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International Journal of Current Research
Vol. 7, Issue, 12, pp.24628-24632, December, 2015

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCHARTICLE

THE KINETICS OF SERUM PROCALCITONIN AND ITS SIGNIFICANE IN PREDICTING OUTCOME FOLLOWING ORTHOPEDIC SURGERY

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ARTICLE INFO

Article History:
Received 15th September, 2015
Received in revised form
28th October, 2015
Accepted 27th November, 2015
Published online 30th December, 2015

Key words:

Serum,
Procalcitonin,
SSI,
Wound complication,
Orthopaedic,
Marker.

ABSTRACT

Background: Despite many recent advances in the field of orthopedic surgery, the early diagnosis of SSI is still a challenge to orthopedic surgeon as there is lack of reliable bio marker of infection. In this regard we aimed to find out the diagnostic power of PCT as a marker of SSI and its kinetics in patients who have undergone orthopedic surgical procedure.
Material and Methods: After getting informed consent, patients who had undergone orthopaedic surgery were included in this study. It was a prospective study. Those patients who developed post-operative wound discharge were followed up for the development of SSI and wound complications. Serum levels of procalcitonin was measured pre operatively, POD1, POD3. First wound check was done on POD4.So at the end of the study, patients were classified into 3 groups: Group 1 -with SSI: Group 2- wound discharge, Group 3-No wound discharge. The serum levels of PCT was compared among above three groups and results were drawn.
Results: Group 1 had higher mean PCT levels than Group 2 ($p < 0.05$), Group 2 had higher mean level of PCT than Group-3($p < 0.05$),
Conclusion: A persistent level of PCT is predictive of SSI and wound complications Level of evidence-4

Citation: **Ali Mohammed, P., Deep Sharma, Dilip Kumar Patro, Jagdish Menon and Pooja Dhiman, 2015.** "The kinetics of serum Procalcitonin and its significane in predicting outcome following orthopedic surgery", *International Journal of Current Research,* 07, (12), 24628-24632.

INTRODUCTION

Surgical site infection can be catastrophic in patients after orthopedic surgery as infection leads, to prolonged hospital stay and other complications (Merle *et al*., 2000). According to CDC guidelines 2013, SSI (surgical site infection) (Owens *et al*., 2014) is defined as Infection which occurs within 30 days following a surgical procedure, However if any artificial implant is left in situ any infection occurring locally for up to 90 days is classified as surgical site infection. It may involve the skin or subcutaneous tissue/ deep soft tissues (e.g., fascial and muscle layers of the incision) and patient should have at least one of the following:

a. Purulent drainage from the superficial incision
b. Organisms isolated from an aseptically obtained culture of fluid or tissue from the surgical site.
c. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness or heat, and if surgical incision is deliberately opened by surgeon, and is culture-positive or is not cultured (a culture-negative finding does not meet this criterion)
d. Diagnosis of superficial incisional surgical infection is made by the surgeon or attending physician

Jadranka Maksimovic *et al*. in a prospective study with 6 month follow up with 277 patients had 63 post-operative surgical site infections and concluded that surgical site infection is associated with increased blood sugar, open fracture, pre-operative shaving with razor blade, increase time period from shaving to operation, larger number of persons in

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the operating room. Amount and drainage duration, high degree of contamination, and elevated ASA score (Jadranka Maksimovic *et al*., 2008). So assessment of risk factors and early detection of post surgical infection is important in preventing morbidity and mortality associated with infection. It has been identified that PROCALCITONIN is elevated in human body as a part of pro-inflammatory response of the innate immune system. Procalcitonin is an accurate marker for differentiating bacterial infection from the non infective causes of inflammation or viral infection (Sabina hunziker *et al*., 20l0). PROCALCITONIN level increases faster than C reactive protein levels followed by rapid decrease and this decrease in PROCALCITONIN level is supporting evidence that the source of bacterial infection is responding to antibiotic treatment (Pundiche *et al*., 2012). Elevated serum procalcitonin has been found to be having higher diagnostic accuracy than clinical findings or standard laboratory markers for the diagnosis of bacterial infections, parameters, such as WBC and serum C reactive protein level Sabina hunziker *et al*., 20l0).

Philpp *et al*. in his study shows that PROCALCITONIN can be used as a biomarker for the assessment of disease severity and for guidance of treatment in bacterial infections (Philpp schuetz *et al*., 2008). PROCALCITONIN has been identified to be a useful biomarker in endocarditis, febrile neutropenia and conditions of immunocompromised states (Andra L Blamkalns, 2007). Numerous studies have shown that PROCALCITONIN is significantly increased in septic states and correlates with disease severity and is a specific marker of bacterial infection (Sabina hunziker *et al*., 20l0; Philpp schuetz *et al*., 2008; Yadolla zahedpasha*et al*., 2009).We aimed to study the kinetics of procalcitonin in patients who have undergone orthopedic surgical procedure and to determine its predictive efficacy as a marker of surgical site infection mostly because other markers like CRP, WBC may not reliably differentiate between systemic inflammatory response and sepsis.

Aims & Objectives

1. To investigate the kinetics of procalcitonin in patients following orthopedic surgery and to determine the diagnostic significance of PCT as biomarker for surgical site infection.

MATERIALS AND METHODS

This study was done in a tertiary care hospital .Those patients who had undergone clean elective orthopedic surgical procedure were included in this study. It was a prospective study and was carried out from September 2012 to June 2014. Study approval was obtained from the institute PG thesis review meeting and ethical clearance was obtained from the Institute Ethics Committee of JIPMER. Intra mural fund was granted by jipmer institute. The purpose and details of the study protocol was explained to the subjects and informed consent was obtained. The study comprised of a single study group of two hundred and forty nine patients. Subjects were enrolled into the study based on the following inclusion and exclusion criteria.

(i) Inclusion criteria

1. All patients undergoing any clean elective orthopedic surgical procedure were included in the study.

(ii) Exclusion criteria

1. Those patients who failed to consent for inclusion in study,
2. Those patients who had some other known source of infection (respiratory or urinary infection) or any other septic foci.
3. Those patients who deviated from our study protocol.
4. Known immune deficiency state.
5. Proven pre-op infection.

Brief Procedure

All the patients undergoing any clean elective orthopedic surgical procedure between 2012-2014 who did not have any pre existing foci of infection were followed up according to the existing departmental protocol for antibiotic prophylaxis, pre operative preparation and post operative wound care. Pre operative patient preparation was started two days prior to surgery which involved removal of hair from the local part one day prior to surgery/ on the table or no shaving based on patients characteristics. A thorough once a day scrubbing with chlorhexidine followed by application of a sterile towel to cover the local parts. This same preparation was also followed on the morning of the day of surgery. Inside operation theatre another scrubbing of the local parts was done by 1% w/v aqueous iodine solution before cleaning and draping is done for the operative procedure.One injection of intra venous antibiotic (Third generation cephalosporin-ceftriaxone) was administered at the time of induction of anesthesia and it was repeated if the operative time exceeds more than 4 hours. Following surgery the patient was kept in the post op ward for three days and same IV antibiotic was continued for two days. The wound inspection was routinely performed on post op day 4 and post op day 8, unless required otherwise.

Serum samples for all the patients were collected on day 0 (On the day of surgery before induction of anesthesia), post op day 1, and post op day 3 and were stored at -70 degree C. 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, complete hemogram with peripheral smear, ESR and CRP levels. 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 complication and surgical site infection were noted and were grouped as patients with wound infection and patients with wound complications. At the end of the study a similar age and sex matched group was formed from the non infected patients (non infection group). At the end of the study the serum samples from all the groups were tested for the levels of Procalcitonin and the values of procalcitonin were compared between three groups using the appropriate statistical analysis.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

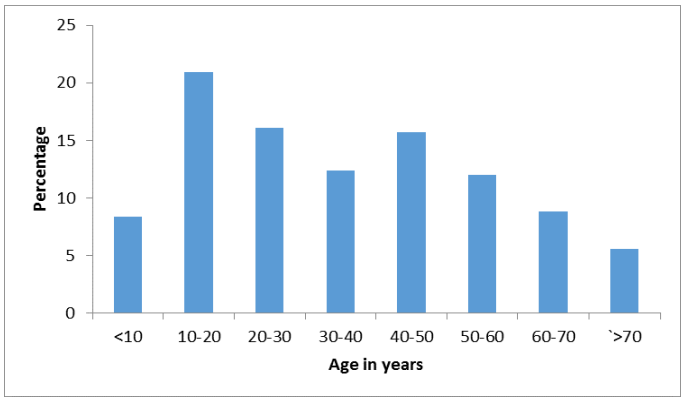
DESCRIPTIVE STATISTICS

Age

A total of 249 patients were included in the study. No drop outs were noted during study period. The age wise distribution of study participants is given in Table 1.

Table 1.

Age in years	Frequency	Percent
<10	21	8.4
10-20	52	20.9
20-30	40	16.1
30-40	31	12.4
40-50	39	15.7
50-60	30	12.0
60-70	22	8.8
`>70	14	5.6
Total	249	100.0



Sex

Sex distribution of participants in this study is as per the Table 2 given below.

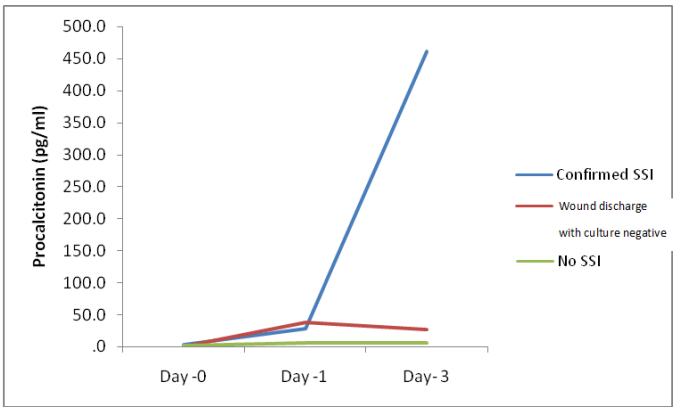
Table 2.

Sex	Frequency	Percent
Male	167	67.1
Female	82	32.9
Total	249	100.0

Procalcitonin

Out of total 249 patients enrolled in the study, the serum levels of procalcitonin was measured in 116 patients by ELISA method in the stored serum samples collected on the day of surgery(pre op),post op day 1,and post op day 3 in these patients. It was found that serum level of procacitonin in day 0, varied with a minimum value of 0 to maximum value of 12.14 with mean value of 1.3 and standard deviation of 2.8. Patients serum value of procalcitonin in day 1 was varied between a of minimum value of 0 to a maximum of 133.84 with a mean value of 12.7 and standard deviation of 25.7and on post-operative day 3 it varied between a minimum value of 0 to maximum value of 1239.59 with a mean value of 48.2 and standard deviation of 167.6. The serum level of procalcitonin in three group of patients is given below

Boxplot diagram describing Procalcitonin level among different categories.



The above graph illustrates that in patients with no post operative infection the level of serum procalcitonin shows mild increase on post op day-1 and touching base line on post op dy 3.

In patients with confirmed infection value of serum procalcitonin increases gradually on post op day 1 with rapid elevation on post op day 3.It is very clear from above graph that in patients with wound discharge without bacteriological culture positivity there is rise in level of PCT on post op day 1 with subsequent drop in level on post op day 3.

Comparison of serum Procalcitonin level among different group of patients (pre op, post op day 1, post op 3)

		N	Mean	sd	F	p.
DAY -0	Confirmed SSI(Culture positive wound discharge)	10	2.7	5.3	1.218	.300
	Wound discharge with culture negative	19	1.0	2.1		
	No SSI(No wound discharge and normal wound healing)	87	1.3	2.5		
	Total	116	1.3	2.8		
POD 1	Confirmed SSI(Culture positive wound discharge)	10	28.1	42.8	18.594	<0.001
	Wound discharge with culture negative	19	37.8	40.3		
	No SSI(No wound discharge and normal wound healing)	87	5.5	11.6		
	Total	116	12.7	25.7		
POD3	Confirmed SSI(Culture positive wound discharge)	10	460.7	385.4	77.645	<0.001
	Wound discharge with culture negative	19	26.8	31.0		
	No SSI(No wound discharge and normal wound healing)	87	5.4	8.8		
	Total	116	48.2	167.6		

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) It has been studied that there is elevation of serum markers of infection level immediately after surgical procedure as a part of stress response of immune system (Laffey *et al*., 2002).We have many laboratory parameters used in the early diagnosis of infections. But markers like WBC, ESR and CRP are not specific for infection as the inflammatory reaction caused by the surgery have serious impacts on these parameters.(Jaye and Waites, 1997; Larsson *et al*., 1992; Scherer *et al*., 2001)

This nonspecific systemic as well as local inflammatory response without bacterial infection makes the differentation of bacterial infection difficut (Dupont *et al*., 2008). It has been studied that there is a correlation between an initial high level of PCT patients with trauma and their risk for development of complications, in terms of sepsis, and prolonged hospital stay (Rajkumari *et al*., 2013). In our study on analyzing the levels of procalcitonin prior to surgery(day-0) and on post-op day1 we found the levels increased from a mean value of 1.3pg/ml to 12.5pg/ml which is expected as it has been shown by various studies indicating 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). We also found that these levels fell rapidly to the baseline values in patients with no wound complications. However in patients who had developed early post-operative wound discharge these levels continued to rise and this rise was much more in patients who had shown a culture positive wound discharge.

It is very clear from our study that level of serum procalcitonin among patients with SSI was found to be elevated on post op day 1 with a significant continuous increase on post op day 3 unlike among patients without SSI where its serum level shows initial rise followed by rapid fall on post op day 3.This persistent elevation of PCT levels make the presence of a complicating bacterial infection likely and once again, stresses the importance of follow-up measurement (Christ-Crain and Muller, 2006; Christ-Crain *et al*., 2004). So we conclude that persistent elevation of procalcitonin levels during post operative period is indicative of SSI and wound complication. So a serial estimation of marker is highly reliable in early detection of SSI as compared to single measurement. But this study is having its own limitations as our sample size is small and also due to lack of funds to measure PCT in all patientsone important drawback of PCT is its high cost, so that serial measurement of the same becomes difficult as compared to conventional infective markers.

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