Original Article
Orthopaedics

SERUM PROCALCITONIN LEVELS EFFECTIVENESS FOR DIFFERENTIATING INFECTIOUS FROM NON-INFECTIOUS CAUSES OF FEVER AFTER SURGERY- AN ORIGINAL STUDY

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Submitted on: 02 Aug. 2016
Accepted on: 06 Aug. 2016

Abstract:

Aims And Objectives: To study the effectiveness of serum procalcitonin levels for differentiating infectious from non-infectious causes of fever after surgery.

Material And Methods: The study was conducted on 400 patients having post operative fever. To differentiate infectious from non infectious causes serum procalcitonin levels are measured and aided by serum C-reactive protein levels to conclude that the fever is due to non infectious or infectious cause.

Conclusion: Positive correlation between serum procalcitonin and surgical site infection was seen after orthopaedic surgery. The sensitivity and specificity of serum procalcitonin in evaluating postoperative infection is high. Serum procalcitonin is a good marker of postoperative infection and could help limit the number of investigations.

Key-words: *Serum Procalcitonin,Fever,Postoperative Infection*

Introduction:

Postoperative fever is common after orthopaedics and trauma surgery and can be caused by infectious or non-infectious conditions.[1,2,3] Damaged tissue due to trauma and surgical interventions and the postoperative healing process can lead to production of proinflammatory response syndrome without true infections.[4] In addition, other factors such as hematoma in surgical site, transfusion of blood or blood products, lung atelectasis, deep vein thrombosis, and adverse drug reactions also may provoke postoperative fever.

Surgical Site Infections (SSIs), previously called post operative wound infections, result from bacterial contamination during or after a surgical procedure. Surgical site infections are the third most common hospital associated infection, accounting for 14% to 16% of all infections in hospitalized patients. Among surgical patients, surgical site infections are the most frequent cause of such infections, accounting for 38% of the total. Despite every effort to maintain asepsis, most surgical wounds are contaminated to some extent. However infection rarely develops if contamination is minimal, if thewound has been made without undue injury, if the subcutaneous tissue is well perfused and well oxygenated and if there is no dead space. The criteria used to define surgical site infections have been standardized and described three different anatomic levels of infection: superficial incisional surgical site infection, deep incisional surgical siteinfection and organ/space surgical site infection.[5]

Wound infections usually appear between fifth and tenth post operative day, but they may appear as early as first post operative day or even years later. The first sign is usually fever, and post operative fever requires inspection of the wound. The patient may complain of pain at the surgical site. The wound rarely appear severely inflamed, butedema may be obvious because the skin sutures appear tight.[5]

Systemic inflammatory response syndrome (SIRS) can be defined as the systemic inflammatory response to a variety of severe clinical insults. The response is manifested by two or more of the following conditions: temperature >38°C or <36°C; heart rate >90 beats/min; respiratory rate >20 breaths/min or PaCO2 <32 torr (4.3 kPa); WBC >12,000 cells/mm3<4000 cells/mm3 or 10% immature (band) forms.

Infection is defined as microbial phenomenon characterized by an inflammatory response to the presence of micro-organismsor the invasion of normally sterile host tissue by those organisms.

Procalcitonin:

Procalcitonin (PCT) is a peptide precursor of the hormone calcitonin, the latter being involved with calcium homeostasis. It is composed of 116 amino acids and is produced by parafollicular cells (C cells) of the thyroid and by the neuroendocrine cells of the lung and the intestine.

The level of procalcitonin in the blood stream of healthy individuals is below the limit of detection of clinical assays.[6]The level of serum procalcitonin rises in a response to a proinflammatory stimulus, especially of bacterial origin. The risk of local bacterial infection occurs when the value of serum procalcitonin exceeds 0.25 ng/ml. The risk of systemic bacterial infection occurs, when the value of serum procalcitonin exceeds 0.5ng/ml. It is produced mainly by the cells of the lung and the intestine. It does not rise significantly with viral or non-infectious inflammations. With the derangements that a severe infection with an associated systemic response brings, the blood levels of procalcitonin may rise to 100ng/ml. In serum, procalcitonin has a half-life of 25 to 30 hours. Remarkably the high procalcitonin levels produced during infections are not followed by parallel increase in calcitonin or serum measurement of procalcitonin can be used as a marker of severe sepsis caused by bacteria and generally grades well with the degree of sepsis although levels of calcitonin in the blood are very low.[7]Procalcitonin has the greatest sensitivity (85%) and specificity (91%) for differentiating patients with systemic inflammatory response syndrome (SIRS) from those with sepsis, when compared with IL-2, IL-6, IL-8, C–reactive proteins and TNF-alpha.[8]Evidence is emerging that procalcitonin levels can reduce unnecessary antibiotic prescribing to people with lower respiratory tract infections.

Aims And Objectives:

1. To study the effectiveness of serum procalcitonin levels for differentiating infectious from non-infectious causes of fever after surgery.
2. To allow the initiation of empirical antibiotic therapy rapidly in patients having fever due to infection and to avoid unnecessary antimicrobial usage in patients without having an infection, thereby saving health care cost and preventing the development of antimicrobial resistance.

Materials and methods:

The present study was conducted in department of orthopaedics in collaboration with department of biochemistry, Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar.

Study design The present study was conducted on 400 patients having post operative fever (>18 years of age). These 400 patients were divided into two groups as follows:

Group A 200 cases having fever and raised abnormal serum TLC (total leukocyte count) levels and raised abnormal ANC (absolute neutrophil count).

Group B 200 cases having fever but normal TLC (total leukocyte count) levels and normal ANC (absolute neutrophil count).

Further to differentiate infectious from non infectious causes serum procalcitonin levels are measured and aided by serum C-reactive protein levels to conclude that the fever is due to non infectious or infectious cause.

Inclusion criteria:

1. All patients having fever within 10 days of orthopaedic surgery.
2. Patients more than 18 years of age.
3. Patient having fever >38.5 degree Celsius (>101.3 degree F) at single reading or >38 degree Celsius (100.4 degree F) on two consecutive readings 1 hour apart.
4. Patients who are willing to undergo study and sign the informed consent.

Exclusion criteria:

1. Patients having fever on the day of surgery.
2. Patients in any incubatory phase of any disease.
3. Patients those have taken antibiotics before surgery.
4. Patients who are not willing to undergo study.

Test principal and method:

The quantitative measurement of human procalcitonin was done by using the RD191006200R Human Procalcitonin ELISA sandwich enzyme immunoassay.

First of all 20µL or 3 ml of venous blood samplewas collected under all aseptic conditions in red or yellow cap vacutainer and was send to laboratory within 60 minutes for serum procalcitonin assay.

In the Human Procalcitonin ELISA, standards, quality controls and samples were incubated in microplate wells pre-coated with polyclonal anti-human procalcitonin antibody. After 120 minutesincubation and washing, biotin labelled polyclonal anti-human procalcitonin antibody was added and incubated with captured procalcitonin for 60 minutes. After another washing, streptavidin-HRP conjugate was added. After 30 minutes incubation and the last washing step, the remaining conjugate was allowed to react with the substrate solution. The reaction was stopped by addition of acidic solution and absorbance of the resulting yellow product was measured. The absorbance was proportional to the concentration of procalcitonin. A standard curve was constructed by plotting absorbance values versus procalcitonin concentrations of standards, and concentrations of unknown samples were determined using this standard curve.

Serum total leukocyte count was measured by Automated Cell Counter and the normal reference range for TLC is between 4000 to 11000 mm^3.

Absolute neutrophil count (ANC) was calculated from TLC by the formula:

ANC = (%neutrophil + %bands) * (TLC) / 100

Or

ANC = (Absolute-Polymorphs + Absolute-Bands)

The reference range for ANC in adults is 1500 to 8000 cells per microliter.

Serum C-reactive protein was measured by Turbidimeter and the normal reference range for C-reactive protein was taken as <5 mg/l.

History and examination:

On arrival detailed history with respect to the age, sex, mode of injury, duration of injury, limb affected, drug intake i.e. steroids, anti-epileptics, antibiotics and other associated injuries were recorded. Type of treatment if any, prior to admission was also recorded. Along with this following histories were ruled out like history of burning micturition, ear or nasal discharge, ear ache, sore throat

Observations:

Sex

Among 400 patients enrolled in the study 296 (74%) were males and 104 (26%) were females.

Age

400 patients were enrolled in our study of them 112 (28%) were in age group <30 years, 140 (35%) were in age group of 31 to 50 years, 128 (32%) were in age group of 51 to 70 years and 20 (5%) were in age group of >70 years. Mean age was 43 years. Youngest patient was 18 year old and eldest patient was 85 years old. Following table show age distribution:

Distribution Of Patients According To Diabetic Status

In this study, out of 400 patients 84 were patients with diabetes mellitus type 2, 48 patients out of them were included in study group and 36 served as controls. The statistically analysis showed that the difference between study group and control group was statistically insignificant as p value was >0.05 as shown by following table:

Table 1: Distribution of patients according to diabetic status

Diabetic status	Study group	Control group	Total
Diabetics	48 24.0%	36 18.0%	84 21.0%
Non-diabetics	152 76.0%	164 82.0%	316 79.0%
Total	200 100.0%	200 100.0%	400 100.0%

P value 0.461(statistically insignificant)

Trends of C-Reactive Protien Levels:

In this study of 400 patients, 384 had an abnormal C-reactive protein levels out of them 188 were included in study group and 196 were taken as controls, only 16 had normal C-reactive protein levels. Out them 12 patients were included in study group and one patient served as control. The statistical analysis showed that the difference between these two groups was statistically insignificant as p value was 0.307 as shown by following table:

Table 2: Trends Of C-Reactive Protien Levels In Study

C-reactive protein	Study group	Control group	Total
Within normal limits	12 6.0%	4 2.0%	16 4.0%
Abnormal	188 94.0%	196 98.0%	384 96.0%
Total	200 100.0%	200 100.0%	400 100.0%

P value 0.307 (statistically insignificant)

Trends Of Serum Procalcitonin:

In this study of 100 patients 44 patients had an abnormal serum procalcitonin levels and all of them were included in study group. 356 patients had normal serum procalcitonin levels out of them 156 were included in study group and 200 were served as controls.The statistical analysis showed that there was difference between two groups because only 44 patients in this study had abnormal serum procalcitonin levels and all of them were enrolled in study group. So this difference was also statistically significant as p value was <0.05 as shown in the following table:

Table 3: Serum Procalcitonin Levels

Serum procalcitonin	Study group	Control group	Total
Within normal limits (<0.5 ng/ml)	156 78.0%	200 100.0%	356 89.0%
Abnormal(>0.5 ng/ml)	44 22.0%	0 0.0%	44 11.0%
Total	200 100.0%	200 100.0%	200 100.0%

P value <0.05(statistically significant)

Comparison Of Serum Procalcitonin With Fracture Type

In this study there were 200 patients included in study group. Out of 200 patients 136 patients had compound fracture at the time of admission to the hospital. In these 136 patients 100 had normal serum procalcitonin levels and 36 had abnormal procalcitonin levels. 64 patients out of 200 study group patients had simple fracture. In those 64 patients 56 had normal serum procalcitonin levels and only two patients had an abnormal serum procalcitonin level. The statistical analysis showed that the difference between these two groups was statistically insignificant as p value was 0.266 that is >0.05 as shown by following table:

Table 4: Comparison Of Serum Procalcitonin With Fracture Type In Study Group

Fracture type	Normal levels of serum procalcitonin	Abnormal levels of serum procalcitonin	Total
Compound fracture	100	36	136
Simple fracture	56	8	64
Total	156	44	200

P value 0.266 (statistically insignificant)

Comparison Between Serum Procalcitonin And C-Reactive Protein:

In this study, there were 200 study group patients. Out of these 200 patients there were 12 patients who had normal serum procalcitonin levels and normal serum C-reactive protein level. There was no patient with normal C-reactive protein and abnormal serum procalcitonin levels. There were 144 patients who had abnormal C-reactive protein level but normal serum procalcitonin level. There were 44 patients who had both abnormal C-reactive protein level and serum procalcitonin level. The statistical analysis showed that the difference between these two groups was statistically insignificant because the p value was>0.05 as shown in table below:

Table 5: Comparison between serum procalcitonin and C-reactive protein

C-reactive protein	Normal serum procalcitonin	Abnormal serum procalcitonin	Total
Normal	12	0	12
Abnormal	144	44	188
Total	156	44	200

P value 0.343(statistically insignificant)

Comparison Of Wound Condition With Serum Procalcitonin In Study Group:

In this study, there were 200 patients included in study group. Out of 200 patients 28 patients had an unhealthy wound after surgery and all of them had an abnormal serum procalcitonin level. Rest 172 patients had healthy wound after surgery and out of them 16 had abnormal serum procalcitonin levels and 156 had normal serum procalcitonin levels. The statistical analysis showed that the difference in these groups was statistically significant as p value was <0.05 as shown in table below:

Table 6: comparisom of serum procalcitonin with wound Condition in study group

Wound condition after surgery	Normal serum procalcitonin	Abnormal serum procalcitonin	Total
Healthy	156	16	172
Unhealthy	0	28	28
Total	156	44	200

P value is <0.05(statistically significant)

Comparison Of Serum Procalcitonin With Time Of Fever After Surgery:

In study group of 200 patients, 48 patients were having fever on 2nd day of surgery and all of them had normal serum

procalcitonin levels. 68 patients were having fever on 3rd day of surgery, out of them 8 patients had abnormal procalcitonin levels and 60 had normal serum procalcitonin levels. 52 patients were having fever on 4th day of surgery, out of them 12 patients had abnormal serum procalcitonin levels and 40 had normal serum procalcitonin levels. 28patients were having fever on 5th day of surgery, out of them 24 had abnormal serum procalcitonin levels and only 4 patients had normal serum procalcitonin levels. Only 4 patients were having fever on 6th day after surgery and serum procalcitonin levels were normal in those patients.

The statistical analysis showed that the difference in these groups was statistically significant as p value was<0.05 as shown in following table:

Table 7: Comparison Of Serum Procalcitonin With Time Of Fever After Surgery In Study Group

Time of fever	Normal serum procalcitonin	Abnormal serum procalcitonin	Total
Day 2	48	0	48
Day 3	60	8	68
Day 4	40	12	52
Day 5	4	24	28
Day 6	4	0	4
Total	156	44	200

P value <0.05 (statistically significant)

Sensitivity And Specificity Of Serum Procalcitonin

In total 200 study group patients there were 28 true positive cases, 16 cases were false positive, 156 cases were true negative and no case was false negative. So, according to our study positive predictive value of serum procalcitonin test 63.64% but negative predictive value was 100%. Sensitivity of this test was 100% and specificity of serum procalcitonin in our study was 90.70% as shown in following table:

Table 8: Various Statistical Parameters Of Serum Procalcitonin

True Positive	28
False Positive	16
True Negative	156
False Negative	0
N	200
Sensitivity (%)	100%
Specificity (%)	90.70%
Positive Predictive Value (%)	63.64%
Negative Predictive Value (%)	100%
Accuracy (%)	92%

Discussion:

Postoperative fever is common after orthopaedics and trauma surgery and can be caused by infectious or non-infectious conditions.[1,2,3] Damaged tissue due to trauma and surgical interventions and the postoperative healing process can lead to production of proinflammatory response syndrome without true infections.[4] In addition, other factors such as hematoma in surgical site, transfusion of blood or blood products, lung atelectasis, deep vein thrombosis, and adverse drug reactions also may provoke postoperative fever.

Before serum procalcitonin mainly TLC (total leukocyte count) and C-reactive proteins were used to rule out infections. Now a day serum procalcitonin has emerged as a better diagnostic marker to rule out infectious from non infectious cause of fever.

The level of procalcitonin in the blood stream of healthy individuals is below the limit of detection of clinical assays.[8]The level of serum procalcitonin rises in a response to a proinflammatory stimulus, especially of bacterial origin. The risk of local

bacterial infection occurs when the value of serum procalcitonin exceeds 0.25 ng/ml. The risk of systemic bacterial infection occurs, when the value of serum procalcitonin exceeds 0.5ng/ml.

In our study, comparison between diabetic status of patients with serum total leukocyte count proved to be statistically insignificant as p value was >0.5 (Table 3). This may be due to small sample size in our study.

In our study, comparison of C-reactive protein with total leukocyte count, proved to be statistically insignificant as p value was 0.307 (Table 4). C-reactive protein levels were high in both study and control group. These findings were in accordance with Clayton N Kraft et al who observed that serum C-reactive protein level was high in all patients after spinal surgery and kept on rising up to day 4 after the surgery and then started falling in cases with no post operative complication and normal value was reached after 14 days. However, in patients with postoperative infection, levels of C-reactive protein remained elevated for a prolonged period of time.[9]

In our study, total leukocyte count did not show a definitive trend after the surgery as it was raised in 200 patients that were included in test group and was within normal limits in those that served as controls. This finding was also observed by Clayton N Kraft et al who showed that total leukocyte count after complication-free spinal surgery did not show a typical (and therefore interpretable) profile, making it of secondary value only as a serum parameter for early detection of infectious complications.[9]

In our study, comparison of serum procalcitonin with total leukocyte count proved statistically significant as p value was<0.05(Table 5). Serum procalcitonin levels were higher in study group in which levels of serum total leukocyte count were high. These findings correlate with study done by Era Grace M.Lee and Marvin B. Harper who showed in their study that white blood cell count and absolute neutrophil count were best predictor for occult bacteremia.[10] Similarly in our study serum procalcitonin was positive in 22% cases who had raised total leukocyte count and was normal in control group in whom total leukocyte count was within normal limits.

Comparison between serum procalcitonin with fracture type in our study showed that the difference between these two groups was statistically insignificant as p value was 0.226 (Table 6). This shows that there was no correlation between type of fracture and serum procalcitonin after surgery. These findings are in accordance with Yasmin Det al who studied Effects of fracture and fracture surgery to serum procalcitonin levels and the value of procalcitonin in differentiating inflammatory reaction caused by fracture surgery from postoperative infective complications.

In their study, 29 patients who underwent surgery for pertrochanteric fractures were evaluated. Procalcitonin, C-reactive protein (CRP), white blood cell count and body temperature were measured before surgery and for five days postoperatively. In their study nine patients developed complications; postoperative wound infection occurred in one and one was lost due to sepsis. Mean preoperative C-reactive protein level was five times above the normal. It made a peak on the second day, then began to decrease, but still was four times higher than the preoperative level on the fifth day. Preoperatively, mean procalcitonin level was lower than the normal in all patients. It made a peak on the first postoperative day without exceeding the normal range and returned to the preoperative level on the fifth day. In contrast to C-reactive protein levels which were above the normal in all patients, procalcitonin levels were higher than the normal only in patients who developed complications.[11]

In our study we did a comparison between serum procalcitonin and C-reactive protein. The statistical analysis showed that the difference between these two groups was statistically insignificant because the p value was 0.343 (Table 7). These findings are in accordance with Carboni GL et alwho showed in their study that due to infection serum procalcitonin and C-reactive protein were elevated preoperatively. In the postoperative course both serum procalcitonin and C-reactive protein reached peak-levels on day 2 with values up to 43.55 ng/ml and 384.00 mg/l, respectively. In serum procalcitonin the rise was followed by a clear decrease in 20 (90.9%) patients until day 7. In contrast the C-reactive proteins levels decreased slowly and only 28 (54.5%) patients had values of 100 mg/l or below on day 7. Serum procalcitonin showed a better correlation with septic course than C-reactive protein does.[12]

A ouifi A et al also showed in their study that C-reactive proteinconcentration was increased about twentyfold to forty fold in all patients after cardiac surgery, and levels remained high through out the three-day observation period. Procalcitonin kinetics was also studied in a cohort of patients undergoing elective cardiac surgery. The investigators reported that, in the presence of fever, procalcitonin was a

reliable marker for infection and more relevant than C-reactive protein for the diagnosis of postoperative infection.[13]

Also Clayton N Kraft et al observed that serum C-reactive protein level was high in all patients after spinal surgery and kept on rising up to day 4 after the surgery and then started falling in cases with no post operative complication and normal value was reached after 14 days. However, in patients with postoperative infection, levels of C-reactive proteins remained elevated for a prolonged period of time beyond day 4 after orthopaedic surgery.[9]

Comparison between serum procalcitonin and surgical site/wound condition in our study showed that the difference in these 2 entities was statistically significant as p value was<0.05 (Table 8). This shows that there was fair correlation between infection at surgical site and raised levels of serum procalcitonin. In our study there are total 44 patients with unhealthy wound condition that was surgical site infection. Out of these 44 patients 28 had abnormally high serum procalcitonin levels. These findings are in accordance with Hunziker S et al who showed in their study that unlike C-reactive protein levels and white blood-cell counts, procalcitonin values were significantly higher in patients with infection compared with patients without infection on the day of fever onset.[14]

Beloborodova NV, Popov DA also observed in their study that the persistence of the high level of serum procalcitonin in patients having infectious complications. As compared with the traditional clinical and laboratory criteria (fever, leukocytosis), Procalcitonin was the earliest and most specific marker of bacterial infection in cardiosurgical patients in the early postoperative period. The level of procalcitonin> 3.5 ng/ml within the first 24 hours after surgery is shown to be a predictor of postoperative infectious complications.[15]

In our study out of 200 patients 44 patients had abnormal serum procalcitonin levels and the rest 156 patients had normal serum procalcitonin levels even though in these patients, serum C-reactive proteins and total leukocyte count was found to be raised and also having fever. The reason that these 156 patients did not have abnormally high serum procalcitonin levels could be due to local low grade wound infection which did not cause a significant increase in serum procalcitonin. This finding is in accordance with finding of Assicot M et al who showed in their study that serum procalcitonin levels remained normal in patients with local infections.[16]

In the present study when comparison between serum procalcitonin and time of onset offever after orthopaedic surgery was done it was observed that difference between these two groups was statistically significant as p value was<0.05 (Table 10). These findings are in accordance with Baykut Det al who showed in their study that patients predisposed to an infection had continuously high temperature, leukocytes, C-reactive protein and procalcitonin until 4th day after surgery with leukocytes and C-reactive protein decreasing after 4th postoperative day. Procalcitonin however showed a divergent course with a second increase in these patients between 4th to 6thpostoperative day (p<0.001). At this time, no clinical sign of an infection was evident. The increase of procalcitonin was independent of infection type, but most apparent in bacteriemia/sepsis.[17]

Hunziker S et al also showed in their study that procalcitonin values were significantly higher in patients with infection compared with patients without infection on the day of fever onset (p = 0.04), day 1 (p = 0.07), and day 3 (p = 0.003). In our study 9 patients out of 11 patients had abnormal serum procalcitonin values in whom onset of fever was in between 4 to 6 days after surgery.[14]

Chirouze C et al demonstrated that procalcitonin findings arehighly discriminative and can accurately predict bacteremia in patients havingfever, with 0.4 ng/mL as cutoff value. Therefore, we suggest that procalcitonin measurement be included in the initial diagnosis strategy of such patients.They advocate that the procalcitonin level be measured when the first blood sample wasobtained for culture. If the procalcitonin level turns out to be <0.4 ng/mL in the absence of clinical evidence of severity, antibioticadministration could be deferred until further diagnostic informationbecomes available, and no additional blood culturewould be necessary.[18]

In total 200 study group patients there were 28 true positive cases, 16 cases were false positive, 156 cases were true negative and no case was false negative. So, according to our study positive predictive value of serum procalcitonin test 63.64% but negative predictive value was 100%. Sensitivity of this test was 100% and specificity of serum procalcitonin in our study was 90.70% (Table 10).

Conclusion:

There is positive correlation between serum procalcitonin and surgical site infection after orthopaedic surgery. The sensitivity and specificity

of serum procalcitonin in evaluating postoperative infection is high. Serum procalcitonin is a good marker of postoperative infection and could help limit the number of investigations, as well as the number of antibiotic prescriptions, presumablyresulting in both favourable economic and ecological effects by reducing antimicrobial resistance.

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