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PROCALCITONIN - IS IT THE END OF ROAD TO SEPSIS DIAGNOSIS?

Internal Medicine

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ABSTRACT

Introduction- Procalcitonin has been extensively used as marker of sepsis. It is a precursor hormone of calcitonin, not detectable in healthy individuals which increase in response to bacterial infections

Material & Methods- The retrospective study was conducted in intensive care setting by the department of critical care in tertiary care hospital in western India. . The patients who had clinical suspicion of sepsis (inclusion and exclusion criteria applied) were investigated using WBC count, PCT and blood culture. The study captured single point investigations done initially at the time of diagnosis of sepsis. Data was collected using laboratory software maintaining confidentiality and statistical analysis was done using medicals online free software.

Results- The study comprised of 50 patients 33(66%) males and 17(34%) females with most common age group been 41-60 years (46%) .All cases were culture positive. They were categorized into three groups on basis of WBC count. 4(8%) patients had WBC count less than 4000/cumm., 39(78%) patients had high WBC count (>10,000/cumm) and 7 (14%) had normal WBC count .PCT correlates with WBC count in culture proven cases of sepsis (R is 0.144, a weak positive correlation) but the result is *not* significant at p < .05(P-Value -0.318429).

Conclusion- The PCT is a unique biomarker for identification of sepsis but has a weak correlation with WBC count that suggests that PCT levels alone may not be enough for sepsis and therefore a combination of biomarkers may be more functional in the case of clinical application , the gold standard till date remains blood culture.

KEYWORDS

Sepsis, Procalcitonin, Culture , Intensive care

INTRODUCTION

Sepsis is the leading cause of non-cardiac causes of death in intensive care units accounting for nearly 30% of death of patients.[1] The management of sepsis could only be done by early diagnosis as well as strong clinical suspicion in the first few hours of triage (2). However, the correct diagnosis and differentiation form non-infectious causes is challenging. In developing countries the correct use of antibiotics, still represents a major issue for treating physicians, particularly if the patient is in intensive care setting. The incorrect application of antimicrobial therapies lead to an increased risk for opportunistic infections, resistances to multiple antimicrobial agents and toxic side effects, which not only increase mortality but also healthcare costs (3,4). The biomarkers like Procalcitonin (PCT) have helped in differentiating bacterial, viral and fungal infections .[7] PCT during the past decade has been approved for guidance of antimicrobial therapies in patients with respiratory infection and sepsis (5- -11).

It is a precursor hormone of calcitonin, not detectable in healthy individuals which increase in response to bacterial infections. (12,13). But there is no universal consensus on the optimal use of PCT in the setting of sepsis (14). As far as sepsis is concerned till date the only available gold standard is blood culture which again is time consuming therefore reliance on blood markers of sepsis has been emphasized in literature with use of WBC count, C reactive protein and PCT. [15,16] The blood cultures however are not positive in all cases rather in 40–90% of patients with an assumed systemic infection, the results are negative blood culture, with no growing pathogens (17-19).

MATERIALAND METHODS

The present study was conducted in intensive care setting by the department of critical care in tertiary care hospital in western India. The retrospective study we as done between July 2020 for a month in medical intensive care setting of the hospital. The patient identity was anonym zed and no extra investigations for the purpose of study were ordered .

The patients with clinical suspicion of sepsis were included in study after fulfilling following inclusion criteria as under:

a. Age > 18 years
b. Available serum PCT levels
c. A positive blood culture

Only those subjects who satisfied all three above mentioned criterion were included in study

Exclusion Criteria:

a. Age < 18 years
b. Sepsis at the time of admission in Intensive care unit
c. A negative blood culture

The presence of any one of the above exclusion criteria dropped subjects from study group. The patients who had clinical suspicion of sepsis were investigated using WBC count, PCT and blood culture. The study captured single point investigations done initially at the time of diagnosis of sepsis. Data was collected using laboratory software maintaining confidentiality and statistical analysis was done using medicals online free software.

RESULTS

The study comprised of 50 patients 33(66%) males and 17(34%) females with most common age group been 41-60 years (46%) (Table-1)All cases were culture positive. They were categorized into three groups on basis of WBC count. 4(8%) patients had WBC count less than 4000/cumm., 39(78%) patients had high WBC count (>10,000/cumm) and 7 (14%) had normal WBC count(Table-2). PCT correlates with WBC count in culture proven cases of sepsis (R is 0.144, a weak positive correlation) but the result is *not* significant at p < .05(P-Value -0.318429) (Table-3).

Table 1 Age and sex wise distribution

Age distribution (Years)	Male	Female	Total
18-40	8	2	10 (12%)
41-60	14	5	19 (46%)
>60	11	10	21 (42%)
Total	33 (66%)	17 (34%)	

Table 2 Categorization as per WBC cunts

WBC (per mm3)	Total
Less than 4000	4(8%)
Between 4000-10000	7(14%)
More than 10,000	39(78%)
Grand Total	50

Table -3 Procalcitonin and WBC count

	Procacitonin (PCT)				
	< 0.5	0.5-2.0	2-10	>10	Grand Total
Less than 4000	4	0	0	0	4
Between 4000-10000	0	0	6	1	7
More than 10,000	3	14	10	12	39
Grand Total	7	14	16	13	50
The value of R is 0.144. A weak positive correlation between variables. The P-Value is .318429. The result is *not* significant at p < .05.					

DISCUSSION

The PCT as a biomarker proved successfully its clinical usefulness in determining the presence of sepsis. It is not detectable in healthy individuals since the protein is not released into the blood in absence of systematic inflammation [20-23]. In case of a sepsis caused by bacterial infections, however, PCT synthesis is induced in practically all tissues and therefore, detectable in the blood. PCT synthesis is triggered by bacterial toxins, such as endotoxin and cytokines [e.g., interleukin (IL)-1beta, interleukin-6 and tumor necrosis factor (TNF)-alpha] [24]. Due to cytokines released during viral infections that inhibit the production of TNF-alpha, PCT synthesis is not induced in the most viral infections [20-23] Thus, PCT has good discriminatory properties for the differentiation between bacterial and viral inflammations with rapidly available results. PCT *per se* cannot isolate or detect specific pathogens, but the level of PCT may be useful to estimate the probability of a severe bacterial infection [22,23, 25].

Apart from sepsis PCT is also used in other clinical conditions. It serves as an important tool in differentiating between acute rejection of an organ transplant and bacterial infection as initial symptoms make diagnosis difficult and so PCT has been proposed as a diagnostic tool for this purpose [26].

PCT also serves as marker to differentiate respiratory illness from cardiovascular disease [27]. Recently the European Society of Cardiology released PCT guided algorithm for administerating antibiotics in patients with dyspnea and suspected heart failure and gave a cut off of 0.2 ng/ml above which antibiotics to be given[28].

PCT as a marker of infection is used to differentiate or ruling out bacterial infection in meningitis [29], in patients of chronic kidney disease receiving hemodialysis [30] and in diagnosis of infectious complications in gastrointestinal diseases[31].

Septic arthritis [32], medullary carcinoma thyroid [33] and urinary tract infections [34] are other infections where PCt find usefulness. The levels of PCT are spuriously elevated in amphetamine over dose [35].

Rapid detection of bacteremia facilitates early implementation of therapy and identifies patients at high risk for complications. Previous studies demonstrated that various clinical markers have poor sensitivity and specificity for predicting early bacteremia in febrile patients. Similarly, ruling out bacterial sepsis in febrile patients has substantial benefits, including reduction of hospitalization and antimicrobial use and facilitating clinician focus on alternative diagnostic pathways.

CONCLUSION

The PCT is a unique biomarker for identification of sepsis but has a weak correlation with WBC count that suggests that PCT levels alone may not be enough for sepsis and therefore a combination of biomarkers may be more functional in the case of clinical application , the gold standard till date remains blood culture.

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REFERENCES

1. Levy MM, Dellinger RP, Townsend SR, Linde-Zwirble WT, Marshall JC, Bion J, Schorr C, Artigas A, Ramsay G, Beale R, Parker MM, Gerlach H, Reinhart K, Silva E, Harvey M, Regan S, Angus DC; Surviving Sepsis Campaign. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. Crit Care Med. 2010 Feb;38(2):367-74. doi: 10.1097/ CCM. 0b013e 3181 cb0 cdc. PMID: 20035219.
2. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med* 2017;43:304-77. 10.1007/s00134-017-4683-6
3. Zilahi G, McMahon MA, Povoa P, et al. Duration of antibiotic therapy in the intensive care unit. *J Thorac Dis* 2016;8:3774-80. 10.21037/jtd.2016.12.89
4. Jee Y, Carlson J, Rafai E, et al. Antimicrobial resistance: a threat to global health. *Lancet Infect Dis* 2018;18:939-40. 10.1016/S1473-3099(18)30471-7
5. Annane D, Maxime V, Faller JP, et al. Procalcitonin levels to guide antibiotic therapy in adults with non-microbiologically proven apparent severe sepsis: a randomised controlled trial. *BMJ Open* 2013;3. doi: .10.1136/bmjopen-2012-002186
6. Bloos F, Trips E, Nierhaus A, et al. Effect of Sodium Selenite Administration and Procalcitonin-Guided Therapy on Mortality in Patients With Severe Sepsis or Septic Shock: A Randomized Clinical Trial. *JAMA Intern Med* 2016;176:1266-76. 10.1001/ jamainternmed.2016.2514
7. de Jong E, van Oers JA, Beishuizen A, et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. *Lancet Infect Dis* 2016;16:819-27. 10.1016/S 1473-3099(16)00053-0
8. Deliberato RO, Marra AR, Sanches PR, et al. Clinical and economic impact of procalcitonin to shorten antimicrobial therapy in septic patients with proven bacterial infection in an intensive care setting. *Diagn Microbiol Infect*
9. *Dis* 2013;76:266-71. 10.1016/j.diagmicrobio.2013.03.027 Huang HB, Peng JM, Weng L, et al. Procalcitonin-guided antibiotic therapy in intensive care unit patients: a systematic review and meta-analysis. *Ann Intensive Care* 2017;7:114. 10.1186/s13613-017-0338-6
10. Iankova I, Thompson-Leduc P, Kirson NY, et al. Efficacy and Safety of Procalcitonin Guidance in Patients With Suspected or Confirmed Sepsis: A Systematic Review and Meta-Analysis. *Crit Care Med* 2018;46:691-8. 10.1097/CCM.0000000000002928
11. Lamping F, Jack T, Rubsamen N, et al. Development and validation of a diagnostic model for early differentiation of sepsis and non-infectious SIRS in critically ill children - a data-driven approach using machine-learning algorithms. *BMC Pediatr* 2018;18:112. 10.1186/s12887-018-1082-2
12. Schuetz P, Birkhahn R, Sherwin R, et al. Serial Procalcitonin Predicts Mortality in Severe Sepsis Patients: Results From the Multicenter Procalcitonin MOnitoring SEpsis (MOSES) Study. *Crit Care Med* 2017;45:781-9. 10.1097/CCM.0000000000002321
13. Wacker C, Prkno A, Brunkhorst FM, et al. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. *Lancet Infect Dis* 2013;13:426-35. 10.1016/S1473-3099(12)70323-7 .
14. Schuetz P, Beishuizen A, Broyles M, et al. Procalcitonin (PCT)-guided antibiotic stewardship: an international experts consensus on optimized clinical use. *Clin Chem Lab Med* 2019;57:1308-18. 10.1515/cclm-2018-1181.
15. Sager R, Kutz A, Mueller B, et al. Procalcitonin-guided diagnosis and antibiotic stewardship revisited. *BMC Med* 2017;15:15. 10.1186/s12916-017-0795.
16. Rhee C, Kadri SS, Danner RL, et al. Diagnosing sepsis is subjective and highly variable: a survey of intensivists using case vignettes. *Crit Care* 2016;20:89. 10.1186/s13054-016-1266-9.
17. Laukemann S, Kasper N, Kulkarni P, et al. Can We Reduce Negative Blood Cultures With Clinical Scores and Blood Markers? Results From an Observational Cohort Study. *Medicine (Baltimore)* 2015;94:e2264. 10.1097/MD.0000000000002264.
18. Vincent JL, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med* 2006;34:344-53. 10.1097/01. CCM.0000 194725. 48928.3A
19. Muller B, Schuetz P, Trampuz A. Circulating biomarkers as surrogates for bloodstream infections. *Int J Antimicrob Agents* 2007;30 Suppl 1:S16-23. 10.1016/ j.ijantimicag. 2007. 06.032 .
20. Becker KL, Nylen ES, White JC, et al. Clinical review 167: Procalcitonin and the calcitonin gene family of peptides in inflammation, infection, and sepsis: a journey from calcitonin back to its precursors. *J Clin Endocrinol Metab* 2004;89:1512-25. 10.1210/jc.2002-021444.
21. 28. Christ-Crain M, Muller B. Procalcitonin in bacterial infections--hype, hope, more or less? *Swiss Med Wkly* 2005;135:451-60.
22. 29. Gilbert DN. Use of plasma procalcitonin levels as an adjunct to clinical microbiology. *J Clin Microbiol* 2010;48:2325-9. 10.1128/JCM.00655-10
23. 30. Maruna P, Nedelnikova K, Gurlich R. Physiology and genetics of procalcitonin. *Physiol Res* 2000;49 Suppl 1:S57-61.
24. Linscheid P, Seboek D, Schaer DJ, et al. Expression and secretion of procalcitonin and calcitonin gene-related peptide by adherent monocytes and by macrophage-activated adipocytes. *Crit Care Med* 2004;32:1715-21. 10.1097/01.CCM.0000134404.63292.71.
25. Schuetz P, Wirz Y, Sager R, et al. Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis. *Lancet Infect Dis* 2018;18:95-107. 10.1016/S1473-3099(17)30592-3.
26. u, X. -Y.; Wang, Y.; Zhong, H.; Dou, Q. -L.; Song, Y. -L.; Wen, H. (2014-01-01). "Diagnostic Value of Serum Procalcitonin in Solid Organ Transplant Recipients: A Systematic Review and Meta-analysis". *Transplantation Proceedings*. **46** (1): 26–32. doi:10.1016/j.transproceed.2013.07.074. ISSN 0041-1345. PMID 24507021
27. Schuetz P, Daniels LB, Kulkarni P, Anker SD, Mueller B (November 2016). "Procalcitonin: A new biomarker for the cardiologist". *International Journal of Cardiology*. **223**: 390–397. doi:10.1016/j.ijcard.2016.08.204. PMID 27543716
28. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P (July 2016). "2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC". *European Heart Journal*. **37** (27): 2129–2200. doi:10.1093/eurheartj/ehw128. PMID 27206819
29. Wei TT, Hu ZD, Qin BD, Ma N, Tang QQ, Wang LL, Zhou L, Zhong RQ (March 2016). "Diagnostic Accuracy of Procalcitonin in Bacterial Meningitis Versus Nonbacterial Meningitis: A Systematic Review and Meta-Analysis". *Medicine*. **95** (11): e3079. doi:10.1097/MD.0000000000003079. PMC 4839921. PMID 26986140
30. Grace E, Turner RM (December 2014). "Use of procalcitonin in patients with various degrees of chronic kidney disease including renal replacement therapy". *Clinical Infectious Diseases*. **59** (12): 1761–7. doi:10.1093/cid/ciu732. PMID 25228701
31. Lippi G, Sanchis-Gomar F (December 2017). "Procalcitonin in inflammatory bowel disease: Drawbacks and opportunities". *World Journal of Gastroenterology*. **23** (47): 8283–8290. doi:10.3748/wjg.v23.i47.8283. PMC 5743499. PMID 29307988
32. Zhao J, Zhang S, Zhang L, Dong X, Li J, Wang Y, Yao Y (August 2017). "Serum procalcitonin levels as a diagnostic marker for septic arthritis: A meta-analysis". *The American Journal of Emergency Medicine*. **35** (8): 1166–1171.
33. Trimboli P, Giovanella L (June 2018). "Procalcitonin as Marker of Recurrent Medullary Thyroid Carcinoma: A Systematic Review and Meta-Analysis". *Endocrinology and Metabolism*. **33** (2): 204–210. doi:10.3803/EnM.2018.33.2.204. PMC 6021302. PMID 29947178
34. Memar MY, Varshochi M, Shokouhi B, Asgharzadeh M, Kafil HS (December 2017). "Procalcitonin: The marker of pediatric bacterial infection". *Biomedicine & Pharmacotherapy*. **96**: 936–943. doi:10.1016/j.biopha.2017.11.149. PMID 29203386
35. van der Does Y, Rood PP, Haagsma JA, Patka P, van Gorp EC, Limper M (July 2016). "Procalcitonin-guided therapy for the initiation of antibiotics in the ED: a systematic review". *The American Journal of Emergency Medicine*. **34** (7): 1286–93. doi:10.1016/j.ajem.2016.03.065. PMID 27130585.