Section: Orthopaedics

Original Research Article

ACCURACY OF SERUM PROCALCITONIN TO DIFFERENTIATE POST-OPERATIVE FEVER SECONDARY TO INFECTIOUS OR NON-INFECTIOUS CAUSE AFTER ORTHOPAEDIC SURGERY

Milan Manjunath Reddy[1], Channareddy H[2], Palakshaih L[3]

[1]*Post Graduate, Department of Orthopaedics, Basaveshwara Medical College and Hospital, Chitradurga, Karnataka, India.*
[2,3]*Professor, Department of Orthopaedics, Basaveshwara medical college and hospital, Chitradurga, Karnataka, India.*

Received *: 13/10/2024*
Received in revised form *: 02/12/2024*
Accepted *: 17/12/2024*

Corresponding Author:
Dr. Milan Manjunath Reddy,
Post Graduate, Department of Orthopaedics, Basaveshwara Medical College and Hospital Chitradurga, Karnataka, India.
Email: milan.reddy1996@gmail.com

DOI: 10.70034/ijmedph.2024.4.202

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2024; 14 (4); 1109-1114

ABSTRACT

Background: Post-operative fever being common after orthopaedic surgery can be due to infectious or non-infectious causes. Identifying infectious cause early is very important to start antimicrobial therapy. Routine investigations (CBC, CRP) are non-specifically raised even in Non-infectious fevers. However, Procalcitonin levels has been found to be a reliable marker specifically raised only when there is an infectious process occurring within the body. Procalcitonin levels have been a reliable marker to identify infections after other major surgeries (Cardiac, Abdominal and Neurosurgeries). The reliability of serum procalcitonin to diagnose infections after orthopaedic surgeries has not been established and studies are lacking. Thus, we assess the reliability of serum procalcitonin to diagnose infections after orthopaedic surgeries in this study.

Material and Methods: We performed a study on 58 patients developing fever within 14 days post orthopaedic surgery. Conventional Biomarkers (CBC, CRP) and Serum procalcitonin was sent for on day 0, day 1 and day 3 after onset of fever. To confirm fever due to infectious cause blood culture and other supportive investigations were sent on the day of onset of fever. We compared the conventional biomarkers to serum procalcitonin and studied the trend of these biomarkers. Using this data, the accuracy of serum procalcitonin in diagnosing infectious fevers after orthopaedic surgery was assessed.

Results: Of the total number of patients studied (n=58), 33 patients were allocated into the Non-infectious fever group and 25 patients were allocated into the infectious group after complete clinical and laboratory and radiological evaluation. The area under ROC curve for procalcitonin on Day 3 (0.837) was the highest among all parameters while CRP on day 3 (0.610) had a significantly lesser area under the ROC curve. Procalcitonin had a sensitivity of 80% and specificity of 64% on Day 0 and it showed highest sensitivity of 84% and specificity of 96% on Day 3 for Cut off value of ≥ 0.25 ng/ml.

Conclusion: Procalcitonin is more accurate than other biomarkers (WBC Counts, CRP) in diagnosing post-operative fever due to infection. Procalcitonin is more sensitive (84%) and specific (96%) to differentiate post-operative fever due to infection and fever due to non-infectious causes (Systemic inflammatory response syndrome - SIRS) with cut-off value of ≥ 0.25 ng/ml on Day 3.

Keywords: Orthopaedic surgery, Post operative fever, Procalcitonin, Infection, Sepsis, ROC curve.

INTRODUCTION

Postoperative fever is common after orthopaedic and trauma surgery and can be caused by infections or non-infectious conditions.[1-3] Damaged tissue due to trauma and surgical intervention and the postoperative healing process can lead to the production of pro-inflammatory cytokines and can induce a non-specific systemic inflammatory response syndrome,[4] (SIRS) causing fever without true infection. In addition, other factors such as hematoma in the surgical site, transfusion of blood or blood products, lung atelectasis, deep venous thrombosis, adverse drug reactions and inflammatory disorders (RA, gout, etc) also may provoke postoperative fever. It is important to distinguish the non-infective causes from infective causes of fever at the earliest as infective fevers warrant early initiation of anti-microbial therapy. However, initiating anti-microbial therapy non-specifically without true infection can be of limited use and detrimental to the patient in terms of increased costs of treatment, irrational antibiotic use and development of antibiotic resistant and adverse effects of the antibiotic administered. Conventional laboratory parameters (WBC, CRP) are often non-specifically elevated after surgery and are frequently not helpful in differentiating infectious from non-infectious causes of postoperative fever. For the diagnosis of bacterial infections (Surgical Site Infections, pneumonia, UTI, Bone and Joint infection, prosthetic infection, etc), elevated serum procalcitonin has been demonstrated to have higher diagnostic accuracy than clinical findings or standard laboratory parameters, such as the white blood-cell count and serum C-reactive protein levels, in various clinical settings.[5-17] The value of elevated serum procalcitonin in the diagnosis of infections has been demonstrated for specific surgical settings, such as cardiac surgery after cardiopulmonary bypass, lung decortications, major neurosurgery, and abdominal surgery.[5,18-24] Considering the specificity of serum procalcitonin to infections as described in literature, it can be a promising biomarker aiding in the early identification of infection and thereby differentiating non-infectious and infectious fever post-operatively after orthopaedic surgeries. However, the diagnostic accuracy of procalcitonin levels to distinguish infectious from non-infectious causes of fever in patients after orthopaedic surgery has not been adequately studied. In this study, we assess the accuracy of serum procalcitonin as a marker of post-operative infection after orthopaedic surgery and compare with traditional biomarkers of infection – WBC, CRP.

MATERIALS AND METHODS

This study was performed in Basaveshwara Medical College Hospital and Research Centre, Chitradurga, Karnataka. Post-operative patients satisfying inclusion criteria admitted in Department of Orthopedics in Basaveshwara Medical College Hospital & Research Centre during the period of August 2023 to January 2024 were included in the study.

Inclusion Criteria

- Those who have undergone orthopaedic surgery for any cause (fracture fixation, arthroplasty, etc) and
- Developing new onset of **Fever upto 14 days** (2 weeks) post-operatively
- Age > 18 years
- Those willing to give consent

Exclusion Criteria

- Patients with suspicion of pre-existing infections / fever prior to surgery
- Patients on corticosteroids within the preceding week of admission

After obtaining approval and clearance from the institutional ethics committee, the patients fulfilling the inclusion criteria were enrolled for the study after obtaining informed consent.

Methodology

Patients who developed fever post-operatively, were investigated with WBC Counts, CRP and Serum Procalcitonin on Days 0, 1 and 3 after onset of post-operative fever. Assessors evaluated if the fever was of infectious or non-infectious type based on history, clinical examination, laboratory parameters and other relevant investigations, except serum procalcitonin. In brief, ***Pneumonia*** was defined as the presence of (1) at least one respiratory symptom (cough, sputum production, dyspnoea, tachypnoea, or pleuritic pain) and at least one finding during auscultation (rales or crepitation), or (2) one sign of infection (a core body temperature of >38.0°C, shivering, or a white blood-cell count of >10 x 10^9/L or <4 x 10^9/L) and a new infiltrate on a chest radiograph;

Urinary tract infection was defined as (1) substantial leukocyturia (>10 white blood cells per visual field on microscopy of sediment per high-power field) or (2) substantial bacteriuria (>10^5 CFU/ml of urine).

Surgical site infection was defined as microbiologically proven superficial incisional, deep incisional, or organ and/or space infection; prosthetic joint infection was defined as the presence of (1) visible purulence, (2) acute inflammation on histopathological analysis, (3) a sinus track, or (4) microbial growth in synovial fluid or periprosthetic tissue;

Bloodstream infection was defined as growth of relevant bacteria in blood cultures.

The assessors are blinded to the serum procalcitonin values. The accuracy of serum procalcitonin to differentiate infective from non-infective fever was assessed. The trends of Serum procalcitonin was also compared to the trends of conventional biomarkers -WBC counts and CRP. To

evaluate differences between groups, the unpaired Student t test for continuous variables and the chi-square test for categorical variables were used. The area under the receiver-operating characteristic (ROC) curve was considered to be the overall performance measure of the accuracy of the laboratory parameter to distinguish patients with infectious fevers from those with non-infectious fevers. Further using receiver-operating characteristic analysis we reported sensitivity, specificity, Positive Predictive Value and Negative Predictive Value of procalcitonin at different cut-off points. A p value of <0.05 was considered significant.

RESULTS

Of the total number of patients studied (n=58), 33 patients were allocated into the Non-infectious fever group and 25 patients were allocated into the infectious group after complete evaluation of the cause of fever. The mean values of serum procalcitonin were significantly higher (p <0.001) in the infectious group in comparison to the non-infectious fever group on all days of evaluation yielding 0.65 ± 0.442, 0.84 ± 0.539 and 0.48 ± 0.168 (infectious group) when compared to 0.25 ± 0.115, 0.23 ± 0.08 and 0.16 ± 0.057 (non-infectious group) respectively on days 0, 1 and 3 post onset of fever. The mean CRP values in the infectious group were higher in comparison to the non-infectious group on all days of evaluation but results were non-significant with p values of 0.431, 0.563 and 0.631 respectively. The WBC Counts on day 0 were significantly (p <0.001) more in the infectious group (10.4 ± 1.30) in comparison to the non-infectious group (8.4 ± 0.902), but this pattern did not translate to day 1 and day 3 of evaluation, thereby indicating the unreliability of WBC counts. The area under ROC curve for procalcitonin was more on all days of evaluation in comparison to the area under ROC curve for WBC Counts or CRP, thereby indicating serum procalcitonin to be a more reliable marker. The area under ROC curve of procalcitonin on Day 3 (0.837) was the highest among all parameters while CRP on day 3 (0.610) had a significantly lesser area under the ROC curve with WBC Counts having least area under ROC curve on Day 3 (0.465). Procalcitonin had a sensitivity of 80% and specificity of 64% on Day 0 for cut off value of 0.25 ng/ml. Interestingly, procalcitonin showed highest sensitivity of 84% and specificity of 96% on Day 3 for Cut off value of ≥ 0.25 ng/ml. Hence, procalcitonin is more accurate to diagnose infectious fever than CRP or WBC counts, postoperatively.

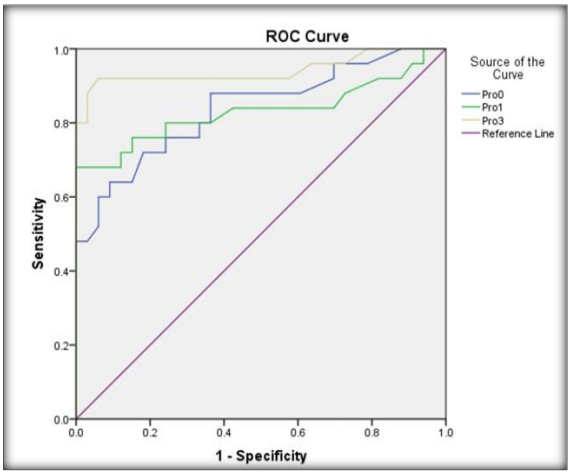

Figure 1: Area under ROC of procalcitonin on Day 0,1 and 3. Maximum area under ROC curve was maximum for Procalcitonin on Day 3. So, procalcitonin is more specific on Day 3 of onset of fever.

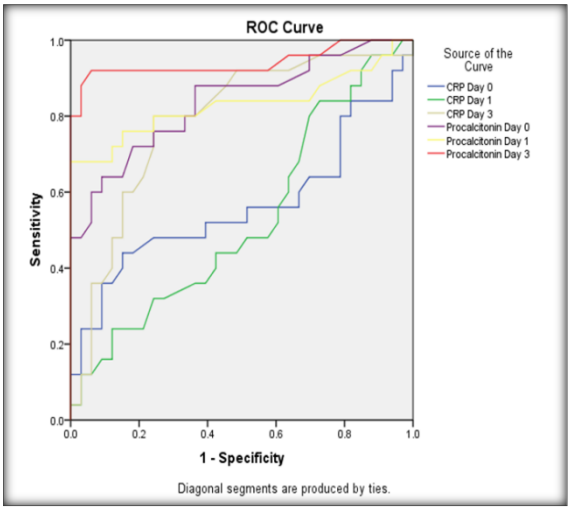

Figure 2: Comparison of Area under ROC of Procalcitonin and CRP on Days 0, 1 and 3 respectively. Procalcitonin occupied more area under the ROC curve compared to CRP on all the 3 days. Hence, Procalcitonin is more specific than CRP on all given days.

Table 1: Showing the distribution of the primary source of various infections in the infectious group

Sl. No.	Infection Source	No. Of Patients Affected
1	Surgical Site Infections	2
2	Pneumonia	14
3	Urinary Tract Infection	8
4	Bed Sore Infection	1

Table 2: The mean duration to onset of fever in both the Infectious and Non-Infectious groups.

Sl. No.	Group	Mean Duration to onset of fever*
1.	Infectious Group	5.4
2.	Non-Infectious Group	2.6

***Calculated from the day of surgery**

Table 3: Non-Infectious causes of post-operative fever

Sl. No.	Non-Infectious causes of fever (n=33)	No. Of Patients Affected
1	SIRS	17
2	Blood and blood product transfusions	6
3	Lung Atelectasis	3
4	Haematoma	3
5	Deep Vein Thrombosis	2
6	Adverse Drug Reactions	2

Table 4: Showing mean values (with range) of WBC counts, CRP and Procalcitonin on Days 0,1, and 3 with comparison among infectious and non-infectious group with respective area under ROC curves and p-values
P-values are significant on days 0 ,1 and 3 for procalcitonin and only on Day 0 for WBC Counts.

PARAMETER	NON-INFECTIOUS N=33 MEAN ± SD (RANGE)	INFECTIOUS N= 25 MEAN ± SD (RANGE)	AREA UNDER ROC	P- VALUE
WBC COUNT				
DAY 0	8.4 ± 0.902 (7.4 – 10.6)	10.4 ± 1.30 (8.9 – 12.6)	0.769	<0.001 , S
DAY 1	8.1 ± 1.029 (6.5 – 9.7)	8.7 ± 0.843 (7.5 – 11.0)	0.488	0.362 , NS
DAY 3	7.45 ± 1.092 (6.0 – 9.5)	7.16± 1.028 (6.8 – 10.8)	0.465	0.412 , NS
CRP				
DAY 0	140 ± 26.629 (94 – 202)	151 ± 55.085 (78 -237)	0.610	0.431 , NS
DAY 1	126 ± 26.787 (85 – 190)	132 ± 40.625 (88 – 251)	0.532	0.563 , NS
DAY 3	58 ± 16.761 (45 – 130)	60 ± 23.18 (44-152)	0.481	0.631 , NS
PROCALCITONIN				
DAY 0	0.25 ± 0.115 (0.12 – 0.53)	0.65 ± 0.442 (0.14 – 1.89)	0.837	<0.001 , S
DAY 1	0.23 ± 0.08 (0.10 – 0.42)	0.84 ± 0.539 (0.13 – 1.72)	0.831	<0.001 , S
DAY 3	0.16 ± 0.057 (0.07 – 0.23)	0.48 ± 0.168 (0.11 – 0.69)	0.941	<0.001 , S

Table 5: Showing sensitivity, specificity, positive and negative predictive values of procalcitonin on days 0,1 and 3. Procalcitonin has highest sensitivity (84%) and specificity (96.97%) on day 3 for cut-off value of 0.25 ng/ml.

CUT-OFF VALUE OF PROCALCITONIN	SENSITIVITY CI* = 95% (%)	SPECIFICITY CI* =95%(%)	POSITIVE LIKELIHOOD RATIO	NEGATIVE LIKELIHOOD RATIO
DAY 0				
0.25	**80% (59.3-93.2)**	**63.64% (45.1-79.6)**	**2.20**	**0.31**
0.50	56% (34.9-75.6)	93.94% (79.8-99.3)	9.24	0.47
1.02	16%(4.5-36.1)	100%(89.4-100)	-	0.84
1.6	4%(0.1-20.4)	100% (89.4-100)	-	0.96
DAY 1				
0.25	80% (59.3-93.2)	75.76%(57.7-88.9)	3.3	0.26
0.4 7	60% (38.7-78.9)	100% (89.4-100)	-	0.4
1.14	44% (24.4-65.1)	100% (89.4-100)	-	0.56
1.60	4% (0.1-20.4)	100% (89.4-100)	-	0.96
DAY 3				
0.25	**84% (63.9-95.5)**	**96.97% (84.2-99.9)**	**27.7**	**0.17**
0.50	52% (31.3-72.2)	100% (89.4-100)	-	0.48
0.69	0% (0-13.7)	100% (89.4-100)	-	1

***CI- Confidence Interval**

DISCUSSION

Fever is regarded as an important clinical clue in identifying patients with underlying infection; yet the presence of fever is non-specific. Febrile reactions are caused by a variety of conditions in addition to infection. Various investigators have observed that fevers which occur in the first 24 hours postoperatively generally resolve without therapy. Infections in the postoperative course after orthopaedic surgery can lead to prolonged hospitalization, increased morbidity and mortality, and high costs 1-3 Timely administration of adequate antibiotic therapy is an important factor to reduce morbidity and mortality in patients with postoperative infections, and thus a thorough clinical examination and diagnostic workup is mandatory.

In patients with a new onset of fever after an orthopaedic procedure, various laboratory parameters are frequently used in the routine setting to differentiate infectious from non-infectious causes. However, parameters such as C-reactive protein level and white blood-cell count may be misleading since they are increased in all patients in the postoperative period due to tissue damage resulting in SIRS or other non-infectious causes of fever like hematoma in the surgical site, transfusion of blood or blood products, lung atelectasis, deep venous thrombosis, adverse drug reactions and inflammatory disorders and are not specific for underlying infection; therefore, they are of limited

clinical utility. Infection and bacterial endotoxins are stimuli for the induction of pro-calcitonin.[26]

We used the clinical evaluation of the patients based on a comprehensive diagnostic and microbiological workup as the method to diagnose infectious fever. Using this, we could categorize patients into infectious and non-infectious groups and assess the accuracy of each modality in identifying the cause of fever; whether infectious or non-infectious.

Endotoxin liberation or bacterial translocation within the intestine to various degrees has been reported after different types of surgery.[27] On a transcriptional level, a stimulatory effect on messenger RNA (mRNA) production of procalcitonin has been reported for different proinflammatory cytokines including tumour necrosis factor (TNF)-a, interleukin (IL)-6, and IL-1b, which may be upregulated as a result of fractures, tissue damage, and the surgical procedure.[5,26,28,29] Thus, there is a broad range of possible stimuli that might contribute to pro-calcitonin induction after orthopaedic surgery. The nonspecific induction of procalcitonin production by trauma or tissue injury, however, seems to be lower compared with a specific induction by bacterial infections. In accordance with other studies, C-reactive protein concentrations were increased about twentyfold to fortyfold in all patients after surgery, and levels remained high throughout the three-day observation period.[18-22] Hence, the reliability of C-reactive protein is hampered by a protracted response with late peak levels and a low specificity in patients with systemic inflammatory response syndrome, whereas procalcitonin is more specific for distinguishing infectious from non-infectious febrile episodes.

Yasmin et al,[30] in their study found that The PCT levels were above 0.5 ng/ml in all of the patients with systemic complications. Reith et al,[31] reported that patients with a PCT level over 1.5 ng/ml at the post- operative days 1 and 2 are likely to develop complications. In our study, Serum procalcitonin value of ≥ 0.25 ng/ml was found to be significantly associated with infectious fever with a high sensitivity and specificity, especially on Day 3 of onset of post-operative fever.

Mokart et. Al,[32] in their study on patients developing post-operative sepsis after undergoing major surgery for cancer , concluded that Serum procalcitonin on Day 1 after surgery was a reliable marker of post-operative sepsis with a sensitivity of 81% and specificity of 72%. In our study, serum procalcitonin showed highest sensitivity of 84% and specificity of 96% on Day 3 for Cut off value of ≥ 0.25 ng/ml.

In general, fever developing within the first 2-3 days post operatively are usually due to non-infectious (Table 2.) causes as explained by previous articles. Most of the fevers developing secondary to infectious causes occur after the 3rd post-operative day and the same has been found in our study (Table 2.).

The peculiarity of serum procalcitonin levels for the diagnosis of infections varies in different surgical settings. In cardiothoracic settings. In cardiothoracic surgery, elevation of procalcitonin level is >7 ng/dL whereas in Orthopaedic surgery the elevation of procalcitonin level of >0.25 ng/dL is suggestive of post-operative infection as found in our study.

Kilger E et. Al,[33] in their study on patients undergoing cardiac surgery, found that serum procalcitonin levels peak to a value of 7 ng/ml 24 hours after cardiac surgery and the values fall to below 0.1 ng/ml by Day 7 post-operatively in uncomplicated cases. But rise of procalcitonin is not to such a level post orthopaedic surgery, and the same was found in our study.

CONCLUSION

Procalcitonin is more accurate than other biomarkers (WBC Counts, CRP) in diagnosing post-operative fever due to infection. Also, it is more sensitive (84%) and specific (97%) to differentiate post-operative fever due to infection and fever due to non-infectious causes (Systemic inflammatory response syndrome - SIRS) with cut-off value of ≥ 0.25 ng/ml.

REFERENCES

1. Garibaldi RA, Brodine S, Matsumiya S, Coleman M. Evidence for the non-infectious etiology of early postoperative fever. Infect Control. 1985; 6:273-7.
2. Than P, Malovics I. [Significance of postoperative fever after hip prosthesis implantation].Z Orthop Ihre Grenzgeb. 2000; 138:430-5. German.
3. Gaynes RP, Culver DH, Horan TC, Edwards JR, Richards C, Tolson JS. Surgical site infection (SSI) rates in the United States, 1992-1998: the National Nosocomial Infections Surveillance System basic SSI risk index. Clin Infect Dis. 2001;33 Suppl 2:S69-77.
4. Laffey JG, Boylan JF, Cheng DC. The systemic inflammatory response to cardiac surgery: implications for the anesthesiologist. Anesthesiology. 2002; 97:215-52.
5. Gurlich R, Maruna P, Cermak J. [Use of procalcitonin in surgery]. Rozhl Chir.1999;78:292-4. Czech.
6. Stolz D, Christ-Crain M, Bingisser R, Leuppi J, Miedinger D, M¨uller C, Huber P, M¨uller B, Tamm M. Antibiotic treatment of exacerbations of COPD: a randomized controlled trial comparing procalcitonin-guidance with standard therapy. Chest.2007;131:9-19.
7. Schuetz P, Christ-Crain M, Wolbers M, Schild U, Thomann R, Falconnier C, Widmer I, Neidert S, Blum CA, Sch¨onenberger R, Henzen C, Bregenzer T, Hoess C,Krause M, Bucher HC, Zimmerli W, M¨uller B; ProHOSP Study Group. Procalcitonin guided antibiotic therapy and hospitalization in patients with lower respiratory tract infections: a prospective, multicenter, randomized controlled trial. BMC Health Serv Res. 2007; 7:102.
8. Christ-Crain M, Stolz D, Bingisser R, M¨uller C, Miedinger D, Huber PR, Zimmerli W, Harbarth S, Tamm M, M¨uller B. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. Am J Respir Crit Care Med.2006; 174:84-93.
9. Christ-Crain M, Jaccard-Stolz D, Bingisser R, Gencay MM, Huber PR, Tamm M, M¨uller B. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. Lancet. 2004; 363:600-7.
10. Briel M, Schuetz P, Mueller B, Young J, Schild U, Nusbaumer C, P´eriat P, Bucher HC, Christ-Crain M.

Procalcitonin-guided antibiotic use vs a standard approach for acute respiratory tract infections in primary care. Arch Intern Med. 2008;168: 2000-8.
11. Muller B, Schuetz P, Trampuz A. Circulating biomarkers as surrogates for bloodstream infections. Int J Antimicrob Agents. 2007;30 Suppl 1:S16-23.
12. Christ-Crain M, Muller B. Procalcitonin in bacterial infections—hype, hope, more or less? Swiss Med Wkly. 2005; 135:451-60.
13. Schuetz P, Christ-Crain M, Muller B. Biomarkers to improve diagnostic and prognostic accuracy in systemic infections. Curr Opin Crit Care. 2007; 13:578-85.
14. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. Clin Infect Dis. 2004; 39:206-17. Erratum in: Clin Infect Dis. 2005; 40:1386-8.
15. de Bont ES, Vellenga E, Swaanenburg J, Kamps W. Procalcitonin: a diagnostic marker of bacterial infection in neutropenic cancer patients with fever? Infection. 2000; 28:398-400.
16. von Lilienfeld-Toal M, Dietrich MP, Glasmacher A, Lehmann L, Breig P, Hahn C, Schmidt-Wolf IG, Marklein G, Schroeder S, Stuber F. Markers of bacteremia in febrile neutropenic patients with hematological malignancies: procalcitonin and IL-6 are more reliable than C-reactive protein. Eur J Clin Microbiol Infect Dis. 2004; 23:539-44.
17. Haimi-Cohen Y, Vellozzi EM, Rubin LG. Initial concentration of Staphylococcus epidermidis in simulated pediatric blood cultures correlates with time to positive results with the automated, continuously monitored BACTEC blood culture system. J Clin Microbiol. 2002; 40:898-901.
18. Aouifi A, Piriou V, Bastien O, Blanc P, Bouvier H, Evans R, Ce´lard M, Vandenesch F, Rousson R, Lehot JJ. Usefulness of procalcitonin for diagnosis of infection in cardiac surgical patients. Crit Care Med. 2000; 28:3171-6.
19. Carboni GL, Fahrner R, Gazdhar A, Printzen G, Schmid RA, Hoksch B. Com- parison of procalcitonin and CrP in the postoperative course after lung decortication. Eur J Cardiothorac Surg. 2008; 33:777-80.
20. Dorge H, Schondube FA, Dorge P, Seipelt R, Voss M, Messmer BJ. Procalcitonin is a valuable prognostic marker in cardiac surgery but not specific for infection. Thorac Cardiovasc Surg. 2003; 51:322-6.
21. Laifer G, Wasner M, Sendi P, Graber P, Gratzl O, Huber P, Fluckiger U, Zimmerli W. Dynamics of serum procalcitonin in patients after major neurosurgery. Clin Mi- crobiol Infect. 2005; 11:679-81.
22. Oberhofer D, Rumenjak V, Lazic J, Vucic N. [Inflammatory indicators in pa- tients after surgery of the large intestine]. Acta Med Croatica. 2006; 60:429-33. Croatian.
23. Sponholz C, Sakr Y, Reinhart K, Brunkhorst F. Diagnostic value and prognostic implications of serum procalcitonin after cardiac surgery: a systematic review of the literature. Crit Care. 2006;10: R145.
24. Meisner M, Tschaikowsky K, Hutzler A, Schick C, Schuttler J. Postoperative plasma concentrations of procalcitonin after different types of surgery. 1998; 24:680-4.
25. Garibaldi RA, Brodine S, Matsumiya S, Coleman M. Evidence for the non-infectious etiology of early postoperative fever. Infect Control. 1985 Jul;6(7):273-7. doi: 10.1017/s0195941700061749. PMID: 3847403.
26. Muller B, White JC, Nylen ES, Snider RH, Becker KL, Habener JF. Ubiquitous expression of the calcitonin-I gene in multiple tissues in response to sepsis. J Clin Endocrinol Metab. 2001; 86:396-404.
27. MacFie J, O'Boyle C, Mitchell CJ, Buckley PM, Johnstone D, Sudworth P. Gut origin of sepsis: a prospective study investigating associations between bacterial translocation, gastric microflora, and septic morbidity. Gut. 1999; 45:223-8.
28. MeisnerM.Pathobiochemistryandclinicaluseofprocalcitonin. ClinChimActa. 2002;323:17-29.
29. Maruna P, Nedelnikova K, Gurlich R. Physiology and genetics of procalcitonin. Physiol Res. 2000;49 Suppl 1:S57-61.
30. Yasmin D, Bulut G, Yildiz M. [Can procalcitonin be used for the diagnosis and follow-up of postoperative complications after fracture surgery?]. Acta Orthop Traumatol Turc. 2006; 40:15-21.
31. Reith HB, Mittelkotter U, Debus ES, Kussner C, Thiede A. Procalcitonin in early detection of postoperative complica-tions. Dig Surg 1998; 15:260-5.
32. Mokart D, Merlin M, Sannini A, Brun JP, Delpero JR, Houvenaeghel G, Moutardier V, Blache JL. Procalcitonin, interleukin 6 and systemic inflammatory response syndrome (SIRS): early markers of postoperative sepsis after major surgery. Br J Anaesth. 2005 Jun;94(6):767-73. doi: 10.1093/bja/aei143. Epub 2005 Apr 22. PMID: 15849208.
33. Kilger E, Pichler B, Goetz AE, Rank N, Welte M, Mörstedt K, Vetter HO, Gödje O, Schmitz C, Lamm P, Engelschalk E, Muehlbeyer D, Frey L. Procalcitonin as a marker of systemic inflammation after conventional or minimally invasive coronary artery bypass grafting. Thorac Cardiovasc Surg. 1998 Jun;46(3):130-3. doi: 10.1055/s-2007-1010209. PMID: 9714487.