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The Role of Procalcitonin as a Biomarker in Odontogenic Space Infection – A Review of Literature

Sharad Gowda*, Zeniya Hashmi, Sahil Prashar, Sukhwinder Pal Singh
Department of Family Oral Health, Punjab Government Dental College and Hospital, India

ABSTRACT

Biomarkers to guide antibiotic treatment decisions have been proposed as an effective means of promoting more appropriate antibiotic use. Procalcitonin (PCT) is synthesized by a variety of tissues and organs in response to invasion by pathogenic bacteria, fungi, and some parasites. The favourable kinetics of PCT may allow earlier diagnosis of sepsis and better monitoring of its progression. Thus, the primary utility of PCT is to detect the presence of systemic bacterial infections such as sepsis, and numerous studies have investigated the potential role of PCT in diagnosis and treatment. Clinically, the values of PCT can help determine the need for empirical antibiotic therapy, control of the source of infection, and duration of antibiotic therapy. In this review, the evidence for the usefulness of PCT in the diagnosis and treatment of odontogenic infections is discussed with its reliability and limitations to provide an overview of the potential of PCT to guide antibiotic therapy.

Keywords: Biological markers, Procalcitonin, Antibiotic guidance, Sepsis

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Corresponding author: Sharad Gowda
E-mail✉: gowdasharad.suresh1234@gmail.com
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INTRODUCTION

Pyogenic oro-facial infections are odontogenic in origin in most cases. They can range from periapical abscesses to superficial and deep infections in the neck. If left untreated, they usually spread to the adjacent fascial spaces (masseteric, sublingual, submandibular, temporal, buccal, canine, and parapharyngeal) and may lead to further complications. Therefore, early detection of infection and appropriate therapy are critical [1]. PCT is produced by thyroid neuroendocrine C cells as a 116-amino acid precursor of calcitonin. During bacterial infection, PCT is upregulated and consequently expressed in all cells of the body, but especially in hepatocytes, resulting in increased release of PCT into the bloodstream [2]. PCT increases rapidly after infection and peaks within 12-24 hours. This is earlier than CRP, which peaks after 2-3 days [3]. With a half-life of 24-30 hours, PCT can stimulate the release of pro-inflammatory cytokines, enhancing the inflammatory response [4]. PCT is a better discriminator between viral or bacterial infections compared to CRP [5]. This is because many inflammatory cytokines, including IL -1 and IL -6, contribute to the upregulation of PCT. An exception is interferon-gamma (IFN-γ), which reduces the expression of PCT, leading the lower levels of PCT in viral infections [6]. In healthy individuals, procalcitonin levels are as low as 10 pg/ml-1. CALC -1 Gene expression is markedly increased after microbial infection in all parenchymal tissues and differentiated cell types in the body, leading to a significant increase in levels up to one thousand times normal (1,00,000 pg/ml-1) [7]. PCT Values are related to the severity of bacterial infections and may also be useful in determining the initiation and duration of antibiotic treatment via PCT measurements [8-11]. The aim of this review is to summarize the current evidence for the usefulness of PCT as a diagnostic marker for odontogenic space infections, its reliability, and its limitations when used to guide antimicrobial therapy, as well as the overall usefulness of

PCT analysis for systemic bacterial infections; however, few understand the rationale for using PCT in patients with odontogenic maxillofacial infections.

Procalcitonin

Procalcitonin was originally described in 1984 as a 116-amino acid protein with a molecular mass of 14-5kDa [12]. The PCT gene, referred to as CALC1, is located on chromosome 11p 15.4 and was sequenced in 1989 [13]. From the numerous studies, it can be concluded that the 'normal' plasma/serum levels of PCT in healthy adults measured are < O-5 μg/L [14]. Values below the detection limit calculated [15], i.e., 0-24 μg/L, are frequently reported. Bacterial infections lead to a general increase in CALC -1 gene expression and release of PCT (> 1 μg/ mL) [16]. The expression of this hormone is site-specific [17]. In healthy and uninfected individuals, transcription of PCT occurs only in neuroendocrine tissues, with the exception of thyroid C cells. The formed PCT is then undergoes post-translational modifications, resulting in the production of small peptides and mature CT by removal of the C-terminal glycine from the immature CT by Peptidylglycine A-Amidating Monooxygenase (PAM) [18]. In a microbial infected individual, non-neuroendocrine tissue also secretes PCT by expression of CALC -1. Microbial infection leads to a substantial increase in the expression of CALC -1 , resulting in the production of PCT in all differentiated cell types [19]. The function of PCT, which is synthesized in non-neuroendocrine tissue due to microbial infection, is currently unknown, but, its detection aids in the differentiation of inflammatory processes. PCT is present in the blood during sepsis, and levels increase independently of calcitonin; moreover, levels of PCT were elevated in a septic thyroidectomized patient [20, 21], strongly suggesting that thyroid C cells are not the site of origin of PCT. It is clear that bacterial endotoxin releases PCT into the bloodstream. Healthy volunteers injected with Escherichia coli endotoxin felt ill within 1 h of injection, developed fever within 1- 2 h and developed chills, rigors and myalgia within 1- 3 h. PCT was undetectable in plasma at 2 h but was consistently detected at 4 h, increased rapidly at 6 h and remained elevated at 8 and 24h. The half-life is estimated to be 25-30 h. Plasma TNF-α concentrations increased sharply after 1 h, peaked after 2 h, and declined to baseline by 6 h. Plasma levels of IL -6 peaked after 3 h and returned to baseline by 8 h. The elevation of plasma PCT occurs shortly after cytokine levels peak, which may suggest that these cytokines are the mediators of PCT elevation. Other possible target cells for endotoxin action involved in inflammatory processes and therefore a possible source of procalcitonin are leukocytes and macrophages. Procalcitonin mRNA is expressed in human peripheral blood mononuclear cells, and various proinflammatory cytokines and Lipopolysaccharides (LPS) have a marked stimulatory effect. Approximately one-third of unstimulated human lymphocytes and monocytes contain immunologically detectable PCT protein; this is only slightly induced by bacterial lipopolysaccharide [22-24], but monocytes from a patient with septic shock showed higher basal levels and increased PCT content upon stimulation with LPS. It has also been noted that procalcitonin release can occur from other organs that respond to endotoxin, such as kidney [25], spleen [26], liver [27], and lung [28]. Spleen, liver and lung originate from macrophages, while medullary cells in kidney may also express various peptides in response to endotoxin and cytokines [29].

Procalcitonin As a Diagnostic Biomarker

Biomarkers are needed to help physicians make a correct diagnosis and initiate the right treatment to improve patient outcomes after initial presentation or hospitalisation. An ideal biomarker for bacterial infections should enable early and rapid diagnosis, predict disease progression and prognosis, and guide therapeutic decisions. The main disadvantages of many current microbiological methods are diagnostic delays (e.g., culture methods), suboptimal sensitivity (e.g., blood cultures), and low specificity due to contamination (e.g., sputum cultures), while others are not suitable for routine diagnosis due to their invasive nature (e.g., lung biopsy). PCT is useful for early detection of sepsis as well as for monitoring the antimicrobial treatment regimen. Indeed, PCT can be a useful tool for antimicrobial stewardship, and its use can certainly lead to a significant reduction in the unnecessary administration of antimicrobial therapies [30]. The production of PCT during bacterial illness and its association with sepsis was first demonstrated by Asscot et

al [31]. Numerous studies have demonstrated the clinical utility of PCT as a diagnostic marker in severe infections. Muller and colleagues conducted a study in consecutive critically ill patients to compare the usefulness of serum concentrations of calcitonin precursor, CRP, IL -6, and lactate for the diagnosis of sepsis. Blood samples were collected at different time intervals during the course of illness Systemic Inflammatory Response Syndrome (SIRS), sepsis and severe sepsis, and septic shock. Serum concentrations of calcitonin precursor, CRP, IL -6, and lactate were elevated according to the severity of illness. Based on Receiver Operating Characteristic Curve Analysis (ROC), they concluded that PCT is the most reliable marker for the diagnosis of sepsis with a sensitivity of 89% and a specificity of 94%.

Enguix-Armada A et al. analysed the diagnostic value by Comparing C-Reactive Protein (CRP), Procalcitonin (PCT), presepsin or SCD14- ST and mid-regional pro-adrenomedullin (MR-proADM) measured in the first 24 hours after admission to the ICU, allowing better management of septic patients (diagnostic and prognostic) in both Severe Sepsis (SS) and Septic Shock (SSh). Cohort study of 388 patients admitted to the ICU within 12 months, including 142 controls. Biomarkers were measured by immunoluminometric assays in serum or plasma samples within the first 24 hours after admission. In the cohort studied, PCT had the highest Area Under the Curve (AUC) (0.989) compared with the other biomarkers ($p< 0.01$). PCT was also used to determine the difference between Gram-positive or Gram-negative bacteria [32]. Zhang et al studied PCT and high-sensitivity CRP (hs-CRP) levels in the evaluation of sepsis and septic shock in geriatric patients in the ICU. They found that hs-CRP and PCT were good markers for the diagnosis of sepsis and septic shock in patients older than 85 years [33]. Garnacho-Montero et al. studied PCT and CRP levels in SIRS and concluded that ProCT can be a more reliable biomarker at hospital admission and is superior to CRP [34].

Procalcitonin As A Guide For Antibiotic Therapy

Antimicrobial resistance is a global public health challenge that has been accelerated by the overuse of antibiotics worldwide. Increasing antibiotic resistance is the cause of serious infections, complications; longer hospital stays, and increased mortality. An ideal marker should support early diagnosis and be able to track the disease and facilitate therapeutic interventions and decisions [35]. The PCT is a better choice compared to other markers that meet these characteristics. An algorithm based on serial measurement of PCT can reduce antibiotic exposure in septic patients [36].

Schroeder et al. performed a study in ICU patients with severe sepsis considering two classes: PCT guided and control. In all patients, drug administration was based on the microbiological spectrum. When clinical signs of infection improved and PCT levels decreased to <35% of baseline, antibiotic treatment was discontinued in PCT -guided patients. In the control group, treatment was based on empirical rules. The algorithm based on PCT was found to reduce both the use of antibiotics and the cost of treatment [37]. Nobre et al. conducted a randomized control trial in which patients were randomly assigned to the intervention group. Antibiotics were discontinued when PCT levels had decreased by 90% or more from baseline. For control patients, physicians decided on the duration of antibiotic therapy based on empirical rules. For patients in the PCT group, the average duration of antibiotic therapy for the first episode of infection was 3.5 days shorter than for control subjects. In patients in whom a decision could be taken based on the basis of serial PCT measurements, PCT guidance resulted in a 4-day shorter duration of antibiotic therapy (according to protocol, $n = 68$, $P = 0.003$) and lower total antibiotic exposure ($P = 0.0002$). Patients in the PCT group also had a shorter ICU stay of 2 days ($P = 0.03$) [38]. In a randomized intervention trial studied by Christ-Crain et al, 302 consecutive patients with suspected community-acquired pneumonia were included. The control group ($n = 151$) received antibiotics according to standard practice. In the procalcitonin group ($n = 151$), antibiotic treatment was based on serum procalcitonin concentrations. Procalcitonin guidance reduced overall antibiotic exposure (relative risk, 0.52; 95% confidence interval, 0.48-0.55; $p < 0.001$), antibiotic prescriptions on admission (85 vs. 99%; $p< 0.001$) and duration of antibiotic treatment (median, 5 vs. 12 d; $p < 0.001$) compared with patients treated according to guidelines [39].

Procalcitonin Role In Odontogenic Space Infection

Oral and maxillofacial infections can occur in any age group. Most infections are confined to the soft tissues or underlying fascial space in the maxillofacial region and cause mainly local symptoms. Few patients have a severe course that can lead to a systemic inflammatory response, sepsis, severe sepsis, septic shock, and systemic symptoms, especially in elderly patients. Sepsis is the leading cause of morbidity and mortality worldwide [40]. Therefore, there is a need for a serum biological index that is simple to use and easy to evaluate at the bedside to guide clinical management and assessment. This study by Xin-yan Lin et al. aimed to investigate the effects on severity and prognostic value of serum procalcitonin in elderly patients with oral and maxillofacial infections. They divided 163 elderly patients with severe oral and maxillofacial infections into survival and death groups according to prognosis between June 2015 and May 2021, and measured serum procalcitonin by enzyme immunoassay on the first, second, third, fifth, and seventh days after admission to determine the dynamic changes in serum procalcitonin. Serum procalcitonin level increased significantly in both groups after admission, initially increasing sharply in the survival group and then decreasing rapidly, whereas it continued to increase or decreased slowly in the death group, with the high value fluctuating. After admission, serum procalcitonin level on the third day has great value for prognostic assessment of elderly patients with severe oral and maxillofacial infection [41].

Ji-Kwan Kim, Joe-Hoon Lee enrolled sixty patients, admitted with odontogenic maxillofacial infection from September 2018 to March 2020. White blood cell count, C-reactive protein, and procalcitonin concentration were evaluated. Sixty patients were divided into two groups, the sepsis and non-sepsis groups, based on the systemic inflammatory response syndrome. A Student ttest was performed to statistically analyse the difference in inflammatory markers between sepsis and non-sepsis groups. The mean procalcitonin levels at admission were 7.24 ng/ml (range, 0.09-37.15 ng/ml) and 0.40 ng/ml (range, 0.02-4.94 ng/ml) in the sepsis and nonsepsis groups, respectively. The procalcitonin levels between the two groups showed a significant difference ($P < 0.05$). Therefore, the results recommend that the procalcitonin test should be performed in patients with maxillofacial infections in addition to conventional laboratory tests to diagnose the systemic inflammatory condition of patients. Further studies and research are needed to improve the scientific basis of the usefulness of procalcitonin in the maxillofacial space infections to expand the horizon of knowledge and application in clinical settings.

PCT Assays

Based on a highly sensitive research assay, the normal value of PCT in uninfected individuals is 0.033 ± 0.003 ng/ml. The first commercial PCT assay (LUMI test) has a functional lower sensitivity limit of 0.5 ng/ml. The FDA-approved second-generation PCT assay is technically a Time-Resolved Cryptate Emission Immunoassay (TRACE). The assay quantifies both PCT and a portion of the N-terminal end of the PCT molecule. The functional lower sensitivity limit is 0.05 ng/ml, and the assay has reliable linear quantification up to 1,000 ng/ml. either serum or plasma is used, and results are available within 1 hour or less.

Advantages and Limitations of Pct

Unlike other biomarkers, the production of PCT is virtually unaffected by nonsteroidal or steroidal anti-inflammatory drugs. Moreover, PCT production does not dependent on white blood cells per se, and the levels of PCT increase during systemic bacterial infections in neutropenic patients. Therefore, the levels of PCT remain a valuable marker of the host inflammatory response even when nonsteroidal anti-inflammatory drugs and pharmacological doses of corticosteroids have altered the patient's temperature curve, white blood cell count, and white blood cell differential. There are a number of limitations to the use of PCT as a marker of infection and sepsis. Nonspecific elevations of PCT levels in the absence of bacterial infection may occur in situations of massive stress, such as after major trauma and surgery or in patients with cardiac shock. For this reason, the ability of PCT, to distinguish between sepsis and sterile inflammation is better in medical patients than in surgical patients. In addition, several other causes of nonbacterial systemic inflammation have been reported, including neonatal birth stress, heat shock, and acute graft-versus-host disease, as well as various types of immunotherapies such

as granulocyte transfusions, administration of antilymphocyte globulin or anti-CD3 antibodies, and therapy with cytokines or related antibodies (IL -2 or TNF-α). Some autoimmune diseases such as Kawasaki disease or various types of vasculitis and paraneoplastic syndromes are also associated with elevated PCT levels [42].

CONCLUSION

Determination of procalcitonin in patients may support clinical decisions for early diagnosis of bacterial infections to reduce unnecessary tests, procedures, and hospitalizations. This would reduce overall mortality and overall medical costs. PCT is a unique biomarker that has a wide range of applications in medicine compared to other conventional markers for sepsis. However, to diagnose invasive bacterial infection and its severity, evaluation of PCT values alone may not be sufficient. Given the potential complications of sepsis diagnosis and the difficulty in distinguishing between microbial and non-microbial infections, it is unlikely that a single biomarker can serve as an effective diagnostic tool. A combination of biomarkers might be more appropriate in case of clinical application, but this requires further studies on various aspects as a reliable diagnostic tool. Most studies were limited in their patient sample, which could affect the generalizability of using procalcitonin as an infection marker. Further research is needed to determine whether or not the routine use of procalcitonin should be used in settings other than the emergency department.

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