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THE CUTTING EDGE: RESEARCH UPDATE

Targeting peripheral perfusion versus serum lactate levels in septic shock

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Background

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection [1–2]. Sepsis and septic shock are major healthcare problems, affecting millions of people around the world each year, and killing as many as one in four [3].

Early resuscitation is a key factor for the stabilization of sepsis-induced tissue hypoperfusion and is crucial to limit adverse outcome and death, especially in patients with septic shock.

Serum lactate is widely used in sepsis and, despite it is not a direct measure of tissue perfusion, it can serve as a surrogate. The Surviving Sepsis Campaign proposes to guide resuscitation by reassessment of blood lactate levels every 2–4 h until normalization according to randomized controlled trials [4]. However, the persistent increase of lactate may be related to other causes than tissue hypoperfusion, i.e., severe hypoxemia. Therefore, finding an alternative resuscitation targets becomes relevant in sepsis research.

Capillary refill time (CRT) is a common method to assess peripheral perfusion and, according to recent results, it seems to rapidly respond to resuscitation [5].

No study has previously analysed CRT to early fluid resuscitation; for this reason, Hernandez et al. performed a study to compare peripheral perfusion-targeted to lactate-targeted resuscitation.

Summary

The ANDROMEDA-SHOCK is a randomized clinical trial aimed at assessing whether, in patients with septic shock, the resuscitation guided by peripheral perfusion improved outcome compared to lactate level-targeted strategy (5).

This was an international multi-center, randomized, unblinded trial conducted in Intensive Care Units in South America.

Patients 18 years of age or older with a diagnosis of septic shock were included in the study. Septic shock was defined as suspected or confirmed infection, plus hyperlactatemia (≥ 2 mmol/L) and requirements of vasopressors to maintain a mean arterial pressure (MAP) of 65 mmHg or higher after an adequate intravenous fluid load. Patients were recruited within 4 h after fulfilling criteria. Exclusion criteria included bleeding, severe acute respiratory distress syndrome and do-not-resuscitate status. Eligible patients were randomly allocated to peripheral perfusion or lactate level-targeted resuscitation groups, respectively. Group allocation was only disclosed after the information was centrally checked and recorded.

The intervention period was 8 h and a CRT greater than 3 s was considered altered.

Lactate levels were measured every 2 h, CRT was assessed every 30 min until normalization and then every hour during the intervention period.

The goal for the peripheral perfusion group was to normalize CRT, whereas the goal for the lactate group was to achieve normal level or a 20% reduction every 2 h.

The primary outcome was all-cause mortality at 28 days whereas the secondary outcomes were death within 90 days, organ dysfunction during the first 72 h after randomization, mechanical ventilation-free days within 28 days and ICU/hospital length of stay.

From March, 2017 to March, 2018, 1327 subjects were screened for inclusion; 424 patients (32%) were enrolled,

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212 patients were randomly assigned to peripheral perfusion group and 212 to the lactate one. The two groups resulted to have similar characteristics; 71% of patients were admitted from the emergency department, 17% from wards, 7% from step-down units and 5% from the operating room.

Considering the whole group, lactate levels were significantly lower at 48 and 72 h in the peripheral perfusion group than in the lactate one (mean difference − 0.36 mMol/L [95% CI − 0.62 to − 0.09]; $p = 0.01$ and − 0.34 mMol/L [95% CI − 0.57 to − 0.10]; $p < 0.01$, respectively) whereas no significant difference was observed at 2, 4, 8 and 24 h. CRT values were significantly lower at 4, 8 and 24 h in the peripheral perfusion group than in the lactate group (difference between medians, − 0.45 s [95% CI − 0.78 to − 0.12]; $p = 0.01$ at 4 h, − 0.55 [95% CI − 0.85 to − 0.25]; $p < 0.01$ at 8 h, − 0.42 [95% CI − 0.71 to − 0.13]; $p < 0.01$) at 24 h, no statistically significant differences were found at 2, 48 and 72 h.

The primary outcome did not differ between the two groups; by day 28, 74 patients (34.9%) in the peripheral perfusion group and 92 (43.4%) in the lactate group died (hazard ratio 0.75 [95% CI 0.55–1.02], $p = 0.06$; risk difference, − 8.5% [95% CI − 18.2 to 1.2%]).

The organ dysfunction at 72 h after randomization was significantly lower in the peripheral perfusion group than in the lactate group (mean difference SOFA score, − 1.00 [95% CI − 1.97 to − 0.02], $p = 0.045$). No differences were observed between the two groups in the other six secondary outcomes.

In the subgroup analysis among patients with SOFA less than 10, the primary outcome was 0.46 (95% CI 0.27–0.78), whereas among patients with SOFA score 10 or greater the hazard ratio was 0.98 (95% CI 0.66–1.44).

Strengths of the study

- The topic addressed in the paper is of particular interest and can strongly affect daily clinical practice.
- It was an international multi-center and randomized clinical trial.

Weaknesses of the study

- The authors estimated the sample size of the enrolled population considering significant a reduction in 28-day mortality from 45% in the lactate group to 30% in the peripheral perfusion group, at an α level of 0.05. They calculated that a number of subjects of 420 were sufficient to achieve the primary outcome with a study power of 90%. From a clinical prospective, a 15% reduction in 28-day mortality could be a very ambitious goal; therefore, the lack of statistically significant result in the primary outcome could be mainly due to a not adequate sample size. We wonder if this is the reason why the present study could not highlight an important clinical result.

Question marks

- Although the ANDROMEDA-SHOCK was a multicenter trial, the study was conducted only in South America, we wonder if this could reduce the study external validity.
- The authors concluded that a peripheral perfusion-targeted resuscitation strategy did not result in a significantly lower 28-day mortality when compared with a lactate-targeted strategy. However, even if the result did not reach statistical significance, the upper bound of confidence interval is 1.02. Therefore, we wonder if CRT could be used to guide early resuscitation management and could be more effective than lactate levels in septic shock and in preventing adverse outcome.
- In the peripheral perfusion group, patients were reassessed every 30 min with CRT while every 2 h in the lactate group. We wonder if the possible positive results of the study were related to more frequent reassessment of patients compared to the use of single method, i.e., CRT or lactate levels.

Sponsorship

The study received logistic support from the Pontificia Universidad Catòlica of Chile.

Clinical bottom line

Although the study results do not reach statistical significance, we believe that CRT could be a non-invasive, useful tool in septic shock and, in association with a frequent patients' revaluation, could be a good target in monitoring early resuscitation in septic patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights This article does not contain any studies with human and animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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