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Contribution of the Pre-Hospital Blood Lactate Level in the Pre-Hospital Orientation of Septic Shock: The LAPHSUS Study

Romain Jouffroy[1], Jean Pierre Tourtier[2], Guillaume Debaty[3], Vincent Bounes[4], Papa Gueye-ngalgou[5], Benoit Vivien[1]

[1]Intensive Care Unit, Anesthesiology, SAMU, Necker Enfants Malades Hospital, Assistance Publique - Hôpitaux de Paris, Paris, France
[2]Fire Brigade of Paris, Paris, France
[3]Department of Emergency Medicine, SAMU 38, University Hospital of Grenoble Alps/CNRS/TIMC-IMAG UMR 5525, Grenoble, France
[4]Department of Emergency Medicine, SAMU 31, University Hospital of Toulouse, Toulouse, France
[5]SAMU 972 CHU de Martinique Pierre Zobda -Quitman Hospital 97261 Fort-de-France Martinique, France

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Abstract

Objective: In the pre-hospital setting, the assessment of septic shock severity is essential when determining the optimal initial in-hospital level of care. As clinical signs can be faulted, there is a need for an additional component to enhance the severity assessment and to decide on in-hospital admission in the intensive care unit (ICU) or in the emergency department (ED). Point-of-care medical devices by yielding blood lactate value since the pre-hospital setting may give an easy and valuable component for the severity assessment and decision-making. The aim of this study is to provide clinical evidence that the pre-hospital blood lactate level predicts the 30-day mortality in patients with septic shock.

Methods: This trial is a prospective, observational, non-randomised controlled study. A total of 1,000 patients requiring a mobile ICU intervention for septic shock in the pre-hospital setting will be included. Pre-hospital blood lactate levels will not be taken into account to decide patients' treatments and/or ED or ICU admission. In the pre-hospital setting, each patient will benefit from two measurements of the blood lactate level: initial measurement at the first contact, and final measurement at the hospital admission with a specific point-of-care medical device.

Conclusion: This study could provide clinical evidence that the pre-hospital blood lactate level predicts the 30-day mortality of patients with septic shock. The results from this study could also prove the utility of the pre-hospital blood lactate level for the triage and early orientation of patients with septic shock.

Keywords: Blood lactate, pre-hospital setting, prediction, septic shock, severe sepsis.

Introduction

In the pre-hospital setting, an evaluation of the sepsis severity is fundamental when making a decision on hospital admission in the emergency department (ED) or in the intensive care unit (ICU). The evaluation is based on the anamnesis and clinical signs aiming to look for severity criteria. This evaluation also determines the orientation between the ED and the ICU. Patients without severity criteria are referred to the ED, whereas sicker patients, or those at risk of deterioration, are directly admitted in the ICU.

To date, in France, the decision-making has been based on clinical signs of severe sepsis and/or septic shock according to the French SFAR-SRLF conference 2005 (1). Usual severity scores, SOFA (2), IGS II (3) and SAPS II (4), have been validated only in the ICU. Thus, these scores are not transposable to the pre-hospital setting.

Septic shock induces a decrease in the transport of oxygen to the tissues and an increase in the peripheral extraction of oxygen. When this phenomenon is outdated, oxygen partial tissue pressure decreases below the aerobic thresh-

Corresponding Author: Romain Jouffroy E-mail: romain.jouffroy@gmail.com

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old, guaranteeing the production of tri-phosphate adenosin (ATP) by the Krebs cycle. Thus, the ATP production is based on the sole anaerobic pathway: the lactate pathway. This last pathway produces only eight ATP molecules (against 36 for aerobic glycolysis) and is characterised by the production of lactic acid (or lactate). Septic shock is associated with an increase in the lactic acid level, reflecting the inability of the circulation to provide suitable oxygen transport. It has been observed that the blood lactate level reflects the depth and the duration of hypoxia (5). The relationship between an increased blood lactate level and mortality of septic shock has been well established in the ICU (6-15).

Moreover, the kinetics of the blood lactate level during the first hours, also called the clearance between two times T0 and T1, and defined by [(Lactate T1−Lactate T0)/Lactate T0]/delay T1-T0), constitutes an independent prognostic factor of mortality (5, 8, 9, 16-18). This clearance also provides prognostic information; therefore, the blood lactate normalisation time is also a recognised prognostic factor of mortality (19, 20).

The aim of this study is to provide clinical evidence that pre-hospital blood lactate level predicts the mortality on Day 30.

Methods

This is a prospective, observational, non-randomised controlled study. We will perform the study according to common guidelines for clinical trials (Declaration of Helsinki, International Conference on Harmonisation and the World Health Organisation's Good Clinical Practice standards, including the certification by an external audit).

The trial protocol has been approved by the French ethics committee Paris Ile de France 2 (Reference: CPP 2015-08-03 SC) and the National Heart Agency (ID RCB number: 2015-A01068-41) on 2006/15/19. *The trial is registered on Clinical Trial (NCT03831685).*

Population

In France, out-of-hospital emergencies management is organised around the Service d'Aide Médicale d'Urgence (SAMU), equivalent to the emergency medical service. The SAMU hospital-based team is composed of dispatch operators and physicians. Over the phone, the physician determines the appropriate level of care to dispatch to the scene, based on patient's symptoms communicated by the patient itself, by a relative or a witness. For life-threatening emergencies, a mobile intensive care unit (MICU), composed of a driver, a nurse and an emergency physician, is dispatched to the scene. MICU is equipped with medical devices and drugs allowing initial management of main organs deficiency (neurological, respiratory and cardiovascular) (21).

Patients with pre-hospital septic shock requiring a MICU intervention will be recruited by the MICU physicians of the following hospitals: Necker enfants malades Hospital, Assistance Publique Hôpitaux de Paris, Paris-France; Fire Brigade of Paris, Paris-France, University Grenoble Hospital, Grenoble-France; University Toulouse Hospital, Toulouse-France; Lariboisière Hospital, Paris-France with a target sample size of 1,000 subjects.

The purpose of the study will be explained to the patients or their relatives to obtain their consent prior to the inclusion. An information form will be provided to the participants or their relatives.

Participants will be able to withdraw from the study at any time without consequences. The trial will be executed from April 15th, 2017, to April 15th, 2019. All recruit procedures will be recorded in a computer file.

Inclusion criteria

Patients with septic shock in the pre-hospital setting requiring MICU intervention and meeting the following criteria will be consecutively included:

1. Age >18 years either sex
2. Severe sepsis according to the French SFAR-SRLF conference 2005 (1) defined by the existence of an infectious disease and at least one the following:
    * Low blood pressure prior to volume expansion
    * Glasgow coma scale <13
    * Skin mottling score >2
3. Septic shock according to the French SFAR-SRLF conference 2005 definition (1)

Non-inclusion criteria

Patients meeting one or more of the following criteria will not be included:

1. Age <18 years
2. Pregnancy
3. Serious comorbid conditions with a not-to-be-reanimated status known since pre-hospital setting
4. Patients with guardianship or curatorship

Interventions

The MICU physician will include patients who meet the inclusion criteria and none of the non-inclusion criteria during the pre-hospital stage. Two venous blood samples will be performed to assess blood lactate levels, e.g. at the first medical contact, and the final blood lactate level, e.g. at the hospital admission. Both the measurements will be performed using

the same specific point-of-care medical device (StatStrip Lactates, Nova Biomedical, Waltham, MA, USA).

The initial blood lactate level value will not be taken into account to decide the treatment and/or in the decision-making regarding the ED or the ICU admission.

Outcome measure
The primary endpoint is the mortality 30 days after hospital admission. The secondary endpoints are the in-ICU and in-hospital length of stay, the duration of mechanical ventilation, catecholamine infusion and haemodiafiltration.

Safety
In this study, no intervention or treatment will be decided on the pre-hospital blood lactate level. The treatments provided, whether in the pre-hospital setting and in-hospital, will not depend on the pre-hospital blood lactate level.

Sample size
The expected mortality rate is 30%. The lack of preliminary data did not allow us to perform the sample size calculation.

Due to the prospective design of this observational study, we plan to enrol a total of 1,000 patients considering the 2% of missing data with regard to the primary endpoint.

Statistical analysis
Descriptive statistics will be used to describe the demographic and baseline characteristics of study participants. The predictive ability of the pre-hospital blood lactate level on mortality will be assessed by the ROC curve methodology. Thereafter, the predictive ability of pre-hospital blood lactate level and pre-hospital lactate clearance will be assessed by multiple logistic regressions. The results will be expressed as the odds ratio with 95% confidence intervals.

The accepted level of significance for all analyses will be $p<0.05$. The data analysis will be performed by independent statisticians from the research team. An analysis will be conducted using the R 3.4.2 software (www.R-project.org; the R Foundation for Statistical Computing, Vienna, Austria).

Discussion

To the best of our knowledge, this study is the first prospective observational non-randomised clinical trial to assess the ability of the pre-hospital blood lactate level to predict the Day 30 mortality in patients with severe sepsis and/or septic shock.

Demonstration of a relationship between the pre-hospital blood lactate level and Day 30 mortality of patients with septic shock will be helpful to define, since the pre-hospital setting, the appropriate level of care between the ED or the ICU. It will earn valuable minutes during the first 'golden hours.' The reclassification resulting from the integration of the blood lactate level into the decision-making will also be helpful to improve the patient's flow avoiding the under-and over-triage. The results of this study will provide a new evidence for the relationship between the pre-hospital clearance of lactate. The pre-hospital lactate clearance may, thereafter, be useful to assess the impact of pre-hospital medical cares on mortality.

This study aims to provide a simple, reliable and non-invasive tool for the triage and early orientation of patients with septic shock.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Paris Ile de France 2 (Reference: CPP 2015-08-03 SC).

Informed Consent: Written informed consent will be obtained from patients and patients' parents who will participate in this study.

Peer-review: Externally peer-reviewed.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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