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ORIGINAL RESEARCH

Studying the efficacy of procalcitonin as a potent biomarker in non-sepsis bacterial infections

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ABSTRACT

Background: The calcitonin hormone is vital in regulating phosphorus and calcium homeostasis. Also, in systemic inflammation, such as bacterial infections, procalcitonin is produced in various tissues. The procalcitonin level rises 2-4 hours post-stimulation and reaches a maximum in 6-2 hours. However, the literature data is mainly dependent on sepsis-induced bacterial infection. **Aim:** The present study evaluated the procalcitonin test's ability to discriminate various bacterial (non-sepsis) etiologies in a large population of Indian subjects. **Methods:** The present study was assessed utilizing routine laboratory and clinical data gathered from the Department of Microbiology of the Institute within the defined study period. The data gathered were used to assess the significance of serum biomarker C reactive protein, procalcitonin test, and total leucocyte count for early detection of bacterial infection. **Results:** The study results showed a higher prevalence of increased levels of procalcitonin in cases of gram-negative bacterial infections, particularly in infections of Klebsiella pneumoniae and Escherichia coli in comparison to the population with gram-positive bacterial infections. **Conclusions:** The present study concludes that there is an increase in PCT levels even in subjects with non-septic bacterial infections as an increase in CRP and TLC which are taken as the standard of serum biomarkers in any bacterial infection. It is also seen that the increase in these biomarkers in gram-negative and gram-positive infected subjects is similar irrespective of gender. Also, raised PCT is higher in gram-negative infections compared to gram-positive infections.

Keywords: Biomarkers in bacterial infection, Biomarkers in Gram-negative bacteria infection, Serum PCT in non-sepsis infection, PCT

INTRODUCTION

In healthy subjects, PCT (procalcitonin) is synthesized in the C cells of the thyroid via the CALC-1 gene located on chromosome number 11. The mRNA product formed is then known as preprocacitonin which further undergoes processing to first form calcitonin and further to three molecules N-terminal procalcitonin, ketacalcitonin, and active calcitonin. The calcitonin hormone plays a vital role in the regulation of phosphorus and calcium homeostasis.[1]

In normal situations, increased levels of β-adrenergic stimuli, gastrin, glucagon, CGRP (calcitonin gene-related peptide), and glucocorticoids induce the CALC-1 gene present in thyroid C cells. Further, all the procalcitonin synthetized in these calls is converted to calcitonin which minimizes the release of procalcitonin to circulation and maintains very low levels as 0.05 ng/mL in healthy subjects. During systemic inflammation, especially with bacterial infections, the production of procalcitonin is seen in

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different tissues as adipose tissue, kidney, liver, and lungs mainly via the mentioned two pathways.[2]

LPS (lipopolysaccharide) or other toxic microbial metabolites trigger the direct pathway, whereas, the indirect pathway is started by inflammatory mediators such as TNF-α, IL-6, and others. However, the exact mechanism for the production of procalcitonin during infection is still unclear, it is considered that sepsis-induced cytokines and bacterial LPS influence peripheral blood mononuclear cells and the liver to produce procalcitonin. Microbial infection results in increased CALC-1 gene expression leading to increased procalcitonin levels, sometimes to 1000 times based on mortality and disease severity.[3]

Procalcitonin levels increase is detectable as early as 2-4 hours after stimulation and reaches peak value within 6-24 hours. This can be the reason why unlike CRP (C-reactive protein), procalcitonin is considered a stable and earliest marker and its concentration is not affected by steroidal anti-inflammatory drugs, non-steroidal anti-inflammatory drugs, immunodeficiency, and neutropenia. Also, various reports in literature commonly considered systemic markers such as ESR (Erythrocyte Sedimentation Rate) and CRP (C-reactive protein) as having poor specificity and sensitivity for diagnosis of bacterial infections.[4]

Hence, a biomarker that can accurately and rapidly assess the underlying bacterial infection is needed for use in clinical settings for the prevention of mortality particularly owing to bacterial infection-induced sepsis. The role of procalcitonin as a potential biomarker in subjects with non-sepsis bacterial infection is lacking. The effect of various commonly occurring bacterial infections that can change the level of PCT is also not established well.[5] Hence, the present study aimed to assess the prevalence of various bacterial infections and study the efficacy of various biomarkers as procalcitonin in assessing non-sepsis bacterial infections

MATERIALS AND METHODS

The present longitudinal observational study was aimed at assessing the prevalence of various bacterial infections and studying the efficacy of various biomarkers as procalcitonin in assessing non-sepsis bacterial infections.The study subjects were from the Outpatient Department of the Institute. Verbal and written informed consent were taken from all the subjects before participation.

The study utilized routine laboratory and clinical data in the participants within the defined study period to assess the significance of various biomarkers such as PCT (procalcitonin) count, TLC (total leucocyte count), and CRP (C reactive protein) in early detection of bacterial infection. The study assessed data from 970 subjects aged >18 years who were admitted to the Institute with a primary diagnosis of infection-related concerns such as hypothermia, chills, and fever. There were 544 male and 426 female subjects.

The inclusion criteria for the study were subjects with presentations as hypothermia, chills, and fever, aged 18-45 years, from both genders, diagnosed with acute bacterial infection without septicemia, PCT, CRP, and TLC values of more than 0.25 ng/mL, 10mg/l of blood, and 11000 cells/cu mm, and >80% of neutrophil count in DLC (differential leucocyte counts). The exclusion criteria for the study were subjects with any type of chronic bacterial infection such as tuberculosis, any organic diseases such as hormonal diseases, kidney disease, heart disease, diabetes mellitus, and hypertension. Any autoimmune or malignant disease such as rheumatoid arthritis etc.

For sample collection, subjects diagnosed with acute bacterial infection without septicemia were taken in the study. Various samples as urine, blood, respiratory suction, and wound swabs were used to assess bacterial infection types. Isolated colonies from incubated culture media were stained using gram staining to determine bacterial infection type as gram-negative and positive. In both types, serum biomarker data were gathered to comparatively assess the contribution of various biomarkers in various types of bacterial infection.

Assessment of serum marker for PCT considered the lower detection limit as 0.25ng/mL, whereas, in TLVC and CRP cases, laboratory standard cut-off for abnormal values was taken as 10ng/l for CRP and <11000 cells/cumm of blood respectively. All parameters such as TLC, CRP, and PCT were assessed using a conventional autoanalyzer.

The data gathered were analyzed statistically using SPSS (Statistical Package for the Social Sciences) software version 24.0 (IBM Corp., Armonk. NY, USA) for assessment of descriptive measures, Student t-test, ANOVA (analysis of variance), and Chi-square test. The results were expressed as mean and standard deviation and frequency and percentages. The p-value of <0.05 was considered.

RESULTS

The present longitudinal observational study was aimed at assessing the prevalence of various bacterial infections and studying the efficacy of various biomarkers as procalcitonin in assessing non-sepsis bacterial infections. The study assessed data from 970 subjects aged >18 years who were admitted to the Institute with a primary diagnosis of infection-related concerns such as hypothermia, chills, and fever. There were 544 male and 426 female subjects. Among these subjects, 668 subjects had a gram-negative bacterial infection and 302 subjects had a gram-positive infection. Klebsiella pneumoniae and E.coli were dominant in gram-negative and Staphylococcus sp. In gram-positive infections from all varieties of samples. Enterobacteria was predominantly seen in urine samples beside Staphylococcus.

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The study results showed that PCT was increased in a relatively small number of infected subjects when culture was grown from blood samples and swabs, however, when culture was grown on urine samples or respiratory suction, raised PCT levels were seen in a large number of subjects. However, raised TLC and CRP levels are maximum in urine samples and respiratory suction. This also showed that raised PCT levels were seen in 104 gram-negative infected subjects and raised CRP was seen in nearly 480 gram-negative bacterial infected subjects. Prevalence of increased serum levels of PCT, CRP, and TLC showed that serum PCT was seen in a lesser number of gram-positive bacterial infection-affected subjects irrespective of a variation in the samples.

It was seen that the percentage increase in TLC, PCT, and CRP was significantly higher compared to reference normal levels in both gram-positive and gram-negative bacterial infection-affected subjects. The study results using ANOVA depicted that a percentage increase in PCT, TLC, and CRP in all the subjects from both gram-negative and gram-positive bacterial infection-affected subjects is significantly altered from all the types with $p<0.05$ from their normal cut-offs (Table 1). The study results depicted no significant difference in the percentage increase in CRP in gram-negative infected females and males. Also, there was no gender-based difference in the percentage increase in PCT and TLC. Similar results were seen in gram-positive bacterial infection-affected subjects with no gender-based difference in percentage increase of PCT, TLC, and CRP.

It is seen that however, on comparison of the percentage increase of PCT, TLC, and CRP in uninfected study subjects to gram-positive bacterial infection subjects, no significant difference was seen in the percentage increase of TLC and CRP between two variables. However, a percentage increase of PCT was more profound in gram-negative infected subjects. Also, change in PCT levels in gram-positive bacterial infection subjects is not always in a positive direction. It was also reported that 14% which was a significant number of gram-positive bacterial infection-affected subjects had no change in level of PCT from its cut-off value of 0.25 ng/mL.

Table 1: Comparison of significance level change of various serum biomarkers in bacterial-infected subjects

S. No	Parameter	CRP	TLC	PCT	Total
1.	Number (n)	394	326	328	1080
2.	Mean ± S> D	351.3297±31.19	87.0831±18.53	216.4779±52.52	259.229±0.00

DISCUSSION

The present study assessed data from 970 subjects aged >18 years who were admitted to the Institute with a primary diagnosis of infection-related concerns such as hypothermia, chills, and fever. There were 544 male and 426 female subjects. Among these subjects, 668 subjects had a gram-negative bacterial infection and 302 subjects had a gram-positive infection. Klebsiella pneumoniae and E.coli were dominant in gram-negative and Staphylococcus sp. In gram-positive infections from all varieties of samples. Enterobacteria was predominantly seen in urine samples beside Staphylococcus. These data were comparable to the studies ofShuhua L et al[6] in 2016 and Martini A et al[7] in 2010 where authors assessed subjects with non-sepsis bacterial infections and demographics comparable to the present study in their respective studies.

It was seen that PCT was increased in a relatively small number of infected subjects when culture was grown from blood samples and swabs, however, when culture was grown on urine samples or respiratory suction, raised PCT levels were seen in a large number of subjects. However, raised TLC and CRP levels are maximum in urine samples and respiratory suction. This also showed that raised PCT levels were seen in 104 gram-negative infected subjects and raised CRP was seen in nearly 480 gram-negative bacterial infected subjects. Prevalence of increased serum levels of PCT, CRP, and TLC showed that serum PCT was seen in a lesser number of gram-positive bacterial infection-affected subjects irrespective of any variation in the samples. These results were consistent with the studies ofTavares E et al[8] in 2005 and Elsen G et al[9] in 2007 where authors also reported increased PCT in small subjects in swab and blood culture and a higher number in respiratory suction and urine swabs as seen in the results of the present study.

The study results showed that the percentage increase in TLC, PCT, and CRP was significantly higher compared to reference normal levels in both gram-positive and gram-negative bacterial infection-affected subjects. The study results using ANOVA depicted that a percentage increase in PCT, TLC, and CRP in all the subjects from both gram-negative and gram-positive bacterial infection-affected subjects is significantly altered from all the types with $p<0.05$ from their normal cut-offs (Table 1). The study results depicted no significant difference in the percentage increase in CRP in gram-negative infected females and males. Also, there was no gender-based difference in the percentage increase in PCT and TLC. Similar results were seen in gram-positive bacterial infection-affected subjects with no gender-based difference in percentage increase of PCT, TLC, and CRP. These findings were in agreement with the results ofHatzistilianou M et al[10] in 2010 and Su L et al[11] in 2012 where an increase in PCT, TLC, and CRP in all the subjects from both gram-negative and gram-positive bacterial infection-affected subjectsaltered

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significantly from their cut-off also reported by the authors in their respective studies.

The study results also showed that however, on comparison of the percentage increase of PCT, TLC, and CRP in uninfected study subjects to gram-positive bacterial infection subjects, no significant difference was seen in the percentage increase of TLC and CRP between the two variables. However, a percentage increase of PCT was more profound in gram-negative infected subjects. Also, change in PCT levels in gram-positive bacterial infection subjects is not always in a positive direction. It was also reported that 14% which was a significant number of gram-positive bacterial infection-affected subjects had no change in level of PCT from its cut-off value of 0.25 ng/mL. These results correlated with the findings of Wu SC et al[12] in 2020 and Waterfield T et al[13] in 2020 where authors also reported an increase of PCT as more profound in gram-negative infected subjects as seen in the results of the present study.

CONCLUSIONS

The present study, within its limitations, concludes that there is an increase in PCT levels even in subjects with non-septic bacterial infections as an increase in CRP and TLC which are taken as the standard of serum biomarkers in any bacterial infection. It is also seen that the increase in these biomarkers in gram-negative and gram-positive infected subjects is similar irrespective of gender. Also, raised PCT is higher in gram-negative infections compared to gram-positive infections.

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