrobial-impregnated CVCs. These antimicrobial-impregnated CVCs, which can be coated with either antibiotics (e.g. rifampin, minocycline, etc.) or antiseptics (e.g. chlorohexidine, silver sulphadiazine, benzalkonium chloride, etc.) or both, are proposed to be able to reduce the incidence of CLABSI by inhibiting microorganism colonisation on CVCs. A meta-analysis published in 2018 concluded that antimicrobial-impregnated CVCs were significantly effective in reducing CLABSIs and catheter colonisations (Wang et al., 2018). Nevertheless, its efficacy and beneficial effects, particularly in terms of patients' outcome had not been homogenously demonstrated across literature. Moreover, antimicrobial-impregnated CVCs are more expensive compared to non-impregnated ones, and hence its cost-effectiveness remains doubtful.

To date, in our local setting, no study evaluates the efficacy and economic impact of antimicrobial-impregnated CVCs and on patients' outcome. Cost-effectiveness evaluation is important to provide value-based care in clinical practice. This study aims to evaluate the clinical and economic treatment of antimicrobial-impregnated CVCs vs Non-impregnated CVCs in prevention of CLABSI.

1.1 Research Questions

1. Is there any difference in central line-associated bloodstream infection (CLABSI) rates between patients using antimicrobial-impregnated central venous catheters (CVCs) and non-impregnated CVCs in Malaysia adult Intensive Care Unit (ICU)?

2. Does the use of antimicrobial-impregnated central venous catheters (CVCs) in central line-associated bloodstream infection (CLABSI) prevention in Malaysia adult Intensive Care Unit (ICU) affect patient length of stay when compared to non-impregnated CVCs?
3. Does the use of antimicrobial-impregnated central venous catheters (CVCs) in central line-associated bloodstream infection (CLABSI) prevention in the adult Intensive Care Unit (ICU) setting affect healthcare costs when compared to non-impregnated CVCs?
4. How antimicrobial resistance features of the bacteria causing central line-associated bloodstream infection (CLABSI) may differ in patients using antimicrobial-impregnated central venous catheters (CVCs) compared to non-impregnated CVCs?

2. OBJECTIVES

Primary objective:

- To compare the incidence of central line-associated bloodstream infection (CLABSI) rate in patients using antimicrobial-impregnated central venous catheter (CVCs) and non-impregnated CVCs in Malaysia adult Intensive Care Unit (ICU)

Secondary objectives:

- To determine the length of stay of patients using antimicrobial-impregnated central venous catheter (CVCs) vs non-impregnated CVCs in Malaysia adult Intensive Care Unit (ICU)
- To undertake a cost-effectiveness analysis in prevention of central line-associated bloodstream infection (CLABSI) between patients using antimicrobial-impregnated central venous catheters (CVCs) and non-impregnated CVCs in Malaysia adult Intensive Care Unit (ICU)
- To compare the antimicrobial resistance features of the bacterial species that caused central line-associated bloodstream infection (CLABSI) between patients using antimicrobial-impregnated central venous catheter (CVCs) and that of non-impregnated CVCs in Malaysia adult Intensive Care Unit (ICU)

3. METHODOLOGY

3.1 Study Location

The study will be conducted in the adult Intensive Care Unit (ICU) of Universiti Malaya Medical Centre (UMMC), which is a mixed medical/surgical ICU.

3.2 Study Period

The study will be conducted over a period of one year.

3.3 Study Design

The study will be conducted as a randomised-controlled trial.

3.4 Study Population

Inclusion criteria:

- Patients aged 18 years old and above who are admitted to the ICU of UMMC during the study period
- Patients who require a CVC during ICU stay

Exclusion Criteria:

- Patients who refuse to participate in the study
- Patients with known hypersensitivity reaction to CVC materials
- Patients with pre-existing diagnosis of central line-associated bloodstream infection (CLABSI) upon admission to the ICU
- Patients with pre-existing bloodstream infection upon admission to the ICU
- Patients with a pre-existing CVC, where sterility during placement may be compromised (e.g. in an emergency situation)
- Patients with indwelling CVC less than 48 hours
- Patients who had poor compliance to catheter bundle care during CVC handling throughout the indwelling catheter period
- Patients who require > 1 CVC or other central venous access

3.5 Sampling Method

All adult patients who require a CVC insertion as part of their standard routine treatment in ICU will be recruited. After the recruitment, the patients will be randomly assigned to one of the two different groups using a computer: control group who receives non-impregnated CVC and investigational group who receives antimicrobial-impregnated CVC.

3.6 Sample Size

Our local data at ICU, UMMC reported the incidence of CLABSI per 1000 catheter days in the first 6 months of 2022, to be 12.18. Using SAS® for sample size calculation, in order to detect a clinically significant reduction of CLABSI by 30%, and assuming a two-sided type I error protection of 0.05 and a power of 0.80, we calculated a sample size of 50 patients is required. To incorporate a 10% drop out rate, we therefore aim to recruit 55 patients in each arm (antimicrobial-impregnated CVCs, n=55; non-impregnated CVCs, n=55). This will make up to a total sample size of 110.

3.7 Variables/ Parameters

3.7.1 Dependent Variables

3.7.1.1 Primary Outcome

The primary outcome investigated is the central line-associated bloodstream infection (CLABSI) rate, expressed in cases per 1000 catheter days. The diagnosis of CLABSI will be based on the CDC-NHSN definition.

3.7.1.2 Secondary Outcomes

The secondary outcomes investigated included:

i. ICU Length of stay of patients diagnosed with CLABSI
ii. Healthcare costs of patients diagnosed with CLABSI
iii. Antimicrobial resistance profiles of the bacterial species isolated from patients diagnosed with CLABSI

3.7.2 Other Parameters

Baseline patient data will be included as concomitant study parameters. Relevant patient and clinical data including basic demographic information (age, gender, and ethnicity), known underlying diseases, previous antibiotic exposure within 90 days, and admission date will be extracted from the clinical database for correlation and risk factor analyses.

For patients diagnosed with CLABSI, information including the number of days a patient spent in the hospital prior to strain isolation, number of days and type(s) of antibiotics used in said patient, hospital-generated antibiograms for each strain, patient risk factors for nosocomial infection associated with an isolate, previous surgeries or hospitalizations of the patient prior to isolation, location of a patient within the hospital prior to strain isolation and ICU admission, and any other information pertinent to a specific strain that will not identify a patient will be collected.

3.8 Data Collection

3.8.1 Clinical and patient data collection

A form comprising all study parameters will be prepared for data recording and collection. The data will be collected and handled confidentially by the investigators.

3.8.2 Bacterial strains collection and molecular assays

For patients who develop CLABSI during their ICU stay, routine blood culture will be obtained and processed at the Medical Microbiology Diagnostic Laboratory, UMMC to identify the bacterial species. Bacterial species identification and antimicrobial susceptibility testing will be conducted using an automated VITEK 2 system (bioMerieux, Marcy-l'Etoile, France), according to standardized protocols. All bacterial strains will be transported to the bacteriology research laboratory at the Department of Medical Microbiology, Faculty of Medicine, UM for further molecular analyses. Polymerase chain reaction (PCR) assays will be conducted to further confirm the identity and genotypes of the bacterial isolates and to determine the antimicrobial resistance-conferring genes that corresponded to the antimicrobial resistance phenotypes of the isolates. Established primer sequences from previous studies will be adapted and PCR assays will be performed using optimized laboratory protocols (Ngoi et al., 2021; Muhamad et al., unpublished data). No additional biological samples will be taken in addition to routine practice and no additional invasive procedures will be performed on the study participants. Hence, there will be no added potential harm to the study participants. The costs for further molecular analyses will be covered by the grant and will not be borne by the patients.

3.9 Data Analysis

The data will be analysed using the SPSS Software. Descriptive statistics will be expressed as percentages unless otherwise stated. Categorical variables will be expressed as percentages and compared using the Chi-square or Fisher's exact test, whichever is appropriate. Variables with a univariate test value of less than 0.05 (p-value) will be included in a multivariate analysis using a logistic regression model. Odds ratios (OR) and 95% confidence intervals (CI) will be calculated to identify the risk factors associated with the development of CLABSI in patients. In all instances, a p-value of less than or equal to 0.05 will be considered significant.

FUNDING

This study will be funded by Teleflex Research Grant (RM50000).

RESEARCH DATA MANAGEMENT

All data collected will be handled confidentially according to the Good Clinical Practice Guidelines. The paper case report forms will be stored within a locked cabinet at the Department of Anaesthesiology, Faculty of Medicine, Universiti Malaya. The electronic case report forms will be kept in a password-protected laptop. Only the study investigators will have access to the research data. The data will be kept for seven years upon completion of study. The results of the study will be reported in a thesis. The results will also be presented in conferences and published in scientific journals.

POTENTIAL RESEARCH IMPACT

The usage of antimicrobial-impregnated central venous catheters (CVCs) among adult critically ill patient in the Intensive Care Unit (ICU) can reduce central line-associated bloodstream infections (CLABSIs) and this will translate to reduced patients' length of stay and healthcare costs.

GANTT CHART

	2023										2024											
Research Activities	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Ethics submission																						
Patient recruitment																						
Data collection																						
Data analysis																						
Completion and submission of manuscript																						
Publication and scientific presentations																						

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