Research Paper

Volume : 5 | Issue : 3 | March 2016 • ISSN No 2277 - 8179 | IF : 3.508 | IC Value : 69.48

Evaluation of Usefulness of Quantitative Estimation of Procalcitonin In Diagnosis of Bacterial Sepsis

Medical Science

KEYWORDS : PCT, Procalcitonin, sepsis, septicemia

Dr. Vijay Narayan Kulkarni	Associate Professor, Department of Microbiology, Rajarshi Chhatrapati Shahu Maharaj Govt. Medical College, Kolhapur, CPR General Hospital campus, Dassara Chowk, Kolhapur – 416002, Maharashtra, INDIA
Dr. Shilpa Dayanand Putta,	Asst. Professor , Department of Microbiology, Rajarshi Chhatrapati Shahu Maharaj Govt. Medical College, Kolhapur, CPR General Hospital campus, Dassara Chowk, Kolhapur – 416002, Maharashtra, INDIA
Dr. Manisha Vijay Kulkarni	Consulting Pathologist, MicroPath Laboratory, Om plaza, Konda Lane, Laxmipuri, Kolhapur- 416002, Maharashtra, India.

ABSTRACT

Introduction: Sepsis is one of the leading cause of mortality in majority of hospitals. Procalcitonin (PCT) has recently become choice of interest as a possible marker of the systemic inflammatory response to infection or sepsis estimation. As procalcitonin concentrations have been shown to be elevated in such patients.

Aim: Current study was aimed to evaluate usefulness of quantitative estimation procalcitonin (PCT) in early detection of sepsis or septicemia cases.

Results: Total 454 patients were included in the study for procalcitonin level estimation. PCT levels >0.5 ng/ml were calculated in 87.22% patients. On analysis of results sensitivity and specificity of the PCT test was found to be 88.10% and 34.15 % respectively. PCT test had Positive predictive value of 40.66%. Though PCT test had low positive predictive value , it has a good Negative predictive value i.e. 84.85 %.

Conclusion:

PCT test is a excellent predictor of diagnosis as well as prognosis in assessment of sepsis or systemic inflammatory response to infection. It should be used as an adjunt to the conventional diagnostic test to evaluate and early on effective management of sepsis. a

INTRODUCTION:

Sepsis is leading cause of death in hospitalized patients. Sepsis is the systemic maladaptive response of the pathogenic microorganisms leading to the invasion of normally sterile tissue, fluid or body cavity. The culmination of the complex interactions between the infecting microorganism and the host immune, inflammatory and coagulation responses influences the outcome in sepsis. (Source of Sepsis can be infection at any body site, including lungs, abdomen, skin or soft tissue, or urinary tract and as a result of primary blood stream infection. Bacterial pathogens are most commonly associated with sepsis, although fungi, viruses and parasites can cause sepsis. [1,2]

The eventual cause of mortality in patients with sepsis is multiple organ failure. Patients who are debilitated, immunocompromised are at an increased risk because bacteria may not be cleared from blood for hours . A strong correlation exists between advanced age and incidence of septic shock, with a sharp increase in the number of cases in patients older than 50 years. Advanced age is a risk factor for acquiring nosocomial blood stream infection in the development of severe form of sepsis. [1,2]

Nowadays, in emergency care units of all hospitals majority of patients presented with sepsis. Early diagnosis and effective management of such cases remains main challenge for clinicians. Due to its diagnostic uncertainty may leads to delay in the commencement of lifesaving therapies such as the administration of appropriate antibiotics. Therefore, the expansion of diagnosis for sepsis is expected to encourage improved clinical management of cases. Various range of biomarkers proposed as potential biomarkers in early diagnosis of sepsis. But role of each biomarker in diagnosis is questionable, only few of them created place in diagnosis of sepsis.

Among the battery of biomarkers Procalcitonin (PCT) has documented evidence for discriminating between patients with sepsis or systemic inflammatory response syndrome caused by other disease.[3,4] Many studies showed their role of quantitative procalcitonin values in diagnosis as well as prognosis of the sepsis and systemic inflammatory response syndrome.[3,4] Therefore, this study was formulated mainly to assess the utility of quantitative PCT levels in diagnosis as well as prognosis of sepsis patients. .[3,4]

MATERIAL AND METHODS:

This study was carried out over the period from April 2015 to February 2016. Patients were included presenting to the emergency department with suspected septicemia or sepsis as indicated by a physician for PCT level determination. The demographic and clinical characteristics of patients were recorded on admission. Systemic inflammatory response syndrome, severe sepsis, and septic shock were defined based on the criteria formulated by Consensus Conference of the American Society of Chest Physicians/Society of Critical Care Medicine. [5]

Blood samples were obtained by using standard techniques with aseptic precautions for routine tests such as complete blood count and if needed, culture and sensitivity of appropriate specimens.

Procalcitonin (PCT) test:

Procalcitonin is the prohormone of calcitonin. PCT is secreted by different cells from several organs in response to proinflammatory stimulation, principally mico-organisms invasion especially bacterial stimulation. [6]

The assay principle combines a one-step immunoassay sandwich method with a final fluorescent detection i.e.ELFA. The Solid Phase Receptacle, serves as the solid

phase as well as the pipetting device. All of the assay steps are performed automatically by the instrument.

The specimen needed for PCT test is serum which is collected by using standard technique. Serum sample is transferred into the wells containing anti-procalcitonin antibodies labeled with alkaline phosphatase (conjugate). The sample and conjugate

mixture is cycled in and out of the SPR several times. Unbound compounds are eliminated by washing . This followed by detection response which is two steps reaction. During each step, the substrate used is 4-Methyl-umbelliferyl phosphate which is cycled in and out of the SPR. The conjugate enzyme catalyzes the hydrolysis of this substrate into a fluorescent product (4-Methyl-umbelliferone) the fluorescence of which is measured by using 450 nm filter. The intensity of the fluorescence is proportional to the concentration of antigen present in the given sample. At the end of the assay, results are automatically calculated by the instrument in relation to two calibration curves corresponding to the two detection steps.

According to Procalcitonin values patients were categorized into four groups. [7]

Values	Interpretation
<0.05 ng/ml	Normal values, no SIRS
<0.5 ng/ml	Minor or no significant systemic inflammatory response. Local infection/inflammation possible
0.5 – < 2 g/ml	Moderately severe inflammatory response . Likely infectious cause. Follow up recommended within 6-24 hours
2 - <10 ng/ml	Severe inflammatory response most likely due to infection (sepsis). Daily measurement recommended. If persistently elevated for > 4 days revise treatment
≥ 10 ng/ml	Severe SIRS exclusively due to severe bacterial sepsis or septic shock. Frequently associated with organ dysfunction. High risk of mortality

RESULTS:

A total of 454 patients were included in the current study and 124 cultures were collected as per clinical requirement. Study was evaluated only in adults aged from 18 to 85 years. 23 were having normal values i.e. PCT < 0.05 ng/ml while 117 patients had PCT levels slightly more than normal values but < 0.5 likely suggestive of minor infection. Majority of patients had PCT levels more than 0.5 ng/ml. on further categorizing the patients we had observed 95 (20.93%) had levels between 0.5 – < 2 g/ml i.e. and also 106(23.35%) patients between 2 - <10 ng/ml. PCT levels ≥ 10 ng/ml which is exclusively suggestive of septic shock or sepsis were in 113(24.89%) patients. (Table 1)

About 42 patient samples had been able to isolate the source of the sepsis that means 42 (33.87%) patients had culture positive. (Table 2) Gram negative bacilli 26 (61.90%) were the major pathogens responsible for development of sepsis or other sepsis like severe infections. Among Gram negative bacilli key pathogens were Klebsiella pneumonia 5 (38.46%) followed by Pseudomonas aeruginosa 3 (23.08%). While candida (23.08%) also grown in few cultures of the patients making a hallmark of fungal agents in the etiology of sepsis.

While taking PCT levels >0.5 ng/ml as a cut off we had found overall positivity of PCT for diagnosis of sepsis or sepsis like response or syndrome in 396 (87.22%) patients. To evaluate the usefulness of PCT in diagnosis of Sepsis/ SIRS, these PCT values were compared with culture as though isolation rate is less still culture considered as a gold standard test for confirmation of sepsis or bacteremia. (Table 3 and 4) on further analysis sensitivity and specificity of the PCT test was found to be 88.10% and 34.15 % respectively. PCT test had Positive predictive value of 40.66%. Though PCT test had low positive predictive value it has a good Negative predictive value i.e. 84.85 %. PCT test was found to be statistically significant as compared to culture in diagnosis of septicemia.

Discussion:

Multiple studies were carried out to assess utility of PCT fand they had found PCT as an important tool in diagnosis of blood stream infections and bacteremia. Though culture is considered as gold standard and confirmatory test for evaluation of sepsis and septicemia, culture have some diagnostic limitations. There are numerous factors which can have an effect on isolation of pathogens by culture. A lot of patients landed in sepsis usually referred from other hospitals, majority of patients already have multiple antibiotics which clears organisms from the blood which can create difficulty in detection blood culture.[3,4] Automated blood cultures like BACTEC/ BacT alert have improved yield in isolation of pathogens, still they fail to detect causative agent in most of the cases. [3,4] Also blood culture isolation depends on volume of the blood collected also. As much as blood volume collected for the culture there are increased chances of yield of culture positivity. [3,4] Its not always possible to pull higher quantity of blood in major cases which leads to failure in detection.

In our study we had found sensitivity of the PCT was 88.10% which was found to be higher as compared to Gómez-Cerquera et al,[8] Riedel S et al,[9] Stucker et al[10] studies which had sensitivity of 72%, 75% and 24% respectively. our finding was in discordance with the Yan et al study[11] , they had observed higher sensitivity of 92.4%.

Specificity of test was less 34.15 % which was found in accordance with Raoofi et al[12] in which they had found specificity of 16% within 72 hours of condition and 35% after 72 hours of signs of septicemia or sepsis. There were few studies also which had found much higher specificity for PCT test in diagnosis of bacteremia. [8,9,10,11]. PCT test had very low positive predictive value (40.66%.) still it has high negative predictive value (84.85 %). These findings are in accordance with Raoofi et al[12] and Riedel et al [9] studies which had PPV and NPV 15%, 90% and 17% and 90% respectively. Due to high sensitivity of the test enable it as a useful screening test for detection of cases of septicemia cases.

When we analysed further and compared PCT test with culture results, we had found P value < 0.05 which highlight that PCT test is statically significant as compared to culture as a diagnostic tool in identification of sepsis or septicemia cases.

We considered > 0.5 ng/ml as a cut-off for diagnosis of septicemia and we had found 87.22% patients were had PCT levels > 0.5 ng/ml. Similar findings were observed in Sudhir et al,[13] they had also taken cut-off as > 0.5 ng/ml and 94% patients were having serum PCT levels above cut-off. While different studies found variable results, Raoofi et al[12] had 65% patients PCT levels above cut-off and Gómez-Cerquera et al[8] had found in 72% patients. Considering different studies PCT levels cut-off level >0.5 ng/ml is having good agreement for diagnosis of septicemia cases.

Conclusion:

Considering all observations, PCT test plays key role in early detection of sepsis, SIRS or septicemia cases as compared to other available conventional tests and biomarkers. PCT level estimation is also valuable in assessing prognostic response of the patients towards treatment. Though PCT is very good diagnostic tool, it has some limitations, first cost was the major limitation factor for PCT test. It can be overcome by encouraging use of this test or kit in various government or government aided hospitals so as to maximum people can get benefit of the current test for effective management. Also the study was conducted in single centre, where different factors that can affect PCT levels can differ in different areas or hospitals. So as to overcome this multicentre studies needed to evaluate utility of above test.

Volume : 5 | Issue : 3 | March 2016 • ISSN No 2277 - 8179 | IF : 3.508 | IC Value : 69.48

Finally we conclude here that PCT test should be used as an adjunct to the the conventional gold standard tests for early assessment of severe septicemia or sepsis cases for effective management as well it can be treated as an effective prognostic tool.

Table 1: Categorization on the basis of PCT levels

PCT levels(ng/ml)	No.of patients (Percentage)
< 0.05	23 (5.07%)
< 0.5	117 (25.77%)
0.5 - < 2	95 (20.93%)
2 - > 10	106 (23.35%)
> 10	113 (24.89%)

Table 2: Number of Culture isolates

Name of The isolate	Number of isolates(Percentage)
Klebsiella pneumoniae	10(23.81%%)
E.coli	2(4.76%)
Pseudomonas aeruginosa	6 (14.29%)
Proteus mirabilis	2(4.76%)
Other Non-fermenters	6(14.29%)
Staphylococcus aureus	4(9.52%)
Enterococcus faecalis	8 (19.05%)
Candida	6(14.29%)
Total	42

Table 3: Comparison of PCT test vs Culture

	PCT Test	Culture
< 0.05	23 (5.07%)	0
< 0.5	117 (25.77%)	8 (19.05%)
0.5 - < 2	95 (20.93%)	14 (33.33%)
2 - > 10	106 (23.35%)	10 (23.81%)
> 10	113 (24.89%)	10 (23.81%)
Total	454	42

Table 4: Comparison of PCT test Vs Culture

PCT levels	Culture		Total	Chi-square value	P value
	Growth	Sterile			
> 0.5 ng/ml	37(29.84%)	54(43.55%)	91(73.38%)	7.0349	0.008
< 0.5 ng/ml	5(4.03%)	28(22.58%)	33(26.61%)		
Total	42(33.87%)	82(66.13%)	124		

*P value < 0.05 , taken as statistically highly significant

References:

1. Angus DC, Van der Poll T. Severe sepsis and septic shock. N Eng J Med. 2013;369(9):840-51.
2. Tupchong K, Koyfman A, Foran M. Sepsis, severe sepsis, and septic shock: A review of the literature. Afr J Emer Med. 2015 ;5(3):127-35.
3. Reinhart K, Bauer M, Riedemann NC, Hartog CS. New approaches to sepsis: molecular diagnostics and biomarkers. Clin micro rev. 2012;25(4):609-34.
4. Ward PA. New approaches to the study of sepsis. EMBO molecular medicine. 2012 Dec ;4(12):1234-43.
5. Kenzaka T, Okayama M, Kuroki S, Fukui M, Yahata S, Hayashi H et al. Use of a semiquantitative procalcitonin kit for evaluating severity and predicting mortality in patients with sepsis. Int J Gen Med.2012;5:483-8.
6. Dandona P, Nix D, Wilson MF, Aljada A, Love J, Assicot M, Bohuon CL. Procalcitonin increase after endotoxin injection in normal subjects. J Clin Endo Met. 1994 ;79(6):1605-8.
7. Instruction Manual (version 4.0us) article number: 825.050: Immunofluorescent assay for the determination of PCT (procalcitonin) in human serum and plasma. BRAHMS PCT sensitive KRYPTOR 2015 (Hennigsdorf, Germany).
8. Gómez-Cerquera JM, Daroca-Pérez R, Baeza-Trinidad R, Casañas-Martinez M, Mosquera-Lozano JD, Ramalle-Gómara E. Validity of procalcitonin for the diagnosis of bacterial infection in elderly patients. Enferm Infecc Microbiol Clin. 2015 ;33(8):521-4.
9. Riedel S, Melendez JH, An AT, Rosenbaum JE, Zenilman JM. Procalcitonin as a marker for the detection of bacteremia and sepsis in the emergency department. Amer J clin path. 2011 ;135(2):182-9.
10. Stucker F, Herrmann F, Graf JD, Michel JP, Krause KH, Gavazzi G. Procalcitonin and infection in elderly patients. J Am Geriatr Soc. 2005 ;(8):1392-5.
11. Yan L, Liao P, Xu LL, Zhao Y. Usefulness of procalcitonin in elderly patients with bacterial infection. Clin lab. 2013;60(1):139-42.
12. Raoofi R, Salmani Z, Moradi F, Sotoodeh A, Sobhanian S. Procalcitonin as a marker for early diagnosis of sepsis. Am J Inf Dis. 2014;10(1):15.
13. Sudhir U, Venkatachalaiah RK, Kumar TA, Rao MY, Kempegowda P. Significance of serum procalcitonin in sepsis. Ind J of Crit C Med. 2011;15(1):1.