ANAESTHESIA, PAIN & INTENSIVE CARE
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SPECIAL ARTICLE

Biomarkers in intensive care: C-reactive protein and procalcitonin

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Received: 31 Oct 2018
Reviewed & Corrected: 4 Nov 2018,
Accepted: 10 Nov 2018

ABSTRACT

With the current advances in medicine, we all can experience a paradigm shift of medicine from art to science. Everyone wish their practice to be more accurate and objective rather than being experience based and subjective. We have seen massive developments towards the goal of practicing medicine with precision and uniformity. One such advancement is seen in the form of 'biomarkers'. A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processor, pathogenic processor or pharmacological responses to a therapeutic intervention. Everyday new biomarkers are being found and the pace has been accelerated with rapid progress in the fields of biochemistry, microgenetics and laboratory tool manufacturing.

C-reactive protein and procalcitonin are two important biomarkers, described in this nar-rative review, which are in extensive use in intensive care setting.

Key words: Biomarker; Biological processor; Pathogenic processor; Intensive care; C-reactive protein; Procalcitonin

Citation: Agrawal J, Sharma CK. Biomarkers in intensive care: C-reactive protein and procalcitonin. Anaesth Pain & Intensive Care 2018;22 Suppl 1:S118-S123

INTRODUCTION

The term biomarker or a biological marker refers to a broad subcategory of medical science that is an objective indication of medical state observed from outside the patient, which can be measured accurately and reproducibly. In 1998 the national institute for health biomarkers definitions working group defined a biomarker as a characteristic that is objectively measured and evaluated as an indicator of normal biological processor, pathogenic processor or pharmacological responses to a therapeutic intervention.

Box 1: Characteristics of an ideal biomarker

An ideal biomarker;
- correlate well with disease progression
- can be readily measured in accessible sample
- should have great sensitivity and specificity
- turnaround time for sample should be less
- result should be altered with associated co-morbidities and concurrent organ failures
- should be cost effective
- should be reproducible and not be skill dependent
- should help the clinician in making a decision

Since then many physiological markers are being studied for their role in determination of state of health and prognosis of the disease. The ideal biomarkers should be significantly increased in related disease condition and should have some special characteristics (Box 1).[1]

Critically ill patients are different as compared to others, as here often multiple organ system involvement can alter the level of particular marker. Most commonly used biomarkers in a critical care unit are the biomarkers of sepsis, cardiac biomarkers, and biomarkers for acute kidney injury.

C- REACTIVE PROTEIN (CRP)

CRP is amongst the most used and well-studied marker for sepsis. It is calcium dependent ligand

binding plasma protein. It is synthesized by hepatocytes in response to stimulation by cytokines, notably IL-6. The plasma half-life of CRP is about 19 hours. In healthy young adults, normal concentration of CRP is about 0.8 mg/L.[2,3] During infection or acute inflammation these values can rise to almost 10000 folds.[4] The plasma clearance of CRP is no different in physiological and disease state and therefore synthesis rate is the only significant determinant of its plasma level, making measurement of CRP level a useful objective index of acute phase response.[5]

Normally CRP may act as a pro-inflammatory or in an anti-inflammatory manner to aid host defense. The precise role of CRP is controversial. In-vitro CRP has been shown to increase release of anti-inflammatory cytokines IL-10,[6] and decrease synthesis of several pro-inflammatory cytokines including IL-12, TNF, IFN gamma. It also activates compliment, enhances phagocytosis,[7,8] inhibits activated neutrophils,[9] increases nitric oxide synthetase and induces tissue factors. In 1930s, during initial study CRP was considered specific to bacterial infection, thereafter over a period of time, it was found to be an acute phase protein and is raised in a wide range of disease states, both acute as well as chronic.[1]

It is regularly used in rheumatologic conditions such as rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis. In such cases it is used to monitor the effectiveness of treatment.[10,11] Similarly its values are raised in non-infective inflammatory states such as acute pancreatitis.[12,13] The levels of CRP are studied to correlate the severity of the diseases such as bronchial asthma,[14] chronic obstructive pulmonary disease (COPD)[15,16] and also in acute cardiovascular disease, although it lacks the specificity for the same. CRP can be used as a biomarker of infection and should aid the clinical picture in the field of diagnosis, disease severity, risk stratification and prognosis and therapeutic guidance.[17]

Accurate and rapid diagnosis of infection is important to start the appropriate treatment early.[18] But because of multiple confounding factors such as prior antibiotic use, multi-organ involvement can complicate or delay the decision making.

Many studies have been done to assess the role of CRP as diagnostic marker using a cut off value ranging from 7.9 to 8.7 mg/dL; yielding a sensitivity up to 93% and a specificity of up to 86%.[19] Sierra and colleagues have also reported similar results but they have found median CRP level to be significantly higher in patients with sepsis than in patients with patients with systemic inflammatory response syndrome (SIRS).[20] The combination of CRP along with other signs of sepsis (e.g. temperature, heart rate, white blood cell count, blood pressure) and the sequential organ failure assessment (SOFA) score can more reliably predict the presence of an infection.[21]

For prognostication of the disease, similar to diagnosis it's not the single value of CRP that is helpful. Silvestre and colleagues reported no correlation between concentration of CRP measured on the day of diagnosis and the severity of sepsis in their study conducted on 158 patients with sepsis.[22] However, in a prospective study, Lobo and colleagues reported that ICU admissions with CRP levels more than 10 mg/dL as compared to less than 1 mg/dL carried more risks of organ failures and mortality, moreover they found the mortality rate of 15% in patients whose CRP was more than 10 mg/dL at the time of admission but was reducing at 48 hours, whereas the mortality rate was 61% in patients with CRP more than 10 mg/dL at the time of admission and was showing increasing trend after 48 hours.[23] CRP levels can also be used as a guide for optimal duration of antibiotics. In a retrospective analysis, a decrease in CRP by 25% or more than the previous day's level was supposed to be a good indicator of the resolution of the sepsis, with a sensitivity of 97%, specificity of 95% and a predictive value of 97%. [24] However, any prospective study conclusively confirming these findings is awaited.

PROCALCITONIN (PCT)

Procalcitonin is being studied and evaluated extensively as a marker and thought to be more specific to infection as compared to other biomarkers of infection.

PCT is the prohormone of the hormone calcitonin. Induction of prohormone is differentially regulated during sepsis and infection as for hormonal activity of the hormone.[25] PCT levels start to increase upon an infections stimuli slowly somewhat after 2 hours and peak at 24 hours, provided that no second infection occurs. This response is considerably faster than that of CRP, whose levels increases slowly and only peak at 48 hours. PCT has various immunologic functions, modulating the immune response during sepsis, infection and inflammation. Among those functions are chemotactic functions, modulation of inducible nitric oxide synthetase, and cytokine induction, and the protein interferes with receptor binding of other peptide hormones involved in intravascular fluid and vascular tone (calcitonin - gene related peptide - Adrenomedullin)[26, 27] induction of protein is strictly regulated and depends on cell-cell interactions. Circulating blood cells produce cytokines but no PCT. Migration of adherent monocyte cells into the tissue very clearly plays a major role in PCT induction,

because only adherent monocyte cells produce PCT in a time-dependant manner and contact of such cells with adipocytes, for example triggers a major and a sustained PCT response in vitro.[28] There are several studies done assessing the role of PCT in a systemic inflammatory response caused by infection, differential diagnosis between infections and non-infections causes and the effectiveness of measures of source control.

In the absence of other factors that may induce an increase in PCT levels, a PCT value of 0.25 to 0.5 ng/ml suggests the pressure of a bacterial infection that requires antimicrobial treatment. If PCT levels are less than 0.25 ng/ml, severe bacterial infection and sepsis are very unlikely; however local infection may be present. In patients with septic shock as compared with infected patients without signs of significant inflammation or patients with sterile systemic inflammation, PCT levels are significantly elevated. The odds ratio for increased PCT levels (> 0.5 ng/mL) in a meta-analysis was around 15.7 as compared to 5.4 for CRP levels.[29]

The clinical relevance of the potential of PCT to differentiate between the infections and the non-infectious causes of inflammation has been questioned by many.[30]

Potential benefits of PCT

There are many studies supporting the use of PCT in diagnosing severe sepsis and septic shock where significantly elevated concentrations were found in advanced stages of the disease.[31-38]

PCT levels are significantly higher in patients with bacterial infections as compared to viral or fungal infections.[29,39-42] Any PCT level increase, especially if it does not respond to appropriate antibiotics therapy, may indicate invasive systemic fungal infection.[43-47]

In transplant patients, PCT is superior to conventional markers to differentiate between acute rejection and infections complications.[48-53]

PCT can be used as a marker for effectiveness of source control, where it declines serially in adequate source control, while sustained rise in PCT levels despite source control are associated with poor prognosis.[31, 54-60]

It can be used as a good tool for antibiotic stewardship, where PCT guided antibiotic use may result in 20-70% decrease in antibiotics exposure without a negative effect on patient outcome,[61-64] but there are several studies criticizing these findings. A recent study published in 2018 also has questioned these findings and had concluded that there is not a significant difference in mortality by using PCT guided therapies.

There are also some non-infectious causes of PCT induction, including major surgery or trauma, severe burns, heat shock, different types of immune therapy, such as granulocyte transfusions, administration of antilymphocyte globulin and patients with acute graft versus host disease. Likewise some autoimmune diseases, (Kawasaki disease and other vasculitis) and paraneoplastic syndromes may be associated with elevated PCT levels.[65,66]

Basically, as for all diagnostic tests, the diagnostic accuracy of PCT can be increased, if further clinical data are implicated into decision making.

CRP VERSUS PROCALCITONIN

There is a constant debate regarding the best biomarker available for sepsis. Despite the limitations of PCT, till date there is no other biomarkers that differentiates better between the infectious and non-infectious causes and severity of inflammation in patients with a systemic inflammatory response.[67-71]

However, in patients with acute exacerbations of COPD, Daniel and colleagues reported that CRP levels were higher in patients with sputum positive for bacteria than in those without, whereas PCT levels were the same in 2 groups.[72] In a study conducted on suspected community acquired pneumonia patients, the author has reported that CRP has better diagnostic valve whereas PCT markers, a better severity.[73]

SUMMARY

The quest to find an answer to the question, “am I dealing with a septic patient” is far from over. We need better biomarkers for the same. CRP has benefits of easy availability, ease of use, rapid results and low costs. Whereas, although PCT has benefits of being more specific in diagnosing the infection, assessing the severity, monitoring the progress of the disease and predicting the prognosis, its high cost can be a precluding factor for routine and repeated use.

To conclude the following principles can be remembered

- Clinical judgement should be relied upon more while initiating an antimicrobial therapy empirically. An elevated CRP or PCT value may not necessarily predict infection, while a normal value done early in the course of disease can be misleading.
- CRP / PCT alone cannot be used as diagnostic marker. It should be used to support the clinical decision.

- Serial values are a better indicator of an improving or worsening disease condition than a single value.
- Currently, PCT can be used more reliably as a marker, in the decision making of termination of antimicrobial therapy rather than using it to initiate the antimicrobial therapy.

Conflicts of interests: None
Authors' contribution:
JA: Concept, manuscript editing
CKS: Conduction of the study work

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