EVALUATION OF PROCALCITONIN, VITAMIN D AND C-REACTIVE PROTEIN LEVELS IN SEPTIC PATIENTS WITH POSITIVE EMOCOLTURES. OUR PRELIMINARY EXPERIENCE

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ABSTRACT

Sepsis, the systemic inflammatory response to infection, is the most common cause of death in people hospitalized in intensive care units (ICU). Early diagnosis of infection is crucial to the appropriate management of sepsis, with early antibiotic administration consistently resulting in improved outcomes.

The purpose of this study, although preliminary, was to determine whether vitamin D levels correlate with procalcitonin (PCT) and C-reactive protein (CRP) levels in 59 septic patients, with positive emocoltures.

This study is also aimed to point out new possible diagnostic protocols identifying potential biomarkers for the diagnosis of sepsis, defined according to literature data.

***Keywords**: sepsis, emocoltures, vitamin D, procalcitonin, C-reactive protein.*

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Introduction

Sepsis is a complex syndrome caused by an uncontrolled systemic inflammatory response, of infectious origin, characterized by multiple manifestations and which can result in dysfunction or failure of one or more organs and even death[(1)].

One factor that may contribute to the prognosis of sepsis is vitamin D, that has been recently identified in functions involving regulation of hormone secretion, immune function, cellular proliferation, and differentiation[(2)].

Whether vitamin D and its active metabolite 25-hydroxyvitamin D (25OHD) deficiency or their insufficiency affect the prognosis of sepsis, still remains controversial[(3)].

A study of 3386 patients showed that 25OHD deficiency prior to hospital admission was a significant predictor of sepsis in critically ill patients[(4)]. Conversely, a study of 170 patients admitted to intensive care unit (ICU) didn't show such association[(5)].

Blood procalcitonin (PCT), a precursor hormone derived from pre-procalcitonin, is also an

important host response biomarker of infection, and PCT levels can increase exponentially in sepsis[6].

This increase is largely due to production by parenchymal cells in organs such as the liver, lung, kidney, adipose tissue, and muscle[7]. The magnitude of this increase is correlated with the severity of sepsis and the mortality rate[8].

C-reactive protein (CRP) is an inflammatory marker that has been used in clinical practice for decades[9].

Aim of this work was to determine whether vitamin D levels correlate with PCT and CRP levels in septic patients with adverse outcomes as well as blood culture positivity.

Materials and methods

This is a prospective, observational study of 59 septic patients, with positive emocoltures, admitted to a medical or surgical intensive care unit (ICU) of the University Hospital of Bari, Italy from January to June 2014.

All procedures complied with the Declaration of Helsinki. Informed consent was obtained from each patient's legal guardian(s) at the time of ICU admission.

The criteria used for a diagnosis of sepsis in the present study were taken from the 2008 Surviving Sepsis Campaign international sepsis guidelines[10].

Routine data gathered during hospital stay, including cause of death (during hospital stay) was extracted from the hospital's medical documentation system.

The primary endpoint was the evaluation of the prevalence of vitamin D deficiency and insufficiency. Secondary endpoints included PCT and CRP levels, age and gender.

The following baseline data were collected from patients upon ICU admission: demographics, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, and basic hematological and biochemical test results (including culture results).

Whole blood was collected within 24 hours upon ICU admission. The plasma levels of vitamin D were measured from fresh blood samples on workdays with enzyme immunoassay (LIAISON; DiaSorin).

The serum CRP level was determined by immunoassay (VISTA; Siemens), and the PCT level was assayed by double-antibody sandwich immunochemiluminescence (LIAISON; DiaSorin).

According to a clinical practice guideline, vitamin D deficiency was defined as a serum level of 0.0 to 19.9 ng/mL (0.0 - 49.75 nmol/L, multiplied by 2.5), insufficiency as 20.0 to 29.9 ng/mL (50.0-74.75 nmol/L), and sufficiency as 30.0 ng/mL (75.0 nmol/L). Normal value of CRP and PCT were considered respectively < 2.90 mg/L and 0.0-0.5 ng/ml.

Results

The samples analysis was performed in patients with available blood culture results during hospital stay.

Among 59 patients presented with sepsis, mean age (years, ± standard deviation) was 70.86 ± 10.85; 38 patients were male and 21 female.

All enrolled patients was vitamin D deficient (mean value 13 ng/mL).

Mean PCT and CRP concentrations were respectively 10 (ng/mL) and 135 (mg/L).

Discussion and conclusions

Laboratory, or complementary, evaluation is capable of revealing two distinct aspects of sepsis. The first is related to the search for the aggressive agent, by means of microbiological tracking of the patient; the second relates to the identification of alterations to metabolism or homeostasis, indicative of systemic compromission or of specific organ involvement.

In the case of hospitalized patients, the collection of material for culture should include all devices that breach the host's protective barriers, i.e. venous or arterial catheters (blood from the catheters), urinary catheter, tracheal tube or tracheostoma (tracheal aspirate), and stitches or scars from recent surgery[11].

Despite the great effort made to isolate microorganisms, on average, blood cultures are positive in 34% only of "septic" patients, varying from 9 to 64%[12].

There are almost 200 so-called sepsis markers; therefore, discussing the features of those cannot be integrated into the current study. We will mainly focus on the three most commonly used markers: vitamin D, PCT and CRP.

Despite their popularity, there are still many pros and cons without clear answers regarding their usefulness and interpretation in guiding patient management.

Low vitamin D levels were independently associated with all-cause hospital mortality and remained a significant predictor of mortality after multivariate adjustment for relevant confounders, confirming previous findings of adequately powered studies in the critically ill[13,14].

PCT is detectable in the serum within a few[4-6] hours after the onset of bacterial infection. During the "normal" course of an infection it reaches its peak within 24 hours and then starts its decline in the case of adequate treatment with levels reducing by roughly 50% daily according to its half-life[15].

There is considerable evidence that PCT supported decision making during antibiotic treatment has several beneficial effects[16].

In contrast, CRP moves "slowly," and under similar circumstances it reaches its maximum value usually within 48 hours. However, levels are generally elevated in most ICU patients, making interpretation of CRP very difficult[7].

The other major problem with CRP on the ICU is that it is lagging way behind the actual events of the inflammatory process.

In the present study, concentrations of CRP are expressed in mg/L. Some authors suggest 50 to 100 mg/L as an optimal serum level to separate sepsis from systemic inflammatory response syndrome (SIRS)[17].

Povoa[9] evidenced that a cutoff serum level of 50 mg/L increases the chance of sepsis by fourfold. Pierrakos,[18] however, did not recommend the use of CRP to separate sepsis from inflammatory conditions, deeming it inaccurate for this purpose. The problem is not only the dynamics of CRP variations, already mentioned, but also the lack of a "gold standard" for the diagnosis of sepsis, which is defined by the association between clinical and laboratory data. In general, this makes the determination of biomarkers' sensitivity and specificity harder in this clinical condition. In fact, some studies adopt culture-positive results as a gold standard, which is also questionable, as cases of culture-negative sepsis are frequent[18].

Fan[19] has recently proposed a multipanel approach for the diagnosis of sepsis, including both "new" and well known parameters. But this approach is not easily available in daily practice for a large number of hospitals worldwide.

Certain limitations of this study should be considered. The most important limitation is that it is a single center study, and selection bias may be present. Therefore in this study we have a sample of relatively small size for the detection of less pronounced effects, so we had insufficient data for a statistical association in order to detect weak relationships.

Second, most of the patients who were assessed for inclusion were excluded before the enrollement, which might indicate a limitation to the practical usefulness of the tested protocol. Regarding this point, most exclusions occurred in patients who had "more than 48 hours of antibiotic therapy" as unique criterion.

Finally, for what concern vitamin D levels reduction in the study population, is not yet completely clarified the mechanism behind this decrease.

Therefore, it is helpful the administration of vitamin D in these patients in order to reduce the negative effects of that deficiency. Further studies are necessary to confirm our findings, to better define the mechanisms by which vitamin D is implicated in the immune response and understand the cause of its decrease in patients with sepsis.

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