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The Effect of Non-Invasive Hemodynamic Therapy Guided by Goals on Resuscitation Time in Septic Shock (GENIUS Trial): A Randomized Clinical Trial

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SUMMARY

Title: "The Effect of Non-Invasive Hemodynamic Therapy Guided by Goals on Resuscitation Time in Septic Shock (GENIUS Trial): A Randomized Clinical Trial"

Principal Investigator: Prof. Dr. Ludhmila Abrahão Hajjar

Introduction:

Sepsis is a severe condition where the body responds inadequately to an infection. Septic shock is a subset of sepsis with significantly increased mortality due to severe circulatory and/or cellular metabolism abnormalities. Septic shock involves persistent hypotension (defined as the need for vasopressors to maintain a mean arterial pressure ≥ 65 mm Hg and a serum lactate level < 18 mg/dL [2 mmol/L]) despite adequate fluid resuscitation. Cardiac Output (CO) can be defined as the volume of blood ejected by the left ventricle per minute and is a very useful hemodynamic parameter in monitoring patients with signs of circulatory shock, as it can help define the etiology and manage such patients. Despite this, this parameter is rarely used in patients seen in Emergency Units, as its measurement generally involves invasive methods that are rarely available in this setting.

The pulmonary artery catheter is considered the gold standard in determining CO, but being an invasive method, other devices capable of providing this hemodynamic variable less invasively have been developed over the last decades. Any method capable of providing CO without the need for pulmonary artery catheter insertion is called minimally invasive CO monitoring. The potential advantages of using these methods include easier measurements, faster acquisition of hemodynamic parameters, and the possibility of implementing monitoring strategies in settings such as emergency rooms. The assessment of these parameters allows for quicker determination of the etiology of circulatory shock, enabling early initiation of goal-directed therapy.

It is known that the use of goal-directed therapy has been effective in reducing morbidity and mortality in the perioperative and postoperative periods of high-risk surgical patients; this strategy is also associated with reduced mortality, length of stay in ICU, and mechanical ventilation time in ICU patients who are fluid-responsive. However, there are no data so far regarding the impact of hemodynamic optimization strategies in septic shock patients during the first hours of shock.

Objective:

To evaluate whether goal-directed hemodynamic therapy, through non-invasive hemodynamic monitoring, reduces the time of hemodynamic resuscitation in patients with septic shock.

Methods:

This is a multicenter, randomized, open-label study conducted in Emergency Units, Intensive Care Units, and Wards. Patients over 18 years old who are admitted to the emergency room with signs of septic shock (systolic blood pressure less than 90 mmHg and/or mean arterial pressure less than 65 mmHg and at least one of the following changes: lactate greater than 2 mEq/L, oliguria, neurological alteration, and capillary refill time greater than 3 seconds) and who have signed the Informed Consent Form (ICF) will be included in the study. Included patients will be randomized in a 1:1 ratio into two groups. The Goal-Directed Therapy Group will be monitored by the HemoSphere HPI™ (Edwards Life Sciences, Irvine, CA, USA) in the first 6 hours after randomization, using the parameters cardiac index (CI), stroke volume (SV), systolic blood pressure (SBP), mean arterial pressure (MAP), and HPI to determine medical management; all patients in this group will receive the first dose of antibiotics within the first hour of septic shock diagnosis, along with the infusion of 500ml of crystalloid solution; after this infusion, those with SV less than 35 ml/beat and CI less than 2.2 L/min/m² should receive additional aliquots of crystalloid solution until the SV no longer increases by 10% from the initial value; if after the first fluid infusion the patient presents SV greater than or equal to 35 ml/beat and MAP less than 65 mmHg, a vasoactive drug should be started; if, after achieving hemodynamic stability, the patient develops an HPI value greater than 85%, further aliquots of crystalloid solution and/or adjustments to the dose of the vasoactive drug should be made; patients with SV greater than 35 ml/beat and CI less than 2.2 L/min/m² should be considered for the initiation of inotropic drugs. The Conventional Therapy Group will be assessed with the usual hemodynamic monitoring equipment found in emergency units, with the values of SBP, MAP, oxygen saturation, heart and respiratory rate, in addition to findings from physical examination, being evaluated; all patients should receive the first dose of antibiotics within the first hour of septic shock diagnosis; patients should receive fluid resuscitation with crystalloid solution at a rate of at least 30 ml/kg in the first 3 hours of treatment, and if after this resuscitation the SBP remains less than 90mmHg and/or MAP remains less than 65mmHg, vasoactive

drugs should be started; however, if at the time of septic shock diagnosis the patient presents with SBP< 90mmHg, MAP <65mmHg, or a drop in BP > 40 mmHg, vasoactive drugs such as norepinephrine should be promptly started before fluid resuscitation.

1. INTRODUCTION

Sepsis is a severe condition where the body responds inadequately to an infection. Septic shock is a subset of sepsis with significantly increased mortality due to severe circulatory and/or cellular metabolism abnormalities. Septic shock involves refractory hypotension (defined as the need for vasopressors to maintain a mean arterial pressure ≥ 65 mmHg and a serum lactate level < 18 mg/dL [2 mmol/L]) despite adequate fluid resuscitation.

There are four pathophysiological mechanisms related to the development of circulatory shock. The first is hypovolemia, which leads to a decrease in cardiac output (CO) and consequently reduces tissue oxygen supply due to a decrease in intravascular volume. The second mechanism is cardiogenic, where CO decreases due to reduced left and/or right ventricular contractility or due to a malignant arrhythmia. The third mechanism is obstructive, where CO decreases despite preserved ventricular contractility and euvolemia, caused by cardiac tamponade, pulmonary thromboembolism, or tension pneumothorax. The fourth mechanism is distributive, where there is a decrease in vascular tone, leading to decreased peripheral vascular resistance and poor volume distribution, caused by septic shock, anaphylaxis, or spinal cord injury. These mechanisms may present individually or in combination. CO is defined as the volume of blood ejected by the left ventricle per minute and can be calculated using the formula “Heart Rate x Stroke Volume”. This is a very useful parameter in the hemodynamic monitoring of patients with signs of circulatory shock, as it can help define the etiology and guide the hemodynamic management of patients. Despite this, this parameter is rarely used in patients seen in Emergency Units, as until recently its measurement involved invasive methods that are rarely available in this setting.

Since its first description in 1970 by Drs. Swan and Ganz, the pulmonary artery catheter has been considered the gold standard for measuring CO. However, due to being an invasive method requiring trained professionals for its execution and interpretation, other devices capable of providing this hemodynamic variable in a less or non-invasive way have been developed over the past decades.

Minimally invasive CO monitoring is defined as any technique that provides the parameter without inserting a catheter into the pulmonary artery. Pulse wave analysis is one such method, where algorithms are used to evaluate the characteristics of the arterial

pulse wave, as the shape and speed of the wave depend on various factors, such as vasomotor tone, aortic impedance, and ventricular ejection. This wave can be obtained through the insertion of an arterial catheter or through automatic tonometers located on the fingers and/or radial artery.

By analyzing the arterial pulse wave, it is possible to determine not only CO but also other hemodynamic monitoring parameters (Blood Pressure, Heart Rate, Stroke Volume, Stroke Volume Variation, and Systemic Vascular Resistance) continuously. The potential advantages of non-invasive methods include ease of measurement, quicker skill acquisition, and the possibility of rapidly implementing a monitoring strategy in settings such as emergency rooms.

The evaluation of these different monitoring parameters allows for quicker determination of the etiology of circulatory shock, enabling early initiation of goal-directed therapy, which is defined as a set of measures aimed at preventing tissue hypoxia through well-defined goals of fluid replacement, use of vasopressor and inotropic medications, and blood component transfusion.

It is known that the use of goal-directed therapy has been effective in reducing morbidity and mortality in the perioperative and postoperative periods of high-risk surgical patients, and in reducing morbidity and length of stay in patients undergoing cardiac surgery. This strategy is also associated with reduced mortality, length of stay in ICU, and mechanical ventilation time in ICU patients who respond to fluid replacement. A prospective, international, multicenter study is being conducted to validate the use of a goal-directed hemodynamic strategy in reducing postoperative complications in non-cardiac surgery. The timing of the intervention also appears to be essential for the results of hemodynamic therapy, as Gerent et al. showed that hemodynamic optimization only in the postoperative period, in oncology patients undergoing high-risk surgeries, did not reduce 30-day mortality or severe clinical complications.

There is currently no data regarding the impact of a hemodynamic optimization strategy on patients in the first hours of septic shock.

2. OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective of this study is to evaluate whether goal-directed hemodynamic therapy, using non-invasive hemodynamic monitoring, reduces the time to hemodynamic resuscitation in patients with septic shock.

2.2. SECONDARY OBJECTIVES

1. Identify the number of patients with acute kidney injury within 72 hours;
2. Identify the occurrence of myocardial injury within 30 days;
3. Identify the occurrence of acute myocardial infarction within 30 days;
4. Identify mortality at 30 days and 180 days;
5. Identify the length of hospital stay;
6. Identify the amount of fluid administered, fluid balance, and the amount of vasoactive and inotropic drugs administered at 6, 24, 48, and 72 hours;
7. Identify the cost-effectiveness of therapies;
8. Assess the quality of life of patients after 30 and 180 days of inclusion in the study.

3. STUDY DESIGN

This is a multicenter, randomized, open-label study conducted in Emergency Units, Intensive Care Units, and Wards.

4. INCLUSION CRITERIA

Adult patients who meet the following criteria will be included:

- Age > 18 years;
- Patients admitted to Emergency Units, Intensive Care Units, and Wards within 3 hours of the diagnosis of Septic Shock:
    - Systolic Blood Pressure (SBP) < 90 mmHg and/or Mean Arterial Pressure (MAP) < 65 mmHg (with or without norepinephrine at a dose less than 0.5 mcg/kg/min) + Clinical signs of infection and at least one of the following:
        - Lactate > 2 mEq/L;
        - Oliguria (urine output < 0.5 mL/kg/h for at least 6 hours);

    - Neurological alteration (mental confusion, decreased level of consciousness, psychomotor agitation, temporal-spatial disorientation);
    - Capillary refill time > 3 s (after digital compression for 10 seconds);
    - Poor skin perfusion.
- Signed Informed Consent Form.

5. EXCLUSION CRITERIA

- Hospital admission time greater than 24 hours;
- Significant edema in the fingers;
- Severe peripheral vasoconstriction;
- Use of norepinephrine at a dose greater than or equal to 0.5 mcg/kg/min;
- Presence of significant aortic insufficiency;
- Patients undergoing renal replacement therapy;
- Patients with ST-segment elevation myocardial infarction;
- Patients requiring invasive mechanical ventilation;
- Patients already participating in another study.

6. RANDOMIZATION

Patients who have met the inclusion and exclusion criteria and have signed the Informed Consent Form will undergo randomization.

Randomization will be conducted in a 1:1 ratio into two groups: the Goal-Directed Therapy group and the Conventional Therapy group.

7. PROCEDURES

7.1. NON-INVASIVE CARDIAC OUTPUT MONITORING

Non-invasive cardiac output (CO) monitoring will be performed using the ClearSight™ System (Edwards Life Sciences, Irvine, CA, USA), which continuously provides this hemodynamic parameter by measuring the digital arterial pressure waveform beat-to-beat.

The digital artery pressure is acquired non-invasively using a technique called vascular unloading or “continuous vascular unloading technique,” achieved through a finger cuff placed on the middle phalanx of the second, third, or fourth finger, which utilizes photoplethysmography combined with an external pressurization system. The system's objective is to maintain the blood volume in the vessel constant at the pressure value where the artery oscillation is maximum. The volume variation is detected by measuring the light transmission in an optical system composed of a transmitter and a photodetector positioned opposite each other, with the blood vessel (digital artery) located between them. Volume changes are compensated by the cuff attached to the pressurization system, representing instantaneous arterial pressure. As the blood volume increases/decreases (cardiac systole/diastole), the light transmission decreases/increases, and the cuff pressure increases/decreases, respectively, to maintain the volume constant and the transmural pressure close to zero.

This radial artery pulse wave is transformed into a brachial artery pulse wave through an extensive clinical database within the device's platform, which corrects the pressure gradient that exists between the brachial and digital arteries.

By analyzing the brachial artery pulse wave, the system estimates CO using the hemodynamic version of Ohm's law, demonstrated in the formula $Zin=\Delta P/Q$, where Zin corresponds to the vessel impedance (calculated by peripheral vascular resistance and arterial compliance), ΔP is calculated through systolic blood pressure and the area under the pulse wave curve, and Q is the flow calculated from the previous data.

7.2. TREATMENT PROTOCOL

7.2.1. GOAL-DIRECTED THERAPY GROUP

Patients allocated to the Goal-Directed Therapy group will be monitored using the HemoSphere HPI device (Edwards Life Sciences, Irvine, CA, USA) during the first 6 hours after randomization, which may extend to the first 24 hours of treatment at the discretion of the attending team. The parameters Cardiac Index (CI), Stroke Volume (SV), Systolic Blood Pressure (SBP), Mean Arterial Pressure (MAP), and HPI will be continuously acquired. All patients must receive the first dose of antibiotics within the

first hour after the diagnosis of septic shock, in addition to a rapid infusion (within less than 10 minutes) of 500ml of crystalloid solution.

After this first fluid infusion, patients who present with SV less than 35 ml/beat and CI less than 2.2 L/min/m² should receive additional aliquots of 250ml of crystalloid solution until the SV stops increasing by at least 10% compared to the initial value. If this SV value stops increasing after a new aliquot of crystalloid solution but SBP remains less than 90mmHg and/or MAP remains less than 65mmHg, the use of a vasoactive drug such as norepinephrine should be started.

The treatment goal in this group will be to maintain CI greater than or equal to 2.2 L/min/m², SV greater than or equal to 35 ml/beat, and SBP greater than or equal to 90 mmHg and/or MAP greater than or equal to 65 mmHg. In patients who achieve these goals and develop an HPI value greater than 85%, a new aliquot of 250ml of crystalloid solution and/or a new adjustment in the doses of the vasoactive drug should be administered.

In patients with SV greater than 35 ml/beat and CI less than 2.2 L/min/m², the initiation of inotropic drugs, such as dobutamine, should be considered.

7.2.2. CONVENTIONAL THERAPY GROUP

Patients allocated to the Conventional Therapy group will be monitored using the usual devices found in emergency units. The parameters to be evaluated include invasive or non-invasive blood pressure (depending on the attending team's judgment), heart rate, oxygen saturation, respiratory rate, urine output, and findings from the clinical history and complete physical examination, such as capillary refill time and signs of pulmonary and/or systemic congestion. All patients must receive the first dose of antibiotics within the first hour of septic shock diagnosis.

Patients should receive fluid resuscitation with crystalloid solution, with an infusion of about 30 ml/kg in less than 3 hours. The investigator may evaluate the patient's tolerance and use a lower volume at their discretion. After this resuscitation, for those who still

have refractory hypotension, the use of vasoactive drugs such as norepinephrine should be started (Surviving Sepsis Campaign 3).

The treatment goal will be to maintain SBP greater than or equal to 90 mmHg, MAP greater than or equal to 65 mmHg, heart rate (HR) between 50 and 100 beats per minute, and oxygen saturation greater than or equal to 94%, ideally with perfusion optimization.

Echocardiography will be allowed in both groups, according to the indication of the attending team. It is suggested to maintain hemoglobin levels above 7 g/dl in all study patients, with the prescription of blood components being made at the discretion of the attending team.

7.2.3. SOLUTIONS, DRUGS, AND DILUTIONS USED

The type of solution, vasoactive, and/or inotropic drugs, and dilutions used in patients will be chosen according to the clinical experience of the attending teams. However, the following are suggested:

- Fluid resuscitation**:** administer aliquots of 500 ml or 250 ml of Ringer's Lactate;
- Vasoactive drugs: start with norepinephrine (dilution: 1 ampoule + 100 ml of Normal Saline); if doses greater than 0.2 mcg/kg/min are required, vasopressin may be added (dilution: 1 ampoule + 50 ml of Normal Saline);
- Inotropic drugs: start with dobutamine (dilution: 20 ml + 80 ml of Normal Saline) at a dose of 5 mcg/kg/min.

The dose titrations and medications will be performed periodically by the attending team (suggested every 15 minutes), with the goal of maintaining the hemodynamic parameters at the values established by the protocol.

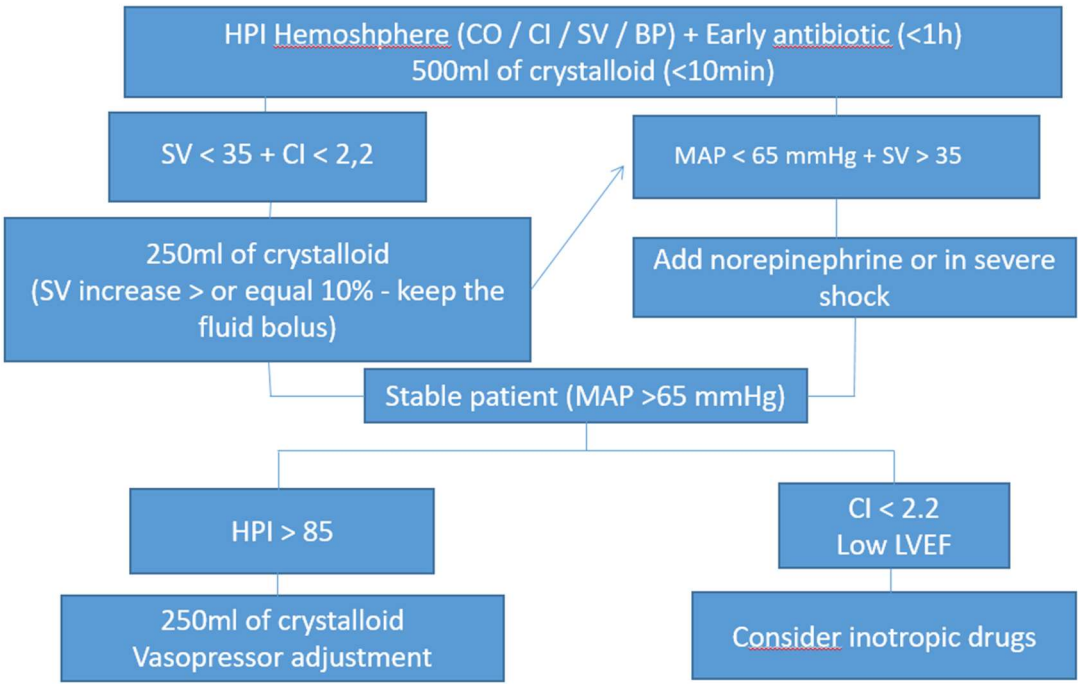

Figure 1: Treatment algorithm for the Goal-Directed Therapy Group. CI: Cardiac Index; SV: Stroke Volume; SBP: Systolic Blood Pressure; MAP: Mean Arterial Pressure.

7.2.4. CLINICAL AND DEMOGRAPHIC DATA ASSESSMENT

The collected data will be stored in an electronic form. At the time of randomization, demographic data, clinical signs and symptoms, personal pathological history, laboratory, and imaging exams from hospital admission will be recorded.

Laboratory tests will be requested and collected according to the attending team, with the following tests suggested at randomization: complete blood count, coagulation profile, C-reactive protein, sodium, potassium, magnesium, ionized calcium, phosphorus, urea, creatinine, AST, ALT, GGT, alkaline phosphatase, total and fractionated bilirubin, albumin, troponin, creatine kinase-MB, creatine phosphokinase, B-type natriuretic peptide, lactate dehydrogenase, D-dimer, lactate, arterial blood gas (pH, pO2, pCO2, bicarbonate, base excess, O2 saturation); after 2 hours and at 6 hours, arterial blood gas and lactate will be collected; after 24 hours, the same tests suggested at randomization; after 72 hours and 7 days, complete blood count, C-reactive protein, urea, creatinine, B-type natriuretic peptide, and troponin will be collected. If the patient is transferred to another hospital sector during hospitalization, these tests will be performed according to the medical team attending the case. Imaging tests will be requested and performed at the

discretion of the attending medical team. The results of both laboratory and imaging tests will be obtained from the patient's medical records during their hospitalization period.

At the time of randomization, 2 hours and 6 hours after, the following parameters will be recorded: heart rate, respiratory rate, systolic, diastolic, and mean arterial pressure, oxygen saturation, and urine output. For patients allocated to the Goal-Directed Therapy group, CI and SV values will also be recorded. The amount and type of fluid administered, fluid balance, the amount and type of vasoactive drugs, and the amount and type of inotropic drugs will be recorded at the following times: randomization, 2 hours, 6 hours, 24 hours, 48 hours, and 72 hours.

Quality of life will be assessed at inclusion, at the 30-day visit, and at the 6-month visit using the EuroQol 5 Dimensions (EQ-5D) questionnaire, which consists of an instrument that evaluates five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), where the patient marks the level of impairment in each dimension, in addition to a visual scale ranging from zero to 100, regarding their perception of health on the day of the test, with 100 indicating the best possible health level, and zero indicating the worst possible level. This questionnaire has been validated for use in the Brazilian population.

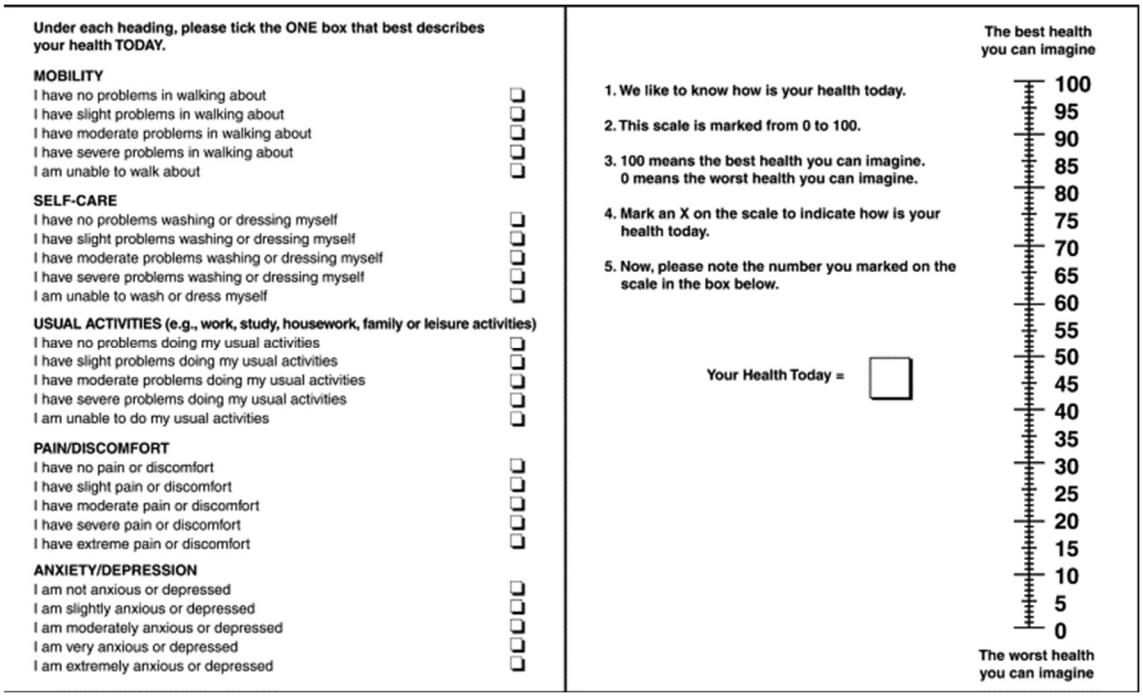

Figure 2: EuroQol 5 Dimensions (EQ-5D) questionnaire.

7.2.5 Visit Procedures

Visit Activity ↓	Inclusion/ Randomization	2hs	6hs	24hs	72hs	7 days	30 days	6 months
Inclusion and exclusion criteria	X							
ICF (Informed Consent Form)	X							
Registration of the following tests (in routine): Complete Blood Count, Coagulation Profile, CRP, Na, K, Mg, Ca, P, Urea, Creatinine, AST, ALT, GGT, ALP, Total and Fractionated Bilirubin, Albumin, Troponin, CK-MB, CPK, BNP, LDH, D-dimer, Lactate, Arterial Blood Gas	X	X		X				
Arterial and venous blood gas, and lactate		X	X					
Complete Blood Count, CRP, Urea, Creatinine, BNP, Troponin.				X	X			
If performed - Record of routine imaging tests (Echocardiogram or MRI). If more than one test is performed, record the result with the most clinically significant alteration	X	X	X	X	X	X		
Application of EQ-5D questionnaire							X	X
Concomitant medications		X	X	X	X			
Recording of the following parameters: HR, RR, SBP, DBP, MAP, Sat O2, urine output		X	X	X	X	X		
Amount and type of fluid administered, fluid balance, vasoactive and inotropic drugs administered	X	X	X	X	X	X		

8. OUTCOMES

8.1. PRIMARY OUTCOME

- Time to resuscitation: After 6 hours of treatment, the number of patients who achieve the following goals:
    - Mean arterial pressure > 65mmHg +
        - Urine output greater than 0.5 mL/kg/h for more than 2 hours, and/or
        - Decrease of more than 10% in serum lactate compared to the initial value

8.2. SECONDARY OUTCOMES

- Number of patients with Acute Kidney Injury within 72 hours
- Occurrence of Myocardial Injury within 30 days
- Occurrence of Acute Myocardial Infarction within 30 days
- Mortality at 30 days and 6 months
- Length of hospital stay
- Amount of fluid administered, fluid balance, and the amount of vasoactive and inotropic drugs administered at the time of randomization, 2 hours, 6 hours, 24 hours, 48 hours, and 72 hours
- Cost-effectiveness of therapies
- Assessment of quality of life at hospital admission, 30 days, and 6 months

9. DEFINITION OF CLINICAL COMPLICATIONS

- Acute Kidney Injury: According to the AKIN classification, acute kidney injury is defined as an abrupt (within 72 hours) reduction in kidney function, characterized by an absolute increase in serum creatinine of ≥ 0.3 mg/dL; or a percentage increase in creatinine of ≥ 50% (1.5 times baseline creatinine); or a reduction in urine output to less than 0.5 mL/kg/h for six hours or more.
- Myocardial Injury: Presence of elevated troponin levels above the 99th percentile.

- Acute Myocardial Infarction: Presence of Myocardial Injury, associated with at least one of the following factors:
    - Symptoms of acute myocardial ischemia;
    - Dynamic changes in the Electrocardiogram;
    - Evidence of new segmental myocardial contractility loss, diagnosed by Echocardiogram and/or Cardiac MRI.

10. STATISTICAL ANALYSIS

The sample size was calculated based on the hypothesis that 60% of patients in the Goal-Directed Therapy group will achieve hemodynamic resuscitation after 6 hours of treatment, while in the Conventional Therapy group, this resuscitation will occur in 45% of patients. With a power of 80% and an alpha error of 0.05, 380 patients will be required, to be randomized into two groups of 190 patients each. Results with descriptive probability levels (p-values) less than 0.05 will be considered significant.

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