Elevated postoperative serum procalcitonin is not indicative of bacterial infection in cardiac surgical patients

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ABSTRACT

**Background:** Identifying infections early, commencing appropriate empiric antibiotic not only helps gain control early, but also reduces mortality and morbidity. Conventional cultures take about 5 days to identify infections. To identify the infections early biomarker like serum procalcitonin (SPC). **Aims:** We studied the correlation of an elevated level of SPC and positive culture in elective adult patients undergoing cardiac surgery. **Methods:** This prospective study was conducted from January to December 2013. SPC was checked in patients showing evidence of sepsis. Simultaneously, relevant culture was also undertaken. Correlation, specificity, and sensitivity of elevated SPC were checked. **Results:** A total of 819 adult patients were included in the study. 43 of them had signs of infection and SPC levels were checked. Based on the level of SPC criteria, 10 patients were diagnosed as “nil”, out of them, 4 had culture-positive infections, 17 were suggested to have “mild infection,” 3 out those had culture positivity. None among the eleven patients suggested to have “moderate infection,” had a positive culture, and one among the five suggested to have a severe infection had a positive culture. The sensitivity was 50% and the specificity 17%. The positive predictive value was 12% and the negative predictive value 60%. **Conclusions:** We failed to elicit positive correlation between elevated SPC levels and postoperative infection in cardio surgical patients.

Key words: Cardiac surgery; hospital-acquired infection; infection; procalcitonin; sepsis

INTRODUCTION

Postoperative infection in cardiac surgical patients increases morbidity and mortality, and the incidence varies between 5% and 21%. Early detection and treatment of infection is vital to improve the outcome. Because of limitations of time required for reporting (up to 5 days), physicians are coerced to seek alternative methods that accurately indicate the presence of bacterial infections earlier. Biomarker such as serum procalcitonin (SPC) is claimed to aid early diagnosis and treatment of bacterial infections. Its utility has been shown in various medical conditions such as cirrhosis, lung cancer, and pulmonary coccidiomycosis. Procalcitonin is a propeptide of calcitonin produced by the thyroid gland and is usually undetectable in the blood of healthy humans. It has been considered as one of the sensitive markers of bacterial sepsis, thus providing a new tool for early diagnosis and prognostic assessment of bacterial infection. We proposed to determine the relevance of elevated SPC level in identifying bacterial infections (confirmed by bacterial culture) in cardiac surgical patients. The possible effect of other factors that could modify like cardiopulmonary bypass that cause changes in the inflammatory response on SPC were also studied.

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MATERIALS AND METHODS

This prospective observational study was performed in the postoperative period in cardiac surgical patients from January to December 2013. Patients were selected based on the presence of one or more of the criteria for diagnosing sepsis as described by Lever et al. Adult cardiac surgical patients over the age of 18 years undergoing an elective procedure, were included in the study. Patients with evidence of preoperative infection/sepsis or preoperative elevation of white cell count, or receiving steroids or antibiotics or preoperative mechanical ventilation were excluded from participation in the study. Patients with low ejection fraction or undergoing repeat surgeries, or prolonged surgeries (more than 8 h) or having chronic inflammatory conditions such as systemic lupus erythematosus, and rheumatoid arthritis, or malignancy were also excluded. Baseline investigations included complete blood cell count, chest radiograph, liver and kidney function tests. As a part of preoperative preparation, all the patients were subjected to 3 days of chlorhexidine bath twice daily, intranasal application of mupirocin ointment twice daily for 5 days. In the operation theater, prophylactic antibiotic (cefuroxime 1.5 g) was administered 15–60 min prior to surgical incision. All the invasive monitoring lines were placed practicing standard universal barrier precautions as recommended by the center for disease control, USA. Body hair at the surgical site was clipped using a clipper and the skin around the surgical site was cleaned with 10% povidone iodine, with a contact time of at least 3 min. Urinary catheter was inserted using standard precautions. As per the institutional policy, an additional dose of the antibiotic was administered either if cardiopulmonary bypass was required or after 4 h into surgery, or if the blood loss was more than 1500 ml. Airway instrumentation and endotracheal intubation was performed while taking care to avoid contaminating or infecting the airway.

All the patients were transferred to the intensive care unit after completion of the surgery. Postoperatively total and differential white cell counts were performed daily, and a chest radiograph was obtained on the first postoperative day. Patients with signs of sepsis as described above, unlikely to be due to underlying cardiac condition or concurrent medication were evaluated by performing SPC values by semiquantitative method and the levels were measured with 2 step 2 site electrochemiluminescence biotin labeled procalcitonin specific antibody and monoclonal procalcitonin specific antibody labeled with ruthenium complex (Elecsys BRAHMS). Along with the SPC testing, suitable specimen culture was ordered (3 sample blood culture, if blood stream infection was suspected, sputum or the bronchoscopic aspiration lavage (BAL) if ventilator-associated pneumonia was suspected). Whenever the source of the infection was not clear, blood, mini BAL, and urine cultures were obtained. As per the institutional protocol, patients with elevated SPC level (>0.5 ng/ml) received the empiric antibiotic - a combination of piperacillin and tazobactam (4.5 G repeated every 8 h) while awaiting the culture and sensitivity reports. After obtaining culture report, specific antibiotic therapy was initiated if hospital-acquired infection was present. In patients who had no positive culture, the empiric antibiotic therapy was ceased. The specificity and sensitivity of SPC levels vis-a-vis culture report was assessed.

Statistical methods

All statistical tests were performed with SPSS for Windows 16.0 (SPSS South Asia Pvt Ltd, Kolkata) statistical package. Statistical differences between groups were assessed by Chi-square test. P < 0.05 was considered significant all the values were mentioned as mean ± standard deviation.

RESULTS

Totally, 819 patients underwent cardiac surgery during the period of January to December 2013 at our facility. Forty-three patients out of them were suspected to have sepsis (as defined above); eight had culture positive infection. The source of the infection was not clear in two patients; therefore blood, mini BAL, and urine were cultured. Table 1 show the interpretation of the severity of infection based on the SPC criteria, as recommended by the manufacturer. Table 2 show the correlation between various degrees of elevated SPC level, culture positivity, specificity, and sensitivity. Among the forty-three patients studied, SPC level suggested no infection in ten, mild in seventeen, moderate in eleven, and severe in five patients. Of these, 10 patients who were considered “nil” infection based on the SPC criteria (<0.05 ng/ml), four showed culture positivity, [Table 2] seventeen patients were who fulfilled the criteria to have “mild infection” as per the SPC level increase, (0.5–2 ng/ml), three patients had positive specimen culture. While eleven patients with SPC level between 2 and 10 ng/ml suggestive of moderate infection
had no specimen culture positive reports and finally, among five patients who had SPC level of >10 ng/ml suggesting severe infection, only one had a positive culture report. In all, eight patients were diagnosed to have hospital acquired infection based on the culture report - 3 patients had central line-associated bloodstream infection, two had catheter-associated urinary tract infection and 3 ventilator-associated pneumonia.

Among the eleven patients in whom SPC levels were suggestive of moderate sepsis and four patients in whom the SPC value was suggestive of severe sepsis only one had positive specimen culture (6%) [Table 3]. In all, a mere 18.6% (8 out of 43) of patients who had elevated SPC showed culture positivity. The sensitivity was 50% (95% confidence interval [CI]: 16.01–83.99%) and the specificity 17.1% (95% CI: 3.48–28.22%) positive predictive value was 12.12% (95% CI: 3.48–28.22%) and the negative predictive value was 60.00% (95% CI: 26.37–87.60%).

**DISCUSSION**

The need for early identification and treatment of hospital-acquired infections is unambiguous. Early diagnosis and prompt treatment has shown to benefit the outcome in surgical patients.[9] The currently available marker such as SPC is claimed to identify bacterial infections early.[10] In our study, we did not find any positive correlation between elevated SPC levels and culture positivity, although several authors in nonsurgical settings have shown good correlation between sepsis and elevated SPC.[3‑7] It is important to use reliable biological markers which are not greatly altered by factors commonly associated with surgical operations such as anesthesia, surgery, cardiopulmonary bypass, blood transfusion, hemodynamic upheavals, and use of vasoactive medications. At our facility, universal prophylaxis for avoiding infections such as preoperative preparation (chlorhexidine bath, intranasal mupirocin, and avoiding hair shaving), aseptic procedural precautions, prophylactic antibiotic administration, hand hygiene compliance, duration of intensive care unit (ICU) stay, mechanical ventilation, techniques of urinary, and central venous catheterization are standardized. Although elevated SPC has been considered an important predictor of onset and severity of infections, in our study of 819 post-cardiac surgery patients (43 had elevated SPC level) it failed to correlate with positive specimen culture report (Chi-square = 0.9). The sensitivity and specificity of the tests in our study suggested poor correlation between elevated SPC levels and bacterial infection.

Patients requiring cardiopulmonary bypass, who had elevated SPC were similarly analyzed using the Chi-square test ($P$ value of 0.995), which suggested absence of positive correlation between the elevated SPC and the inflammatory stress induced by cardiopulmonary bypass.

Kumar et al. studied septic patients in medical intensive care and observed “Elevated SPC has 94% sensitivity in the indication of sepsis”. [11] In contrast to their observations, our study did not show any clinically meaningful sensitivity and specificity with respect to sepsis; Elevation of SPC in our cohort may

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**Table 1: Comparison of probability of infection and procalcitonin level (as recommended by the manufacturer)**

| Procalcitonin level ng/ml | Infection | Culture |
|---------------------------|-----------|---------|
| Test                      | No        | Yes     | Total |
| Nil (<0.5)                | 6         | 4       | 10    |
| Mild (≥0.5<2.0)           | 14        | 3       | 17    |
| Moderate (≥2.0<10.0)      | 11        | 0       | 11    |
| Severe (≥10.0)            | 4         | 1       | 5     |
| Total                     | 35        | 8       | 43    |

Pearson Chi-square $P$=0.135

**Table 2: The distribution of predicted sepsis and culture positivity**

| Procalcitonin test       | Infection_culture | Total |
|--------------------------|-------------------|-------|
|                          | No     | Yes     |       |
| Nil (<0.5)               | 6      | 4       | 10    |
| Mild (≥0.5<2.0)          | 14     | 3       | 17    |
| Moderate (≥2.0<10.0)     | 11     | 0       | 11    |
| Severe (≥10.0)           | 4      | 1       | 5     |
| Total                    | 35     | 8       | 43    |

**Table 3: Predictive values and sensitivity and specificity**

| Test                        | Culture positive | Culture negative | Total |
|-----------------------------|------------------|------------------|-------|
| Procalcitonin test positive | True positive (a) 4 | False positive (b) 29 | (a+b) 33 |
| Procalcitonin test negative | False negative (c) 4 | True negative (d) 6 | (c+d) 10 |
| Total                       | (a+c) 8          | (b+d) 35         | 43    |

Sensitivity=50.00%; 95% CI: 16.01-83.99%, Specificity=17.14%, 95% CI: 6.81-33.66%, Positive predictive value=12.12%, 95% CI: 3.48-28.22%, Negative predictive value=60.00%, 95% CI: 26.37-87.60%. CI: Confidence interval
not have been due to bacterial load; on the other hand, it might be due to one or more of the following factors encountered in cardiac surgery: Stress of surgery, anesthesia, inotropic and/or vasoconstrictor agent use, hemorrhage, hemodynamic changes, and inflammatory mediator release due to CPB, which are absent in medical cases. It was further observed “increase in total leukocyte count has sensitivity and specificity of 75% and 15.8%, respectively, in indicating the sepsis”, which corresponds with our data. It is now known that SPC is elevated in several noninfectious conditions such as myocardial infarction, malaria, severe trauma, surgery, cardiac shock, burns.[12] Considering these etiologies of false positive elevation of SPC, one should be wary of identifying sepsis based merely on elevated SPC levels in surgical patients. After all, fever, leukocytosis and/or elevation of SPC might be due to surgical trauma instead of infection. In a meta-analysis on utility of SPC in surgical patients, the authors Uzzan et al. suggested that elevated SPC alone should not be used as a criterion for diagnosing sepsis.[13] Shehabi and Seppelt opined “It is clear that procalcitonin is not a “magic marker” for the positive diagnosis of sepsis, nor has it yet been sufficiently validated for the negative exclusion of sepsis in intensive care, although it may well fit this role. As a matter of pragmatism, no biomarker should ever be used in isolation for decision-making. It is one tool in the clinician’s armamentarium and must be considered in conjunction with clinical examination, other laboratory tests, and microbiological results”. Tanaka et al. have studied the roles of elevated SPC in patients hemodynamically supported by extracorporeal membrane oxygenator.[15] These authors found a positive correlation between elevated SPC levels and infections in patients undergoing veno-venous extracorporeal membrane oxygenator therapy. Contrastingly, we did not find the highly sensitive and specific correlation observed by Tanaka et al. Other biomarkers such as soluble ST2 have been used to identify sepsis early.[16] The final world on these markers will be known to us when more research in that area is undertaken.

Potential weakness of the study
The study population is small, a larger cohort may provide better picture. The high degree of false negativity might due to the method used in assessing SPC levels; we use semi-quantitative test to measure SPC levels which gives false negative results. Serial measurements of laboratory SPC values have not been performed, thereby making the trend of values unavailable for the study. Prophylactic antibiotic might abort the growth of bacteria in culture samples. Other signs of sepsis such as elevated heart rate, acidosis, and hypotension are not uncommonly found due to cardiac causes. They may have contributed to increase in false positive cases and thus reduced the specificity and sensitivity.

CONCLUSION

The current study did not find a significant correlation between elevated levels of SPC level and infection in cardiac surgical patients.

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Cite this article as: Chakravarthy M, Kavaraganahalli D, Pargaonkar S, Hosur R, Harivelam C, Bharadwaj A, et al. Elevated postoperative serum procalcitonin is not indicative of bacterial infection in cardiac surgical patients. Ann Card Anaesth 2015;18:210-4.

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