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EVALUATION OF SERUM PROCALCITONIN LEVELS AS A DIAGNOSTIC MARKER OF EARLY INFECTION IN PATIENTS WITH ACUTE BONE AND JOINT INFECTION: A HOSPITAL BASED STUDY

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Abstract

Background: Acute osteomyelitis and septic arthritis are most common acute infectious conditions of bone encountered at the emergency or outpatient department at hospitals. Both septic arthritis and osteomyelitis are threat for joint destruction, physal damage and osteonecrosis, which warrants prompt and specific diagnosis and treatment. This study endeavours to evaluate Procalcitonin as diagnostic tool for earliest and specific diagnosis of acute bone and joint infection.

Methods: This is a prospective type hospital based study conducted at a tertiary care hospital, carried out between October 2015 to April 2017 which included total of 78 participants divided in two groups, the cases and control group, each containing 39 patients. Clinical parameters as fever, pain, swelling and laboratory findings as Total Leucocyte Count (TLC), Erythrocyte Sedimentation Rate (ESR), C Reactive protein (CRP) and Procalcitonin (PCT) were measured. Baseline characteristic of the two groups compared. The sensitivity, specificity and p-values were compared using chi square and fisher's exact test, SPSS software version 20 used.

Results: Total of 78 patients participated, 39 taken as cases and 39 as control. Out of 78 patients, males-48 (61.54%), and females-30 (38.46%) with average age of participants as 23.5 years. ESR, CRP and TLC and procalcitonin was found to be elevated in all the cases. The P value for CRP and Procalcitonin was 0.00001 and significant correlation was observed between cases and PCT serum level. For septic arthritis the specificity of Procalcitonin came

out to be 92% and sensitivity as 84%, while for acute osteomyelitis specificity and sensitivity of procalcitonin found out to be 92% and 82 % respectively.

Conclusions: In our study we found that serum Procalcitonin level is a sensitive and specific marker of acute infection of bone and joint. As compared to C reactive protein and total leucocyte count, Procalcitonin is more specific and more sensitive for diagnosis of acute osteomyelitis and septic arthritis. Determined by the statistical analysis procalcitonin is more reliable than C reactive protein or total leucocyte count. Instituting serum procalcitonin level as screening marker for acute bone and joint infection can lead to early diagnosis and treatment of these infection and avoid the grave complications. Though larger trials including more number of participants in each group can be done to establish procalcitonin as a marker for early and specific diagnosis of acute osteomyelitis and septic arthritis.

Keywords: Procalcitonin, osteomyelitis, septic arthritis, C - reactive protein

Introduction

Septic arthritis is bacterial invasion of joint space, which can be Blood borne or by direct inoculation from an injury or operation or an infection from the adjacent tissue with osteomyelitis or cellulitis. Septic arthritis can occur at any age but young children and elderly adults are the most susceptible. Total leucocyte Count, Erythrocyte sedimentation ratio and C reactive protein are seen to establish the infective etiology but these alone are not conclusive¹. Imaging studies like X-ray, Computed tomography scanning and magnetic resonance imaging can be done but are not always necessary, ultrasonography is very helpful in detecting even small collection in the joint. The confirmation of the diagnosis can be arrived at by aspirating the joint effusion and subjecting the aspirate to staining and culture and sensitivity. Acute septic arthritis is a potential for joint destruction, physeal damage, and osteonecrosis, which warrants urgent identification and treatment². Once the diagnosis has been confirmed immediate incision and drainage and thorough lavage of the joint and closure over drain is done and the patient is kept on appropriate intravenous antibiotics.

Osteomyelitis is defined as inflammation of bone caused by an infecting organism.

The infection may be limited to a single portion of bone or may involve numerous regions such as marrow, cortex, periosteum and the surrounding soft tissues. The infection generally is due to a single organism but polymicrobial infection can occur, especially in the diabetic foot. Acute hematogenous osteomyelitis is the most common type of bone infection and usually is seen in

children and staphylococcus aureus is the commonest causative organism isolated³.

Although identifying osteomyelitis is complicated but reliable diagnosis can be made with an integrated approach using clinical suspicion and lab findings like elevated erythrocyte sedimentation rate, C reactive protein total leucocyte count and hyperthermia. Most of the time it requires radiological imaging in addition to clinical and laboratory findings to confirm the diagnosis⁴. X-ray and Computed tomography scan are initial method of diagnosis showing lytic centre with a ring of sclerosis⁵ and cortical destruction of advanced osteomyelitis but can miss the nascent or indolent diagnosis⁶. Confirmation of diagnosis is usually done with Magnetic resonance imaging, but it has some limitations with sensitivity and specificity 90% and 71% respectively⁷, not helpful in patients with metallic prosthesis and in certain situations like Charcot arthropathy. Again MRI could be inconclusive in distinguishing bone infarct from osteomyelitis in patients with Sickel cell anaemia⁸. Bone biopsy subjected to culture and sensitivity confirms the diagnosis. Treatment is appropriate intravenous antibiotics but once abscess is formed open surgery is required. When there is chronicity or acute exacerbation of chronic osteomyelitis where sequestrum is formed, involucrum is opened and sequestrum is removed and saucerization is done. Intravenous antibiotic is continued after surgery. Numerous literatures support the use of hyperbaric oxygen therapy as an useful adjuvant for management of recalcitrant osteomyelitis^{9,10}.

Acute osteomyelitis and septic arthritis have very grave prognosis. So, there is a need of a laboratory test

which can be used to diagnose acute osteomyelitis, septic arthritis at their earlier stage. Procalcitonin (PCT) is a peptide precursor of the hormone calcitonin, the calcitonin is involved with calcium homeostasis. It was first identified by Leonard J. Deftos and Bernard A. Roos in the 1970s¹¹. Prolactin is made up of 116 amino acids and is produced by thyroid gland specifically by parafollicular C cells of thyroid and by the neuroendocrine cells of the intestine and lungs. The blood level of procalcitonin in a normal person is below the limit of detection (0.01 µg/L) of clinical assays¹². The level of procalcitonin rises in a response to any infective inflammatory stimulus, especially of bacterial origin. In such a case, procalcitonin is produced mainly by the cells of the intestine and lungs. It does not rise appreciably with viral or non-infectious inflammations. With the derangements that are brought up by severe infection with an associated systemic response, the blood levels of procalcitonin may sometimes may rise upto 100 µg/L. Procalcitonin has a half-life of 25 to 30 hours in serum. It is remarkable that the high procalcitonin levels produced during infections are not followed by a concomitant increase in calcitonin or a decrease in serum calcium levels. Quantitative values of procalcitonin can be used as a tool for detection of severe sepsis caused by bacteria and generally grades well with the degree of sepsis¹³. Although levels of procalcitonin in the blood are very low, it has the greatest specificity (91%) and sensitivity (85%) as far as differentiating patients with sepsis and systemic inflammatory response syndrome (SIRS) is concerned, when compared with C reactive protein, TNF-alpha and IL-2, IL-6, IL-8¹⁴. Evidences suggest that procalcitonin

levels can reduce unnecessary use of antibiotics to people with lower respiratory tract infections¹⁵. Currently, procalcitonin assays are widely used in the clinical environment¹⁶. Different meta-analysis has reported variable specificity and sensitivity up to 70% and 76% respectively for bacteremia¹⁷.

Materials And Methods

The study was a tertiary care hospital based prospective study which was carried out from October 2015 to April 2017. The study was approved by the Institutional Ethics Committees. Written informed consent was obtained from all patients or their relatives before enrollment. A total of 39 patients presenting to the OPD and emergency medical services of the hospital with suspected septic arthritis and acute osteomyelitis were prospectively included in the study along with 39 normal cases as control. The patients who had previously been given antibiotics or cases with focus of infection elsewhere in body and immunocompromised individuals are excluded from the study. Pus culture and sensitivity was considered gold standard for the diagnosis.

Clinical parametres- Initially when patient presented to our Out Patient Department or emergency department were evaluated carefully for the presence of symptoms like fever, pain, joint/local swelling and painful joint movement in case of septic arthritis. **Laboratory Parameters-** After evaluation of clinical parameters patients were subjected to laboratory test such as total leucocyte count, Erythrocyte Sedimentation Rate, C Reactive Protein and serum Procalcitonin level evaluations.

Radiology and other investigations- Pus was aspirated from joint involved in case of septic arthritis and from local

part involved in case of osteomyelitis and sent for staining and pus culture and sensitivity then X-ray and Ultrasonography was done. Cut off for C reactive Protein was taken as 6 ng/l above which it considered positive. Cut off value for Procalcitonin was taken as 0.5ng/ml above which it was considered positive. Procalcitonin was evaluated using *immunoluminetric assay* with threshold value of 0.1ng/ml.

Statistical analysis- was done using chi square test, fisher exact test.

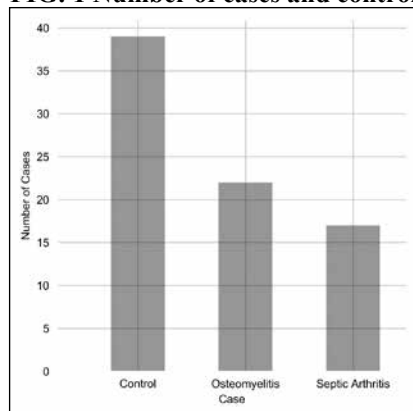
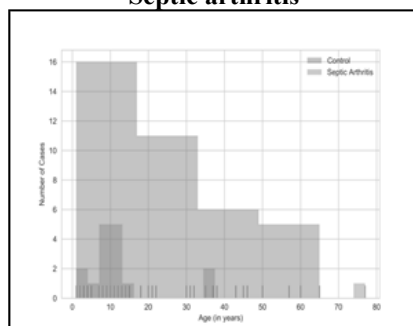
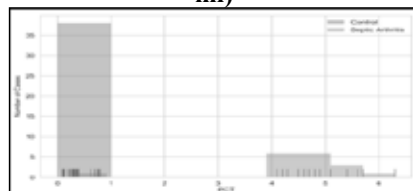
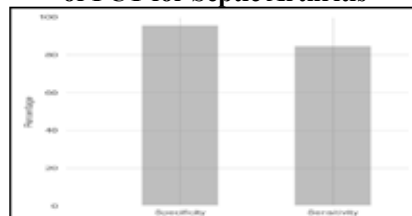
Observations And Results

Total Of 78 participants were included in this study, 39 as cases and the results were compared to equal number of controls. Out of these 78 patients 44 were males (56.41%) and 34 (43.59%) were females. The

youngest age recorded was 1 year while the oldest was 77 years. The mean age of the study group was 23.5 years. In all the cases, ESR, leukocyte count, CRP and PCT were raised and correlating with systemic signs and symptoms clinically confirmed as septic arthritis or Osteomyelitis. Swelling was the commonest clinical manifestation in the study. All the laboratory parameters are increased in patients having septic arthritis and osteomyelitis. A statistically significant correlation was observed with increased CRP among the septic arthritis and osteomyelitis cases in the study. In the study it was found that Procalcitonin has sensitivity of 82% and specificity of 92% in OM patients, whereas in septic arthritis patients procalcitonin has Shown 84% of sensitivity and 92 % specificity.

Table 1: Baseline characteristic of patients in the study

	Cases		Control	P value
	Septic arthritis	Osteomyelitis		
Sex- Male	11	15	22	
Female	6	7	17	
Total	39		39	
Clinical features	17	8	0	
Fever	17	14	0	
Pain	14	14	0	
Swelling				
Laboratory Findings				
Total lucocyte count (cut off 11*10 ⁹ /l)	17			
Elevated	17	8	1	
Within normal limit	0	14	38	
C reactive protein (cutoff 5 mg/ l)				
Elevated	17	12	2	
Within normal limit	0	10	37	
Procalcitonin level (cutoff-0.5ng/ml)	15	19	7	
Elevated	2	3	32	
Within normal limit				0.00001

FIG: 1 Number of cases and control**FIG: 2-Age based distribution of Septic arthritis****FIG: 3 PCT level in Acute Osteomyelitis patients (avg. range below 3ng/ml)****FIG: 4- PCT level in Septic Arthritis patients (avg. range 4-5ng/ml)****FIG: 5- Specificity and Sensitivity of PCT for Acute Osteomyelitis****FIG: 6- Specificity and Sensitivity of PCT for Septic Arthritis**

Discussion

Septic arthritis and acute osteomyelitis are quite frequent problem which are encountered by Orthopaedic surgeons in OPD and emergency services especially in tertiary care centres. Many of these patients who report to tertiary centres receive primary treatment in the form of antibiotic which makes the diagnosis difficult because of earlier administration of empirical antibiotics the considered gold standard test i.e. pus culture and sensitivity give sterile culture after 72 hours of incubation. The sensitivity and specificity of pus culture is 40-60% and 100% respectively^{18,19}. Because of these problems diagnosis and treatment gets delayed in these patients leading to many complications which are very difficult to tackle even with very powerful antibiotics. Use of powerful antibiotics becomes frequent in such circumstances which lead to another bigger problem of development antibiotic resistance in the microorganisms. Which will be difficult to manage because the availability of such strong antibiotics very few in the list^{18,19} and once the microorganism becomes resistant to these strong antibiotics the infection will become life threatening. So we need an accurate and OPD basis test for these patients for early diagnosis and the earliest intervention in these patients to avoid aforesaid problems impending over community. It has been found that Procalcitonin is very

specific of bacterial infection and its sensitivity is also very high so it is very helpful in differentiating septic arthritis and osteomyelitis from other non bacterial conditions and it has been found useful than TLC, ESR and CRP in many bacterial infections like sepsis, respiratory tract infections, pyelonephritis, pneumonia and burns²⁰, that is why we have evaluated the levels of serum Procalcitonin in patients with septic arthritis and osteomyelitis and compared those values from healthy controls. Serum PCT level less than 0.5ng/ml is considered normal. However, investigators around the world have failed to come to an agreement regarding a fixed cut – off for the level of procalcitonin as it is an emerging diagnostic marker and is either extremely low or undetectable in normal person. According to various researchers like Butbul Aviel et al.,⁽¹⁰⁾; Fottner et al.,⁽¹¹⁾; Martinot et al.,⁽¹³⁾ and Faesh et al.,⁽¹⁴⁾ an arbitrary value of 0.5 ng/ml of prolactin as cut – off beyond which it should be considered as a marker of pyogenic infection. However, Hogle et al.,⁽¹²⁾ in their study have taken 0.25 ng/ml to be the cut-off value. This reflects the absence of a general consensus in deciding the cut-off. In our study we have taken 0.5ng/ml as cut off and found out similar sensitivity and specificity 85% and 92% respectively for septic arthritis and osteomyelitis. In many studies PCT has been found to be less sensitive this could be because of low sample size was taken. Limitation of our study was that the sample size was still not large enough and we have not evaluated serial serum PCT levels as our study was focused mainly on the diagnostic values.

Conclusion

In our study we found out that serum PCT is a sensitive and specific marker of septic arthritis and acute osteomyelitis. As compared to C-reactive protein and total leucocyte count, Procalcitonin is more specific and more sensitive for the diagnosis of septic arthritis as well as acute osteomyelitis. Determined by the statistical analysis Procalcitonin is more reliable than for CRP or WBC in the overall analysis. As there are lesser number of participants in the study, larger trials including higher number of patients over a longer duration of time should be done to confirm the high specificity and sensitivity of Procalcitonin assay for septic arthritis and acute osteomyelitis.

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