STUDY PROTOCOL

Pre-hospital early goal directed therapy for septic shock

Samu Save Sepsis - Study

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For the Samu Save Study group

Abstract

Background:

The major prognostic factor in the management of septic shock is the rapidity of the implementation of the effective treatments. To date, 2 early treatments are effective: hemodynamic optimization and antibiotherapy. In France, out of hospital emergencies are managed by the SAMU, corresponding to the emergency medical service. SAMU can dispatch a mobile intensive care unit (MICU) in order to manage the main organs deficiencies since the pre-hospital setting. The management of septic shock by the MICU in the pre-hospital setting is based on fluid volume expansion and oxygenation. Purpura fulminans is the sole situation where antibiotherapy is given without prior blood culture sampling.

The aim of this study is to provide clinical evidence that an "aggressive" strategy, including hemodynamic optimisation and antibiotherapy, instituted during the first 60 minutes in the pre-hospital setting reduce 30 day-mortality of patients with septic shock.

Methods/Design:

This trial is a multi-centric open label, cluster-randomized controlled study.

The study compares 2 strategies of care: one conventional and one “aggressive”.

A total of 550 patients, 275 per arm, with septic shock requiring MICU intervention in the pre-hospital setting will be included. 22 centres, 11 per arm, will participate to the study. Each centre will be allocated to one arm during the whole study (no cross-over).

The primary outcome is the mortality 30 days after hospital admission.

Intervention:

Patients who meet the inclusion criteria and none of the non-inclusion criteria will be included in the pre-hospital setting. In the conventional arm, cares are leaded to the physician discretion. Conversely, in the “aggressive “arm, during the first 60 minutes, the patient will receive antibiotherapy and hemodynamic optimisation (fluid volume expansion and norepinephrine if required) with a target of mean blood pressure of 65mmHg.

Discussion:

It is expected that the "aggressive" strategy in the first 60 minutes in the pre-hospital setting will allow a decrease of 28- and 90 days mortality, as well as the duration of mechanical ventilation and catecholamine’s supports, in-ICU and in-hospital length of stay.

Trial registration: French ethics committee Paris Ile de France 2 on 2015/07/06 and the National Heart Agency (ID RCB number: 2014-A01030-47) approved the protocol on 2015/06/19.

Trial registration: Clinical Trial Number Register: NCT02473263

Keywords: Septic shock, pre-hospital, strategy, optimization, mortality.

Background

Sepsis is a major public health issue with an estimated incidence of 240 per 100 000 inhabitants in the United States (1). The increase of 90% in 10 years observed since 1990 is related to the aging of the population and a greater use of immunosuppressive therapies and invasive devices.

The epidemiology of sepsis, its impact on morbidity and its therapeutic management has been well studied in intensive care unit (ICU) (1 - 9). Most of the time sepsis comes from respiratory tract (50%), from digestive tract (25%) and rarely from urinary tract (5%). Sepsis related mortality remains high, around 30% at 28 days (10, 11) with a 40% overall mortality. The median length of stay is 10-15 days in ICU. For patients surviving to sepsis; the median in hospital length of stay often extends beyond one month. Therefore, sepsis costs are extremely high.

To date, the major prognostic element is the early recognition preceding effective treatment's initiation (12). Rivers et al. observed a significant decrease of mortality using an "aggressive" hemodynamic strategy aiming to early restore tissue perfusion (13).

In France, the management of out-of-hospital emergencies is based on the Service d'Aide Médicale d'Urgence (SAMU) corresponding to the emergency medical service. The SAMU hospital-based team is composed of switchboard 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) (14). To date, the pre-hospital management of septic shock by MICU is still "conventional" based on fluid volume expansion and oxygenation. Antibiotherapy is only given in the presence of purpura

fulminans, without microbiological sampling.

The impact on mortality of a pre-hospital "aggressive" strategy based on hemodynamic optimization and antibiotic therapy, established during the first 60 minutes has never been evaluated.

The aim of this study is to provide clinical evidence that an "aggressive" strategy compared to "conventional" strategy allow a significant mortality decrease.

Methods/Design:

This trial is a multi-centric open label, cluster-randomized controlled study.

The study aims to compare 2 strategies allocated to the conventional arm or to the aggressive arm.

A total of 550 patients, 275 per arm, with septic shock requiring MICU intervention in the pre-hospital setting will be included.

Twenty-two centres, 11 in each arm, will participate to the study.

Each centre will be allocated to one arm during the whole study (no cross-over) after randomisation prior the beginning of the study.

The primary outcome is the mortality 30 days after hospital admission.

French ethics committee Paris Ile de France 2 on 2015/07/06 and the National Heart Agency (ID RCB number: 2014-A01030-47) on 2015/06/19 approved the trial protocol.

This trial was registered with the Clinical Trial Number: NCT02473263.

Population

Patients with pre-hospital septic shock requiring MICU intervention will be recruited by the MICU physicians of the following hospitals: Fire Brigade of Paris, Paris – France; SAMU 75 - Necker enfants malades Hospital, Assistance Publique Hôpitaux de Paris, Paris – France; SAMU 75 - Pitié Salpétrière Hospital, Assistance Publique Hôpitaux de Paris, Paris – France; SAMU 75 - Hotel

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The previous 22 centres will be sampled before the beginning of the study, in 11 centres allocated to the conventional arm and 11 allocated to the aggressive arm.

The target sample size is 550 subjects: 275 in the conventional arm and 275 in the aggressive arm.

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

Participants will be able to withdraw from the study at any time without consequence.

The trial will be executed from May 09th, 2016 to November 09th, 2018.

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 defined by an infectious disease and at least one the following:
    * Low blood pressure prior to volume expansion
    * Glasgow coma scale < 13
    * Skin mottling score > 2
    * Blood lactate level > 4 $mmol.l^{-1}$
3. Septic shock
4. Patient with health insurance
5. No objection to participate to the research expressed by the patient and/or relatives

Non-inclusion criteria

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

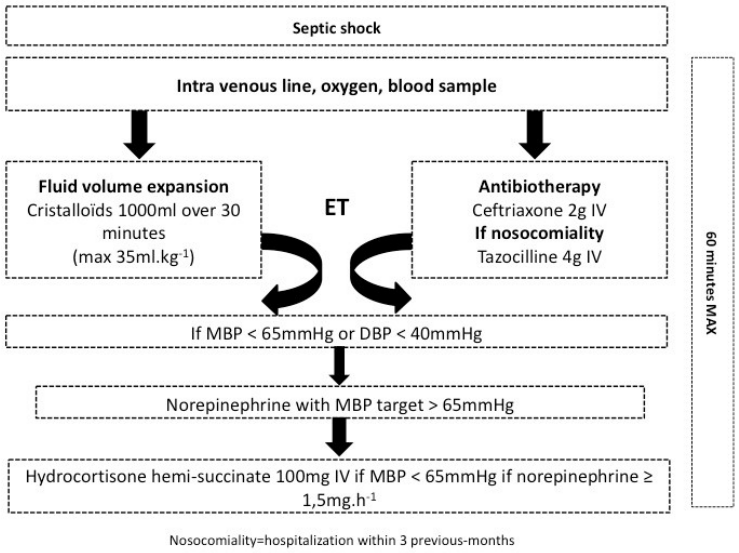
1. Age < 18 years either sex
2. Pregnancy
3. Serious co morbid conditions with a not to be reanimated status known since pre-hospital setting
4. Patients with guardianship or curatorship
5. Purpura fulminans
6. Beta-lactamin allergy
7. Objection to participate to the research expressed by the patient and/or relatives

Interventions

All MICU of a SAMU will perform the same strategy, conventional or "aggressive", during the whole study.

Thus, patients who meet the inclusion criteria and none of the exclusion criteria will benefit form blood culture sampling and thereafter will receive either conventional therapy (fluid volume expansion and oxygenation) either "aggressive" therapy since the pre-hospital setting by MICU during the first 60 minutes.

The "aggressive" therapy consists of antibiotherapy (ceftriaxone 2g for community infection or piperacillin-tazobactam 4g for nosocomiality defined by hospitalization within 3 previous-months) and hemodynamic optimisation based on fluid volume expansion (crystalloids 1000ml with a maximum of 35ml.kg^{-1} over 30 minutes) and norepinephrine if required with a target of mean blood pressure of 65mmHg. If mean blood pressure remains lower than 65mmHg with at least norepinephrine 1.5mg.h^{-1}, a corticosteroid (100mg hydrocortisone hemisuccinate) will be administered (Figure).



Randomization and blinding

To avoid the occurrence of the Hawthorne effect, the methodology of cluster has been chosen.

As the design of the study does not allow blinding, randomization will be performed prior to the beginning of the study.

Primary outcome measure

The primary outcome will be the 28-day mortality.

The mortality will be assessed by a phone-call on day 28 to wards or from medical report. If necessary, a phone call to the patient or relatives will be made.

Secondary outcome measures

Secondary outcomes criteria are:

- The hospital mortality will be evaluated on medical report after leaving the hospital.

If necessary, a phone call to the patient or relatives will be made.

- The 90-day mortality at day 90 will be evaluated by a phone call to wards or from medical reports after leaving the hospital. If necessary, a phone call to the patient or relatives will be made.

- The in-ICU and in-hospital length of stay as the duration of mechanical ventilation, extra-renal and catecholamine's supports will be evaluated from medical records of ICU and/or wards.

Safety

Physician will report any adverse events they experience, including all adverse events related to the study, especially serious adverse events related to treatments administered.

Sample size

We have performed sample size calculations based on ICU statistics relating an average 28-day mortality rate of 30% for septic shock (10, 11). The sample size was calculated, in order to reach 90% power for the demonstration of a 10% (absolute variation) decrease in the 28-day mortality

rate with a bilateral alpha risk of 5%. We hypothesized a 15% reduction in the mortality rate in case of an "aggressive" strategy compared to the conventional strategy.

The average inclusion of each centre is assumed to be near 25 patients over a two-year period.

We plan to enrol a total of 275 patients in each arm.

Data analysis

Descriptive statistics will be used to describe demographic and baseline characteristics of study participants.

The primary outcome will be analyzed using Generalized Estimated Equation (GEE) method taking into account the arm and the centre of allocation.

The accepted level of significance for all analyses will be $p < 0.05$.

Statisticians who are independent of the research team will conduct data analysis.

Discussion

To date, this study is the first open-label cluster randomized controlled clinical trial comparing the efficacy of the instauration of an “aggressive” strategy since the pre-hospital setting for patients with septic shock.

In the management of septic shock, the rapidity of treatments’ instauration is recognized as a major prognostic element. In 2001, Rivers et al. observed the positive impact on mortality of the early hemodynamic optimization (13). In 2009, Arnold et al. observed a further mortality decrease achieved by that by introducing early antibiotherapy (15).

The principle of superiority of an early “aggressive” strategy based on the achievement of predetermined therapeutic objectives, against septic shock remains unclear. This superiority principle is supported by a meta-analysis performed in "high-risk" ICU patients, evaluating the impact of the early cardiac index and / or oxygen transport optimisation compared to a

conventional strategy (16). The positive impact of such a strategy consisting on rapid intervention procedure for the management of patients with shock has been observed in the emergency department as in wards (17).

The results of our study aims to provide a new evidence for the early instauration of an "aggressive" strategy for septic shock since pre-hospital setting.

Trial status

The trial is currently in the recruitment phase.

Funding

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Romain Jouffroy conceived the study and drafted the manuscript.

Jean Paul Mira, Benoit Vivien and Pierre Carli helped to prepare the initial protocol.

All authors read and approved the final manuscript.

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