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Serum procalcitonin as an early indicator for bone and joint infection

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Abstract

Background: Acute bone and joint infection is a common entity in Orthopaedics and very few studies have investigated role of Procalcitoninin the diagnosis of bone and joint infections. In our study the aim was to evaluate role of Serum Procalcitonin as an Early Indicator towards Bone and Joint Infections and to show sensitivity and specificity of Serum procalcitonin in diagnosis of bone and joint infection and to compare the sensitivity of Serum Procalcitonin with other biomarkers of bone and joint infection.

Materials and Method: This was a prospective study conducted in the Dept. of Orthopaedics, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences from the period of August 2013 to August 2015. All the patient attending outdoor, indoor and emergency were clinically screened for bone and joint infection. The patient who showed clinical signs of bone and joint infection were recruited for this study.

Result: Thirty-three patients were admitted between August 2013 to August 2015 in whom clinical suspicion of musculoskeletal infections was made. The youngest patient was 1 month old and oldest 76 years old. The mean age was 25.42 years. Out of 33 patients 17 were males and 16 females.21 patients had CRP positive whereas 12 patients were CRP negative. Out of 33 patients 16 finally had infection whereas 17 did not have infection. Infection in patients was determined by criteria, which was decided. The sensitivity of procalcitonin was found to be 56.3% whereas the specificity of procalcitonin was found to be 82.4%.

Conclusion: Serum Procalcitonin has high sensitivity and specificity in the diagnosis of Septic Arthritis and Acute Osteomyelitis ascompared to traditional biochemical markers.

Keywords: Biomarkers, Serum Procalcitonin, Infection, Bone & Joint

Introduction

Acute bone and joint infections are difficult to diagnose in the Emergency Department. Management of these diseases focuses on providing a rapid etiologic diagnosis since therapies and outcome vary widely depending upon the cause. Delayed diagnosis and treatment can lead to disabling sequelae,[(2)] Functional disabilities can occur in half of cases and can even be life threatening in 5 to 15% of cases.[(3)] Total Leukocyte Count (TLC), Erythrocyte Sedimentation Rate (ESR) and C – Reactive Protein (CRP) are routinely used in the diagnosis of these infections but no specific laboratory test exists with the exception of isolation of pathogenic organism from the bone or synovial fluid.[(4,5)] A positive culture result has high specificity but even this cannot be considered as gold standard because it lacks sensitivity (only40-60%) and the results are available only after 2 to 3days.[(2,3)] Despite this fact, culture is being used by many researchers as positive gold standard and patients without any clinical evidence plus negative culture as negative gold standard even when clinical appearance of pus as an evidence of infection is a late sign.

The lack of sensitive laboratory markers or a gold standard investigation for diagnosing bacterial infections clinically has contributed to the overuse of antibiotics especially in neonates and elderly patients where clinical signs could be very subtle. The concept of antibiotics use can't be used for every suspected infection as it can lead to antimicrobial resistance.

In this regard, there is a need for a biochemical marker, which shows high sensitivity and specificity in diagnosing infection and also as a guide for starting antibiotics. There is now enough evidence to support the role of Procalcitonin (PCT) as a diagnostic and prognostic marker in infective conditions with its very high specificity for bacterial infections.[(9)]

On the contrary, there are only very few studies evaluating its efficacy in Septic Arthritis (SA) and Acute Osteomyelitis (OM) with varying results.[(6-10)] Serum levels of Procalcitonin is very low in healthy individuals (<0.1 ng/ml) and increases rapidly in response to bacterial endotoxin.[(11,12)] These properties together with a half-life of 22 to 29 hours have made Procalcitonin, a convenient tool to monitor serious infections and to discriminate bacterial infections from viral and non-infective inflammatory conditions.[(13,14)]

Owing to its high specificity, Procalcitonin can also be used as a guide for starting antibiotics and monitoring treatment.[(15,16)]

Aim & Objective

Evaluation of serum procalcitonin as an early indicator towards bone and joint infections and to show sensitivity, specificity of Serum procalcitonin as an accurate marker in diagnosis of bone and joint infection and to compare the sensitivity of Serum procalcitonin with other marker of infection for bone and joint infection.

Material and Methods

This was a prospective study was conducted in the Department of Orthopaedics, Jawaharlal Nehru Medical College, Datta Meghe Institute of medical sciences from the period of August 2013 to August 2015.

All the patient attending outdoor, indoor and emergency were clinically screened for bone and joint infection. The patient who showed clinical signs of bone and joint infection were recruited for this study. Blood sample from patient with clinically suspected infection of acute primary (less than 2 weeks of symptoms) bone and joint infection before starting antibiotic treatment within 24 hours of his/her reporting to AVBRH were investigated for serum procalcitonin.

The blood samples were also evaluated for other biochemical markers such as Total leucocyte count, C Reactive Protein and ESR. In cases where abscess was present or in septic arthritis pus /fluid culture sensitivity was done to establish diagnosis.

Serum Procalcitonin investigation was done with help of MINI VIDAS Machine. All the patients were started with standard antibiotic program and the outcome of this patient were recorded.

Infection in patients was decided by following factors:

1) Physical Presence of pus on
   (a) Joint Arthrotomy
   (b) Joint Aspiration.
2) Relief of complains by antibiotics.
3) Patients who did not respond to treatment and deteriorated without use of antibiotics.
4) Progressive increase in total leucocyte count.
5) Local signs of inflammation.

Inclusion criteria: Clinically suspected cases of acute primary (up to 2 weeks of symptoms) bone and joint infection of all age group were included in the study.

Exclusion criteria: Patients with chronic osteomyelitis and chronic arthritis

1. Patients who had taken antibiotics before coming to hospital.
2. Patients with foci of infection somewhere else
3. Immunocompromised hosts.

Observation & Results

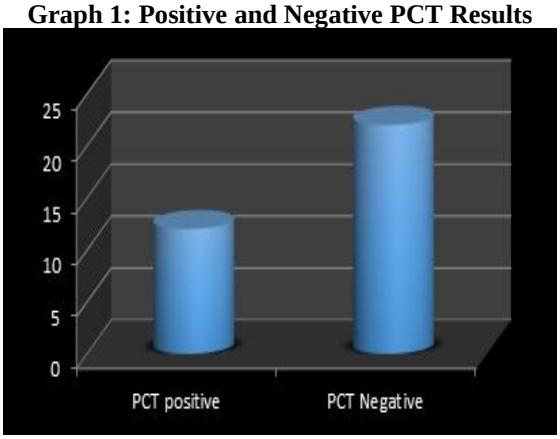
Thirty-three patients were admitted between August 2013 to August 2015 in whom clinical suspicion of musculoskeletal infections was made. Patients who had taken antibiotics prior to coming to hospital were excluded from study. Thirty-three patients were admitted who were suspected of acute bone and joint infection. The youngest patient was 1 month old and oldest 76 years old. The mean age was 25.42 years. Out of 33 patients 17 were males and 16 females. Binomial test for the gender distribution in sample size was calculated and found that the equal distribution of patients from either gender (p value >0.05; 1.000).

Table 1: Duration and Frequency of infection

Duration	Frequency	Percent	Valid Percent
1 week	11	33.3	33.3
2 week	22	66.7	66.7
Total	33	100.0	100.0

Table 1: Shows that out of 33 Patients 11 patients had symptoms for 1 week whereas 22 patients had symptoms for 2 weeks. Graph 1 shows twelve Patients had procalcitonin positive whereas 21 showed negative procalcitonin value. Procalcitonin level done using mini VIDAS®from serum of patient at 0.5 ng/mL was considered positive and <0.5 ng/mL was taken to be negative. Table 2 shows Out of 33 patients 8 had TLC Positive whereas 25 had TLC Negative. Total leucocyte count of more than 11000 was taken to be positive and below 11000 was taken to be negative. Table 2 Out of 33 patients 28 had ESR positive whereas 5 Had ESR Negative. ESR above 10 were considered positive and ESR below 10 were taken to be negative.

Graph 1: Positive and Negative PCT Results



Graph 2: Shows 21 Patients had CRP positive and 12 had CRP negative

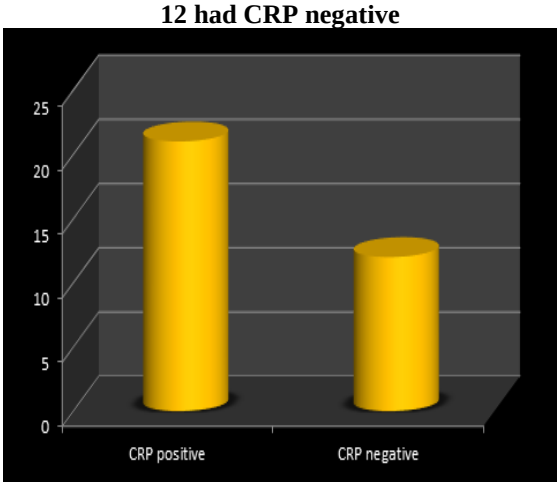


Table 2: Positive and Negative ESR

	Frequency	Percent	Valid Percent
ESR positive	28	75.8	84.8
ESR negative	5	24.2	15.2
Total	33	100.0	100.0

Table 3

	Frequency	Percent	Valid Percent
Presence of infection	16	48.48	48.8
Absence of infection	17	51.52	52,52
Total	33	100.0	100.0

Table 3: Shows out of 33 patients 16 finally had infection whereas 17 did not have infection. Infection in patients was determined by criteria determined.

Table 4

Sensitivity and Specificity of Procalcitonin to diagnose Clinical Infection					
			Infection		
			Presence of Infection	No Infection	Total
Procalcitionin	PCT Positive	Count	9	3	12
		%within Procalcitonin	75.0%	25.0%	100.0%
		% within infection	56.3%	17.6%	36.4%
	PCT Negative	Count	7	14	21
		%within Procalcitonin	33.3%	66.7%	100.0%
		% within infection	43.8%	82.4%	63.6%

Table 4: Shows Out of 12 patients who had procalcitonin positive 9 had infection whereas 3 did not have infection. Out of 21 patients who had procalcitonin negative 14 did not have Infection whereas 7 had infection. The specificity Of Procalcitonin calculated by kappa co efficient was 82.4% and sensitivity was 56.3%.

Table 5

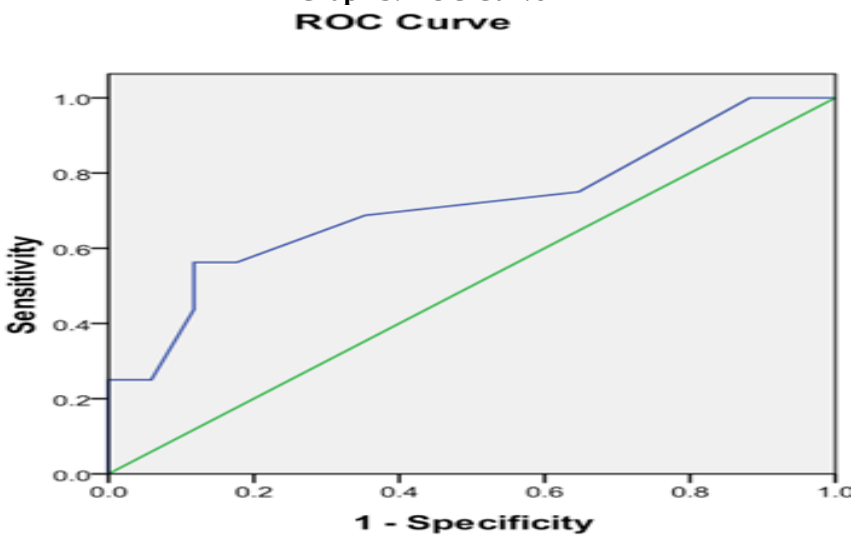
Positive predictive value of PCT	Confidence interval	Negative predictive value of PCT	Confidence interval
75%	42.81% to 94.51%	66.67%	43.03% to 85.41%

Table 5: Table shows that positive predictive value of procalcitonin was 75% with confidence interval of 42.81 to 94.51 %. The negative predictive value of procalcitonin was 66.67% with confidence interval of 43.03% to 85.41%.
Table 6: Table shows that positive likelihood ratio of infection when procalcitonin positive was 3.19 with confidence interval of 1.05 to 9.71and negative likelihood ratio was 0.53% with a confidence interval of 0.29 to 0.97.

Table 6

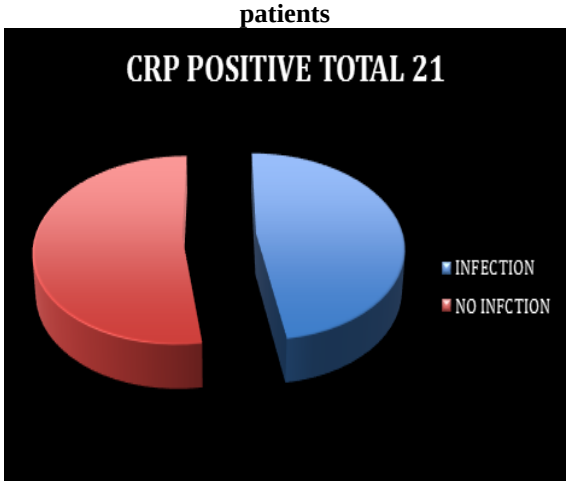
Positive likelihood ratio	Confidence interval	Negative likelihood ratio	Confidence interval
3.19	1.05 to 9.71	0.53	0.29 to 0.97

Graph 3: ROC Curve



The **ROC curve**(Graph 3) is a fundamental tool for evaluation of diagnostic test. The receiver-operating characteristic (ROC) curves comparing presence of infection versus result of procalcitonin in patients are plotted in Fig. The area under the curves (AUC) is .713.

Graph 4: Out of Total Infective and Non – infective patients



Graph 4: Shows out of 21 patients who had CRP positive 10 had infection whereas 11 did not have infection. Out of 12 patients who had CRP negative 6 did not have Infection whereas 7 had infection. The specificity Of CRP calculated by kappa co efficient was 35.3% and sensitivity was 62.5%.

Table 13

Positive predictive value of CRP	Confidence interval	Negative predictive value of CRP	Confidence interval
47.62	25.71 to 70.22	50	21.09 to 78.91

Table 13: Shows that positive predictive value of CRP was 47.62% with confidence interval of 25.71 to 70.22%. The negative predictive value of CRP was 50% with confidence interval of 21.09% to 78.91%.

Table 7

Positive likelihood ratio of CRP	Confidence interval	Negative likelihood ratio of CRP	Confidence interval
0.97	0.58 to 1.62	1.06	0.43 to 2.62

Table 7: Shows that positive likelihood ratio of infection when CRP positive was 0.97 with a confidence interval of 0.58 to 1.62 and negative likelihood ratio was1.06 with a confidence interval of 0.43 to 2.62.

Discussion

Infection of the joint and bone is common in patients. Due to the difficulty in diagnosis Septic arthritis and osteomyelitis patient are advised treatment at tertiary hospitals.

Diagnostic tests to screen musculoskeletal infections have been matter of debate since long time. No test has proved its sensitivity or specificity to become a gold standard test. However, CRP, total leukocytes counts are currently popular tests to screen the infection. Culture sensitivity has low positivity rates therefore cannot be practiced as screening test for infection. There is not a laboratory investigation with high specificity and sensitivity

The complications secondary to delayed diagnosis have decreased due to the availability of powerful antibiotics but this has caused antimicrobial resistance. Hence only few drugs are available now to treat high grade infections.[17- 19]

Procalcitonin can be used for diagnosis of bone and joint infections. Its effectiveness over traditional biomarkers like Total Leukocyte Count, ESR and CRP has been mentioned in several conditions like sepsis, upper respiratory tract infections, pneumonias, burns, pancreatitis, and other conditions.[20,21]

We did study with aim to evaluate sensitivity, specificity of Serum Procalcitonin in early diagnosis of septic arthritis and chronic osteomyelitis

The usefulness of Procalcitonin has been studied in the past. Though there has been paucity of level 1 or level 2 studies available in the literature. A Study was done by E Greeffet[22] to describe role of serum Procalcitonin in diagnosis of infections in 33 pediatric patients. Sabine Faesch[14] did a study in 339 patients on utility of procalcitonin for of osteomyelitis for diagnosis of bone and joint infections. Our study consisted of 33 patients which included adult and pediatric both patients.

Faesch et al[14] evaluated PCT levels in 339 patients presenting in a pediatric patients from age of 1 month to 14 years for suspected infections. Karthikeyan Maharajan[23]conducted a study with mean age of 25.33 years, the oldest patient was 85 years.E Greeff[22] did a study on usefulness of procalcitonin in bone and joint infections The study included patients from 1 to 14 years. In the study conducted by Markus Paakkonen[24] the patients aged 3 months to 15 years. In our study of 33 patients the minimum age of patient was 1 year whereas maximum age was 75 years. The mean age was 25.42 years.

Ernst AA[25] did a study on role of CRP and ESR in septic joints. Of 163 patients the mean CRP for septic joints was 13 and mean ESR was 57. The mean CRP for normal joints was 6 and ESR 43. Markus Paakkonen[24] did a study on Sensitivity of Erythrocyte Sedimentation Rate and C-reactive Protein in Childhood Bone and Joint Infections. E Greef[22] in his study had sensitivity and specificity 100% and 26% respectively. In our study in 33 patients CRP was positive in 22 patients whereas negative in 11 patients. ESR was positive in 27 patients whereas negative in 6 patients. In our study of 33 patients CRP was 62.5% sensitive and 35% specific in diagnosis of bone and joint infection. ESR was not that useful.

E Greeff[22] did a study on Is procalcitonin useful in diagnosing septic arthritis and osteomyelitis in children. In this study the cut off level of procalcitonin was taken to be 0.2 ng/mL. Faesch et al[14] evaluated PCT levels in 339 patients presenting in a paediatric emergency department the cut off level of procalcitonin was taken to be 0.06 to 50 ng/ml. Fottner et al[7] in his study had cut off level of 0.5ng/ml. In our study the cut of level of procalcitonin was taken to be 0.5 ng/ml. Values above 0.5ng/ml were taken to be positive whereas values below 0.5ng/ml were taken to be negative.

E Greeff[22] did a study on Is procalcitonin useful in diagnosing septic arthritis and osteomyelitis in children, the calculated sensitivity of PCT was 92% and specificity was 81% Butbul-Aviel[6] studied role of procalcitonin in 44 patients with suspicion of infection, Sensitivity was 46.3% whereas specificity was 100%. In the study conducted by Fottner[7] the calculated sensitivity of PCT was 53.3% and specificity was 100%. Karthikeyan Maharajan[23] in his study found Serum Procalcitonin as sensitive and specific biomarker for diagnosis of bone and joint infecton. In our study of 33 patients the specificity of Procalcitonin was 82.4% and sensitivity was 56.3%.

E Greeff[22] did a study on Is procalcitonin useful in diagnosing septic arthritis and osteomyelitis in children. The positive predictive value was 73% and negative predictive value was 94; Sabine F in his study had the positive predictive value was 18.2% whereas the negative predictive value was 97.9%. In our study the positive predictive value was 75 % and negative predictive value was 66.67%.

Summary

Serum levels of Procalcitonin are very low in healthy individuals (< 0.1 ng/ml) and increases rapidly in response to bacterial endotoxin. These properties together with a half-life of 22 to 29 hours have made Procalcitonin, a convenient tool to monitor serious infections and to discriminate bacterial infections from viral and non-infective inflammatory conditions. Owing to its high specificity, Procalcitonin can also be used as a guide for starting antibiotics and monitoring treatment. Treatment can be started early resulting in decrease complications.

Conclusion

Our study shows that Serum PCT is a sensitive and specific marker in the diagnosis of Acute Osteomyelitis and Septic Arthritis as compared to other biochemical markers such as CRP, ESR, TLC. Thus Serum Procalcitonin can be used for early diagnosis of bone and joint infections.

Recommendations

Procalcitonin can be used as screening test for acute bone and joint infections. The test is more reliable in terms of specificity than other conventional test such as TLC, CRP. ESR.

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