

National Taiwan University Hospital

Hsinchu Branch

Research Protocol 2018

1. Project name

Title	Prevalence and Outcomes of Peripheral Artery Disease in Sepsis Patients in the Medical Intensive Care Unit
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2. Abstract

Background

The peripheral artery disease (PAD) has been well known for poor cardiovascular outcomes. Its prevalence is high in the elderly, in the diabetic patients, and in the patients receiving hemodialysis. To date, there is no guideline recommendation about screening of PAD in patients admitted to the medical intensive care unit (MICU) for sepsis.

Methods

We designed a prospective cohort study focusing on patients admitted to the MICU with the main diagnosis of sepsis. The ankle-brachial indexes are performed within 4 hours after admission. Invasive arterial line monitoring and standard non-invasive measurements are collected. After confirmation of PAD, standard anti-platelet treatments (aspirin and cilostazol) are initiated. The survival before and after the conduction of this trial is compared to historical records. The outcomes including all-cause mortality, stroke, myocardial infarction, minor amputation, major amputation, and prolonged ventilator dependent are to be collected.

Keywords: peripheral vascular disease, sepsis, outcomes

3. Background

Prior research in this field

Sepsis and peripheral artery disease

According to annual statistics, the sepsis cost 5.2% in 2011 medical cost in the United States. Total \$20 billions were cost for treatment of sepsis and its related medical conditions.¹ In Taiwan, the medical expenditure of patients in the medical intensive care units also is very huge. The peripheral artery disease (PAD) is also prevalent in the elderly and in most situations under-diagnosed. In Taiwan, an accurate data on PAD prevalence is absent. According to the screening program in National Taiwan University Hospital Hsinchu branch, the prevalence of PAD among patients receiving hemodialysis is high (48–30%). Many patients do not receive screening and adequate care.

Peripheral artery disease- its impact on the outcomes

Patients with PAD have four-fold increase in the risk of myocardial infarction and three-fold increase in the risk of stroke.^{2,3}

Medications for treatment of PAD

LEAD (lower extremity artery disease) is a subset of PAD. To date, there is no specific trial addressing the role of antiplatelet agents in the full spectrum of LEAD, including asymptomatic, intermittent claudication, and critical lower limb ischemia.

COMPASS ⁴	Rivaroxaban 5 mg bid Rivaroxaban 2.5 mg bid with aspirin Aspirin	Total 27402 patients with CAD or LEAD	To be reported
CAPRIE ²	Clopidogrel Aspirin		Not focused on PAD
CASPAR ⁵ CHARISMA ⁶	Clopidogrel plus aspirin Aspirin mono-therapy		Not focused on PAD
Fowkes, 2010 ⁷	Aspirin for subclinical LEAD	Asymptomatic LEAD with ABI < 0.95	No benefit
Belch, 2008 ⁸	Aspirin for subclinical diabetic LEAD	Asymptomatic LEAD in diabetic with ABI < 1.0	No benefit
Antithrombotic collaborative ⁹	Aspirin for prevention of MACE	Symptomatic LEAD	Benefit

Clinical needs

There are guidelines for treatment of sepsis and PAD. The diagnosis, treatment, and outcomes are well defined for sepsis and PAD, respectively. However, there is no consensus on the benefit of screening of PAD in patients presented with sepsis. The current diagnosis and treatment are clinically driven by patient's new change in limb physical examinations. Usually, we initiate the work-up for PAD after toe cyanosis or frank gangrene occurs.

4. Previous studies focusing on PAD in sepsis patients

There is a lack of dedicated research of PAD among patients presented with sepsis. With the search term “peripheral artery disease” and “critical care”, there is only one article on PAD and chronic obstructive pulmonary disease”.¹⁰

5. Goals of project

Purpose (for clinicaltrials.gov registration)

- Study type: interventional
- Study Design:
 - Allocation: randomized - Endpoint classification: efficacy study - Intervention model: parallel - Masking: single blind (outcomes assessor) - Primary purpose: treatment
- Official title: as the study project title

Objectives

1. Perform a screening for PAD among patients admitted to the medical intensive care units and meet the sepsis diagnosis criteria (quick SOFA score ≥ 2 points).
2. Follow the outcomes (all cause mortality at 30 days, stroke, myocardial infarction, lower limb ischemia requiring amputation) of patients who have evidence of ABI < 0.9 or PAD by additional vascular Duplex confirmation.
3. To evaluate the prevalence of PAD among patients admitted to our intensive care units.
4. To obtain the diagnosis of PAD early on the admission day among multiple care teams (cardiologists, chest physicians, and critical care specialist) and to give adequate medical treatment as needed (anti-platelet agents).
5. To evaluate whether early diagnosis of PAD in sepsis patients will lead to decision-makings that will influence the patient's survival.
6. To evaluate whether early diagnosis of PAD will lead to decreased complications rate of invasive arterial line monitoring.

6. Methods and procedures

Research design

1. Research design: prospective cohort study
2. Locations: the medical intensive care units (MICU) of National Taiwan University Hospital, Hsinchu Branch.
Patient population: sepsis patients who meet the quick SOFA score ≥ 2 points.
3. The investigator is responsible of this research: Dr. Mu-Yang Hsieh.
4. Study parameters:
 1. The prevalence of PAD among patients admitted to the MICU with sepsis
 2. The outcomes of PAD patients presented with sepsis to the MICU
5. Research field: critical care medicine, cardiovascular disease, peripheral artery disease
6. Keywords: peripheral artery disease, sepsis
7. Study design: observational study (cohort study)
 1. Collection of data: prospective
 2. Inter rim analysis: yes
 3. Investigator manual: yes

2. Study population

1. Patient number: 200 patients
2. Age limitation: 20-100 years old
3. Inclusion criteria:
 1. Admission diagnosis with sepsis, meeting quick SOFA criteria ≥ 2 points (respiratory rate $\geq 22/\text{min}$, altered mentation, systolic blood pressure $\leq 100 \text{ mmHg}$, each item is one point)
 2. Within the study age limitation
 3. Willing to participate the study
4. Exclusion criteria:
 1. Declined to participate
 2. Children and adolescence with age < 20 years, criminal, aboriginal, pregnant women, psychiatric patient, students, colleagues, terminal patients, soldiers,
 3. Cancer and receiving cancer treatment
5. Follow-up period: 3 months
6. Category of study: MICU study
7. Special conditions
 1. No selection by patient gender
 2. No involvement of fetal or pregnancy study of medications
 3. No involvement of healthy volunteer

4. Special protection: MICU patients have ethical committee for palliative care, every patients will have family conference by care team with the family to provide diagnosis explanation, treatment options at the bedside or the meeting room. Palliative care can be initiated anytime.
5. There is no radiation exposure in this study
8. No blood sampling
9. Enrollment procedure
 1. No additional fund will be provided to the participant
 2. The enrollment began when the patient was admitted to the MICU
10. The risk of patients is considered equal either joining in or not in the study
11. There is NO control group in this study

3. Patient information security

1. The data security team of the hospital secures the patient data. The data is located in the REDCap database and secured by the Medical Information Team of the hospital.
2. The researcher can only download de-identified data from the REDCap database (redcap.hch.gov.tw). Only the principal investigator can obtain the full dataset.
3. The following protocols are provided to protect the patient personal information:
 1. The patients can withdrawal the consent anytime. The data will be removed on patient or family's request.
There will be no compromise in the physician-patient relationship.

4. Enrollment

1. The enrollment process involves the investigator, the physicians and the nurses in the MICU.
2. Timing of enrollment: before screen process: at the entrance/meeting room of the MICU, at the time of patient admission, with oral explanation of the study intent and study method (ABI measurements), estimated time of explanation: 5 minutes
3. After the oral consent obtaining, the ABI results will be provided and explained to the family
4. Patient not speaking local language (Chinese, Taiwanese, Hakka Chinese) can still be enrolled, if physician can still communicate with English. If the communication is unsuccessful, the patient will no be enrolled.

5. Inform consent

1. This research will not require a paper inform consent. Because this study has minimal risk for the study participant- the ABI study was non-invasive. And this study will be carried in the medical intensive care units, it is focused on emergency medicine. The patients with sepsis admitted to the MICU usually are already in a critical condition and there is a need to aggressively diagnose any disease that will lead to poor outcomes. The benefits of diagnosing a PAD early outweigh the risk carried by the study method.

6. The study method

1. After enrollment, within 24 hours: the nurse will measure the ankle-brachial index (ABI). The measurements are to be done by A-line at any arteries that physician considered appropriate and additional bilateral lower limb blood pressure measurements. A Doppler scanner is allowed to be used to facilitate the measurement of ABI.
2. The definition of ABI (ankle-brachial index): the leg systolic blood pressure divided by the higher readings of bilateral brachial artery. If ABI < 0.9, a diagnosis of PAD is made.

7. The follow-up

1. At the time of admission: APACHE score
2. The treatment patient received: ventilator, vasopressor, inotropic agent, blood pressure, and the diagnosis.
3. Patient will be followed at 7 days, 30 days, and 90 days.
4. Medications will be recorded, especially: aspirin (Bokey), cilostazol (Pletal), clopidogrel (Plavix), statin.
5. Clinical events will be documented:
 1. Mortality
 2. Acute myocardial infarction
 3. Stroke, ischemic
 4. Limb gangrene resulting in amputation

8. Statistical method

1. We plan to enroll 200 patients. Patients will be grouped into patients with PAOD and patients without PAOD. We then compare them in the following parameters: clinical data, laboratory data, survival and other outcome data. Two-sample student's t tests will be used for the comparisons of continuous variables. Chi-square test will be used to detect difference between categorical variables. Difference is considered statistically significant if $P < 0.05$. All statistics works were analyzed using the SPSS 17.0 software (Chicago, IL, USA), R software (Gimc packages).

7. Anticipated results

1. Evaluate the care process and quality in patients in the MICU
2. Evaluate the prevalence of PAD in patients with sepsis admitted to the MICU
3. Investigate the influence of PAD to the outcomes of sepsis
4. Evaluate the intervention with ABI measurement efficacy: will it decrease the mortality after adequate screening?

8. Study progress plan

9. Assignment of Researcher

Category	Name	Position	Actual role or contribution to the research project
Principal investigator	Mu-Yang Hsieh	Attending physician, Cardiovascular division, NTUH Hsinchu Branch	Research design, data analysis, report writing
Research staff	Mong-Lan Teng	Head nurse, MICU, NTUH Hsinchu Branch	

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