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ResearchArticle

PROCALCITONIN AS A RELIABLE BIO MARKER FOR DETECTION OF SURGICAL SITE INFECTION FOLLOWING ORTHOPAEDIC SURGERY

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ABSTRACT

Background: Early detection of SSI is very important to prevent morbidity and complications.At present there is a lack of biomarker which can accurately diagnose such infections. Serum Procalcitonin (PCT), at 0.09 ng/ml is found to be an accurate marker for early detection of bacterial infections. The objective of this research was to assess the diagnostic significance of procalcitonin as a emerging biomarker in early identification of SSI as other markers like ESR, CRP, WBC may not reliably differentiate between systemic inflammatory response and bacterial infection.

Material andMethods: Patients of all age groups (n = 249) who had undergone orthopaedic surgery were prospectively included in this study. Any patient who developed post operative wound discharge were followed up for the presence SSI. Serum levels of procalcitonin was measured on the day of wound discharge. So at the end of the study, patients were classified into 2 groups: Group 1 = wound discharge with culture positive (Confirmed SSI, n = 10); Group 2=wound discharge with culture negative (No SSI, n=19). The serum levels of PCT was compared among above two groups and results were drawn.

Results: Out of 249 patients 29 patients developed wound discharge in the post-operative period. Only 10 patient showed growth of infective agent. Group 1 had higher mean PCT levels than Group 2 ($p < 0.05$). PCT, at 0.09ng/ml, was 80% sensitive and 94.7% specific in diagnosing SSI.

Conclusion: Serum Procalcitonin, at a cut – off of 0.09 ng/ml, is a sensitive and specific marker in the diagnosis of SSI and helps to differentiate patients with infective wound discharge from non-infective wound discharge. Level of evidence-4

INTRODUCTION

Surgical sit infection is a common complication after surgical procedure and it ranks second among hospital acquired infections (Pittet *et al*., 1999). Its early diagnosis is a challenge to any orthopaedic surgeon as it can lead to various complications if not attended at the earliest. Identification and management of the same if got delayed will lead deep infections, osteomyelitis and septic arthritis causing morbidities in 25 -50% patients and may lead to death in 5 - 15% of patients (Georgens *et al*., 2005; Morrey *et al*., 1975; Mathews *et al*., 2010). It is our routine to use infective marker like blood counts (TC), Erythrocyte Sedimentation Rate (ESR) and C – Reactive Protein (CRP) to diagnosis but it is often unreliable (Unkila-Kallio *et al*., 1994; Levine *et al*., 2003).

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The problem which will arise when we adopt pyogenic culture as a diagnostic modality is, its low sensitivity of 30-40% inspite of its high specificity and another drawback is a time delay of minimum of 2-3 days to get the report and for starting treatment (Morrey *et al*., 1975; Mathews *et al*., 2010). So a sensitive as well as specific infective maker which can differentiate infective from non-infective cause of post-operative wound discharge is required and thus can prevent inappropriate usage of antiobiotis and morbidity associated with SSI.In this regard, we should search for laboratory marker with high sensitivity as well as specificity in differentiating infective post-operative wound discharge from non-infective wound discharge and also as a guide for prompt antibiotic therapy. There are enough studies to reveal the role of Procalcitonin (PCT) as a reliable prognostic and diagnostic infective marker by various researchers (Crain and Muller, 2005; Gendrel and Bohoun, 2000; Ghorbani, 2009; Chan *et al*., 2004). But, only limited number of studies are available which evaluates utility of procalcitonin in post-operative infections (Laffey *et al*., 2002; Jebali *et al*., 2007; Laifer *et al*., 2005; Oberhofer *et al*., 2006). It has been studied that value of Procalcitonin level in serum is undetectable in normal individuals and it will increase in serum as a response to toxins produced by bacteria (endotoxin) as a response to bacterial endotoxin (Barresi *et al*., 2004; Assicot *et al*., 1993). In addition to it, a lower half-life as compared to other infective markers makes procalcitonin a suitable biomarker in differentiating infection from non-infectious conditions (Shimetani *et al*., 2001; Delevaux *et al*., 2003). In this perspective this prospective study was done prospectively with the intention of finding out the diagnostic power of PCT as a reliable marker to differentiate infectious from non-infectious wound discharge.

MATERIALS AND METHODS

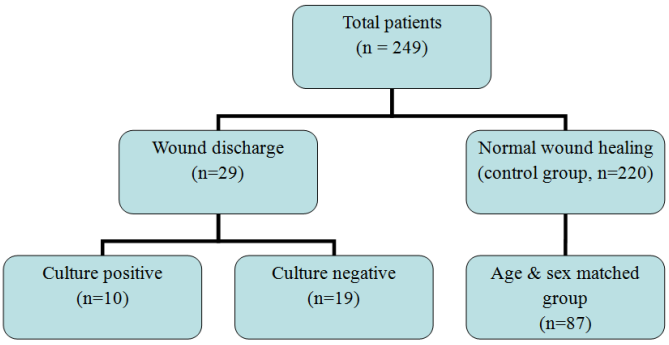
This study was conducted in the Orthopaedic department in a tertiary care centre in south India from January 2013 to July 2014. A total of 249 patients who had undergone clean elective orthopaedic surgical procedure with no other evidence of infection were included in the study. Those patients with immunocompomised states, patients who didn't give consent for inclusion. Those patients who had some other known source of infection (respiratory or urinary infection) or any other septic foci, Those patients who deviated from our study protocol, Proven pre-op infection were excluded from the study. The research was approved by research wing and Ethics Committee of our institute and conducted as per standards of Declaration of Helsinki, 1964. After getting informed consent patients were enrolled into the study were followed up according to the existing departmental protocol for antibiotic prophylaxis, pre-operative preparation and post operative wound care. The epidemiological and clinical factors for all the patients were noted as per our proforma. Any patient who developed a serous discharge from the wound site or presented with signs of inflammation like warmth, redness, induration at the operative site was further evaluated for the presence of surgical site infection. Wound swab was taken and sent for Gram stain along with pyogenic cultures, all the routine clinical and hematological work up were done to look for signs of infection including 4 hourly Temperature chart, pulse charting, WBC count, ESR and CRP levels. Patients of all age groups (n = 249) who had undergone orthopaedic surgery were prospectively included in this study.

Serum levels of procalcitonin was measured on the day of wound discharge from operative site. Collected serum was stored a temperature of -70 degree celcius and PCT was determined by ELISA method (RAY BIOTECH) at the end of the study.The threshold to detect PCT in serum was set by this laboratory was 0.03 ng/ml.Other potential sites of infection such as respiratory and urinary tract infections were ruled out by appropriate clinical examination and lab investigations. All the patients were followed up till surgical wound healing and all the patients with wound discharge along with growth of infective agent by pyogenic culture were noted and were grouped as patients with wound infection (SSI). Those patient who developed wound discharge with no growth of infective agent grouped as culture negative wound discharge.

At the end of the study the serum samples from all patients of two groups were tested for the levels of Procalcitonin and the Mean levels of procalcitonin were compared between the two groups and sensitivity, specificity and predictive values of PCT were assessed using the appropriate statistical analysis (Unpaired t test was used for the comparison of biochemical parameters). The sensitivity, specificity and predictive values were analyzed using SPSS software version 19. AII statistical analysis were carried out at 5% level of significance and a p value < 0.05 was considered significant and results were drawn.

RESULTS

Out of 249 patients minimum age of patient was 2 years and maximum age was 80years. Max patient comprises of 10-20 age group~20%. Male comprises of 67% and males 33%. At the end of the study Patients were grouped as per the following flow chart.



Infection	Frequency	Percent
Confirmed SSI	10	34.4
No SSI	19	65.5
Total	29	100.0

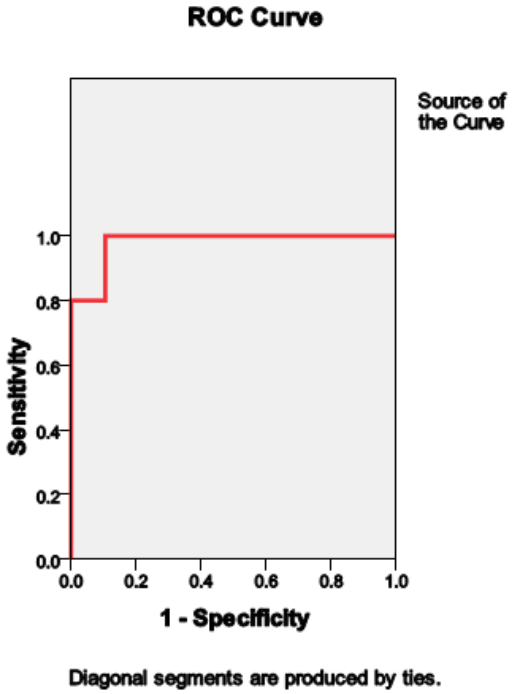
Infective organisms were isolated in 10 patients as given in table below

Culture of infective orga-nism grown	Frequency
No growth	19
MRSA	4
Pseudomonas	1
Klebsiella	2
MRSA+ Pseudomonas	1
MRSA + klebsiella	1
CONS	1
Total	29

Patients with culture positive wound discharge (n=10) vs patients with culture negative wound discharge (n=19)

Serum PCT value On the day of wound discharge	Culture negative	19	26.8	31.0	4.960	<0.001
	Culture positive	10	460.7	385.4		

Results: There is significant rise in procalcitonin level in patients with confirmed surgical site infection on the day of discharge from the surgical site with a p value of <0.001.



Area Under the Curve

Test Result Variable (s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Serum PCT on the day of discharge	.979	.021	.000	.000	1.000

PCT level in patients on the day of wound discharge		Infective vs discharge		
		Wound discharge and Culture positive	Wound discharge and culture negative	Total
	≥90	8	1	9
	<90	2	18	20
Total		10	19	29

DISCUSSION

Surgical site infections (SSI) is a complication associated with excessive morbidity, frequently leading to increased rate of re-operations, long-term use of antibiotics with their associated side effects, pain, and potential prolonged disabilities, increased financial burden to the patient as well as health care system (De Lissovoy *et al*., 2009).

Now a days the rate of surgical site infection has declined due to better understanding of surgical site infection, its risk factors and preventive measures. However the early diagnosis of surgical site infection is a challenge to clinician in day to day practice as there is difficulty in early diagnosis merely based on the clinical assessment and conventional infective markers. This has led to the inadvertent and irrational use of antibiotics leading to antibiotic resistance.

Early diagnosis of surgical site infection is very difficult merely based on clinical and conventional infective markers like total count, differential count, ESR, CRP due to lack of specificity of these markers in diagnosing infection (Unkila-Kallio *et al*., 1994; Levine *et al*., 2003). In this context various studies are being conducted worldwide for a marker with better sensitivity and specificity in diagnosing infection. Meanwhile, the marker for early diagnosis of SSI is still under research.

In our study most of the patients (23 out of 29) developed wound discharge on the post op day 4, two patients on day 7, two patient on day 8 and 1 on postop day 10 showed the appearance of wound discharge. Most of the patients (70%) who had a culture positive wound discharge had to undergo a second surgery in the form of wound exploration and debridement, whereas the remaining 30% patients improved with daily dressings and I/V antibiotics. Amongst those patients who had a culture negative wound discharge only 30% of patients required re-operation in the form of wound lavage and wound debridement.

Studies done in patients undergoing cardiac surgeries and major cancer surgeries have shown that serum procalcitonin to be an effective biochemical marker which can predict the development of early SSI's in these patients (Mokart *et al*., 2005; Pierre-Emmanuel Falcoza *et al*., 2005). Most studies show that the procalcitonin levels increase in the immediate post –operative period but owing to its short half – life of 18 – 24 hours the levels start decreasing rapidly (Davidson *et al*., 2013; Oberhofer *et al*., 2006). A persistently high level and rising levels seen on the 3rd or 5th post-op day have shown a positive correlation with the development of early onset surgical site infection (Mokart *et al*., 2005; Pierre-Emmanuel Falcoza *et al*., 2005). These results prompted us to do this study in orthopedic patients to look for similar results and to identify if serum procalcitonin can be an effective marker in this subset of patients as well. We aimed to determine the diagnostic significance, sensitivity, specificity, positive and negative predictive value of this marker so as to identify its accuracy and clinical significance in our subset of patients.

Various studies indicates that the serum levels of PCT rise following surgery (Davidson *et al*., 2013; Oberhofer *et al*., 2006; Yeon Gu chung *et al*., 2011; Maier *et al*., 2009). On comparing the levels of serum PCT in all the patients who had developed wound discharge during the early post-op period we found that the levels of PCT in serum on the day of wound discharge were significantly higher in patients who had culture proven wound infection and had required a wound debridement as compared to the patients in whom no organism could be isolated from the discharge and most of whom improved with just observation over time. And this difference was also found to be statistically significant with a p value < 0.001.

In most of the previous studies the cut off value was calculated as 0.5 ng/ml for predicting infection (Sabine faesch *et al*., 2009; Butbul *et al*., 2005; Martinot *et al*., 2005; Fottner *et al*., 2008). However, study by Hogle *et al*. (2008) has taken 0.25ng/ml and study by Gunalp Uzun *et al*. (2007). Has taken 80pg/ml as the cut-off. This reveals the absence of a general consensus in determining the cut-off as procalcitonin is a novel and emerging infective laboratory marker. In our study the value of serum procalcitonin in predicting surgical site infection was found to be 0.09 ng/ml as compared to most of other studies with a cut off of >0.5 ng/ml for predicting infection. This result is in accordance with the study showing lower values of procalcitonin in localized infection as compared to patients with generalized infection (Christ-Crain and Muller, 2006; Christ-Crain *et al*., 2004).

The persistent elevation of PCT is indicative of bacterial infection and once again, stresses the importance of follow-up measurement (Christ-Crain and Muller, 2006; Christ-Crain *et al*., 2004). In our study, if we are taking cut off value of PCT as 0.5ng/ml, sensitivity was found to be 40% and specificity 100%. But at a cut off value of 0.09 ng/ml it is having a sensitivity of 80.0% and specificity of 94.7%. It should be emphasized that the cut off value for predicting SSI in our study is below the detection of most of commercially available PCT assays. In this context only sensitive PCT assays should be used for estimation of infective marker in serum for early detection of surgical site infection.

So we postulate that higher serum procalcitonin levels with a cut off level of 0.09ng ml PCT is a very good diagnostic marker of SSI.

Compliance with ethical standards

Ethical standards

This study was done after getting informed consent from all participants and also was done as per ethical standards of the 1964 Declaration of Heinski as revised in 2000.It was approved by the responsible ethics committee of our institute.

Conflict of interest

The authors declare that they have no conflict if interest.

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