International Surgery Journal
John J et al. Int Surg J. 2017 Feb;4(2):628-632
http://www.ijsurgery.com
pISSN 2349-3305 | eISSN 2349-2902

DOI: http://dx.doi.org/10.18203/2349-2902.isj20170204

Original Research Article

C-reactive protein: an early predictor of sepsis in patients with thermal burns

Joby John, Meer M. Chisthi*, Krishnakumar G. Kuttanchettiyar

Department of General Surgery, Government Medical College, Trivandrum, Kerala, India

Received: 08 November 2016
Accepted: 08 December 2016

***Correspondence:**
Dr. Meer M Chisthi,
E-mail: meerchisthi@gmail.com

ABSTRACT

Background: Due to the high mortality rate of established sepsis in patients with burn injuries, it would be beneficial if the onset can be predicted before it is fully established. The objective of the study was to estimate the predictive value of C-reactive protein in thermal burns patients. The secondary objective was to determine how much earlier CRP level allowed the prediction of sepsis in these patients.
Methods: This was a case-control study, conducted prospectively on 60 human patients admitted with thermal burns. Cases were those who developed sepsis following burns and the controls were burns patients without sepsis. All patients underwent serial estimation of C-reactive protein values on alternative days, along with other blood parameters. From the data, the predictive value of C-reactive protein in sepsis was analysed.
Results: A significant higher value of C-reactive protein was found in septic patients. Rise in serum C-reactive protein level predicted sepsis with an efficacy of 87%, while the sensitivity was found to be 93% and the specificity was 80%, with a significant odds ratio of 56. Also a pre-defined rise in C-reactive protein predicted the onset of sepsis about 2 days before the clinical onset.
Conclusions: C-reactive protein is a useful indicator for sepsis in burns patients. In combination with clinical sepsis markers, C-reactive protein can be used to initiate intensive monitoring and appropriate antibiotic therapy.

Keywords: Acute phase reactants, Biomarkers, Burns, C-reactive protein, Sepsis

INTRODUCTION

Burn injuries are among one of the major public health concerns across the globe, particularly in developing countries. Burn is an event that imposes irreplaceable physical, mental, economic, and social consequences, and sometimes death. Sepsis is one of the major causes of death in burn patients. It is estimated that annually, nearly 200,000 people die due to burn injuries around the world.[1] Among this, 30-50% of the deaths are attributed to sepsis and its sequels.[2] Diagnosis of sepsis may be delayed due to the time required for microbiological confirmation of infection. Although advanced mass spectrometry tools in microbiology labs can accelerate the identification of infections in blood, they still require at least 12-24 hours of blood culture before the bacteria reach levels that can be detected.[3] In the absence of sepsis, inappropriate empirical use of antibiotics can have long term consequences for patients by interfering with normal microbiological flora, facilitating development of multidrug resistant bacterial strains, and increasing total cost of hospitalization.

Identifying sepsis early is critical, considering that every 6 hours delay in the diagnosis of sepsis reduces survival by 10%.[4] In contrast to the original idea of explicit

immunological dysfunction as a sequel to an infectious stimulus, sepsis is now seen as a more complex syndrome that is characterized by 'impaired homeostasis'. Modern concepts combine immunological aspects with neuro-endocrine dys-regulation and failure of protective barriers. This newer concept defines sepsis as a syndrome and focus on the fact that non-infectious stimuli also result in the triggering of defence mechanisms and clinical signs, making it impossible to set discrimination between infectious or non-infectious origin. The patho-physiology of sepsis is characterized by impairment of various body systems on cellular, tissue-specific or functional level. Such a complex nature of sepsis complicates the search for new diagnostic targets.

Severe burn injury is accompanied by a systemic inflammatory response, making traditional indicators of sepsis both insensitive and nonspecific. To address this, the American Burn Association (ABA) published diagnostic criteria in 2007 to standardize the definition of sepsis in these patients.[5] These criteria include temperature (>39 °C or <36 °C), progressive tachycardia (>110 beats per minute), progressive tachypnea (>25 breaths per minute not ventilated or minute ventilation >12 L/minute ventilated), thrombocytopenia (<100,000/µl; not applied until 3 days after initial resuscitation), hyperglycaemia (untreated plasma glucose >200 mg/dl, >7 units of insulin/hr intravenous drip, or >25% increase in insulin requirements over 24 hours), and feed intolerance >24 hours (abdominal distension, residuals two times the feeding rate, or diarrhoea > 2500 ml/day).

Biomarkers evaluated in predicting sepsis in burns patients include complement activation (C3), procalcitonin (PCT) and interleukin-6 (IL-6) levels.[6] Another marker is the temporal response of plasma opsonic fibronectin, as measured by both immunoassay and bioassay following burn injury.[7] C-reactive protein (CRP), a plasma biomarker is a serum amyloid P component, belonging to the pentraxin family of calcium-dependent ligand-binding proteins. CRP is synthesized in the liver, triggered by IL-6 in response to tissue damages and inflammatory or infectious stimuli. While pro-inflammatory cytokines (IL-1, IL-6 and tumour necrosis factor α) appear within one hour after the start of infection, and procalcitonin after five hours, CRP appears six to eight hours after onset and peak concentrations reach 36 to 50 hours later.[8] The half-life of CRP is 19 hours and it is cleared mainly by the liver.[9] One of the earliest applications of CRP was in identifying neonates with sepsis in whom clinical manifestations are often nonspecific. CRP levels decrease over the first 48 hours when successful antimicrobial therapy is initiated and hence are used to monitor antibiotic treatment.[10]

Given the lack of an adequate predictive marker, the question whether CRP can serve as a predictor for severe infection or sepsis in burns patients remains unanswered. Therefore, our objective was to investigate in a case control study whether CRP can be used as a predic¬tor for sepsis in adult patients with burns. The primary objective of the study was to estimate the rise in C-reactive protein in burns patients and to establish its predictive value in sepsis. The secondary objective was to determine how much earlier CRP level allowed the prediction of sepsis.

METHODS

This study was carried out at a tertiary level teaching hospital which is one of the biggest health care institutions in the region. Clearance from Institutional Review Committee at Government Medical College Trivandrum, India was obtained before beginning the study. Before data collection, clearance was obtained from the Human Ethics Committee of the institution. All the patients included in the study gave their informed consent.

The study was done as a case control study, at the General Surgery Department of Government Medical College Trivandrum, from November 2008 till December 2009. Human patients who were admitted within 24 hours of injury with a history of thermal burns were selected for the study. For the sake of better uniformity, only those patients with age group between 20 - 70 years and had a burns involving 30 - 70% of the body surface area were included in the study. Also, pregnant patients were excluded from the study. The sample size was set at 60, with equal number of cases and controls.

The American Burn Association (ABA) diagnostic criteria, 2007 was used to standardize the definition of sepsis in these patients.[5] Cases were defined as those patients who developed features of sepsis during the treatment, as given in the defining criteria. Controls were those who had no documented sepsis. Cases and controls were matched with respect to age group, sex and percentage of burns in order to minimize bias. Since the grouping of cases was triggered by the detection of features of sepsis, the stratification could be carried out only in between the study. Hence the sampling was stopped only when the required number of cases and controls were obtained.

After recording general survey, the percentage of body surface area (BSA) affected by burns was estimated by the Wallace' Rule of Nines. All patients underwent the same nutritional treatment according to a standardized protocol. They were all resuscitated within the first 24 hours with Ringer's lactate solution as per the Parkland's formula. Plasma expanders and blood components were administered as indicated. Local care included daily hydrotherapy and local application of silver sulfadiazine ointment. Pain relief was administered by intravenous opiate analgesics. Surgery was reserved for escharotomy.

Daily estimation of temperature, pulse rate, blood pressure, respiratory rate, input-output chart and abdomen

assessment was done. Blood sugar, platelet count, complete blood picture, renal functions and serum electrolytes were estimated daily. From third day onwards, serial wound culture and sensitivity was done for all the patients. In those patients with features of sepsis, a blood culture was also sent. In septic patients, intensive monitoring was instituted and antibiotics were added as per the results of blood and wound cultures.

CRP was estimated on the second post-burn day and third day, thereafter on alternate days till discharge or till death or till the 15th day, whichever occurred first. Sample was collected from an indwelling central venous catheter. CRP was estimated by an immuno-turbidometry method with a commercial kit 'Turbilife CRP test'. CRP in serum lower than 10 mg/dl is considered normal for burn patients. Rise was defined as increase in previous value from 3.9-9 mg/dl which is maintained for two days or a single day increase of 10 mg/dl or more based on previous data. Increase in the first 48 hours after a burn was excluded, as trauma itself can cause this rise. All statistical analyses were performed using 'Epi Info' (centre for diseases control). All values are expressed as Mean±Standard deviation. Statistical association was assessed by calculating the odds' ratio. The level of statistical significance was set at a p value less than 0.05.

RESULTS

For the purpose of analysis, the patients were stratified into 2 groups: 1) moderate burns, where the BSA involved was less than 50%; and 2) severe burns, where the BSA involved was more than 50%. As per this study, maximum numbers of cases were in the age group 21-30 years, while the least were in the age group 51-60. The mean age was 32±9 in the case of cases and 32±12 in controls. Females outnumbered males by a ratio of 5:1. This may be explained by the fact that both intentional and non-intentional burns are much more prevalent in females than males in India, due to the socio-cultural scenario. The mean weight was 64.5 kg and the mean height was 157.2 cm. The mean BMI in cases was 25.78±3.02 while the mean BMI in controls was 25.78±2.64.

Table 1: Mean CRP with standard deviation in cases and controls.

	Day 2	Day 3	Day 5	Day 7	Day 9	Day 11	Day 13	Day 15
Cases	8.4±2.11	15.6±5	21±4.4	21±3.3	19.3±4.7	14.8±3	13.2±3.6	10.3±2.7
Controls	4.4±1.8	6.9±2.3	8.9±2.9	9.7±2.9	8.9±2.5	7.1±2.7	5.6±2.2	4.0±1.6

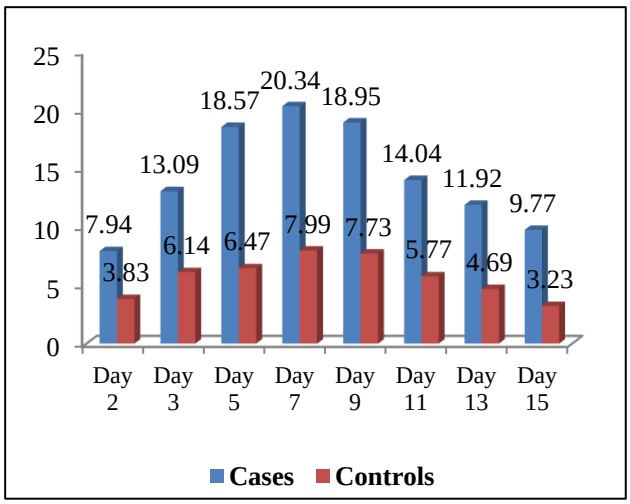

Figure 1: Mean CRP levels in patients with <50% TBSA involved by burns.

The maximum number of patients had involvement of 31-50% of BSA, followed by 51-70%. In the control patients, CRP levels gradually rose from 3rd day and reached a peak on 7th day and attained a plateau by 9th day. Whereas in the septic patients, CRP values rose from 3rd day and peaked on the 5th day itself and attained a plateau on 7th day (Table 1). When a detailed split up was done, CRP reached a peek by 7th day in control patients with moderate burns (involving <50% of BSA) while it reached a peak on the 5th day itself in severely burned patients (involving >50% BSA) (Figure 1, 2). In the case group also, CRP reached a peek on 7th day in patients with moderate burns while it peeked by 5th day in severely burned patients. However the peak values were higher in patients with sepsis than in non-septic patients.

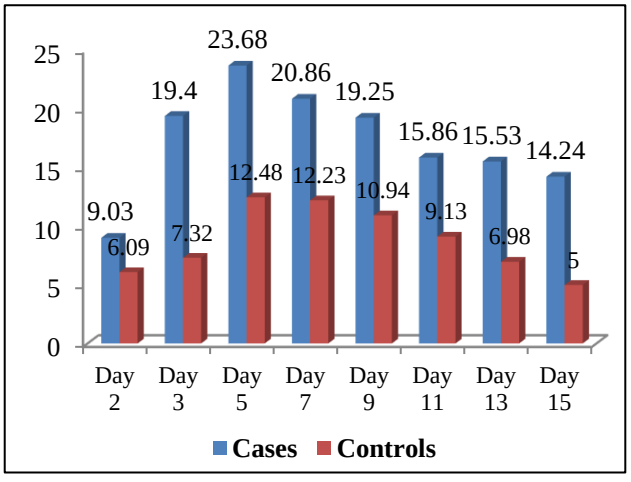

Figure 2: Mean CRP levels in patients with >50% TBSA involved by burns.

Defined rise in CRP levels correctly predicted whether a patient would become septic 87% of the times. Also, on an average, sepsis could be detected two days before the onset of clinically detectable sepsis (Table 2). In aseptic

patients, CRP level reached peak values on 7th day and had a mean peak value of 9.68. In the case of septic patients, the same values peaked on 5th day itself and had a mean value of 20.62 (Figure 3). Of the 34 patients who had a rise in CRP, 28 developed sepsis. Only 2 patients had features of sepsis without concomitant rise in CRP (Table 3).

Table 2: Time of onset of sepsis and defined CRP rise.

Days before onset	Number of patients	Percentage
< 1 day	2	7%
1 day	8	27%
2 days	10	33%
3 days	10	33%

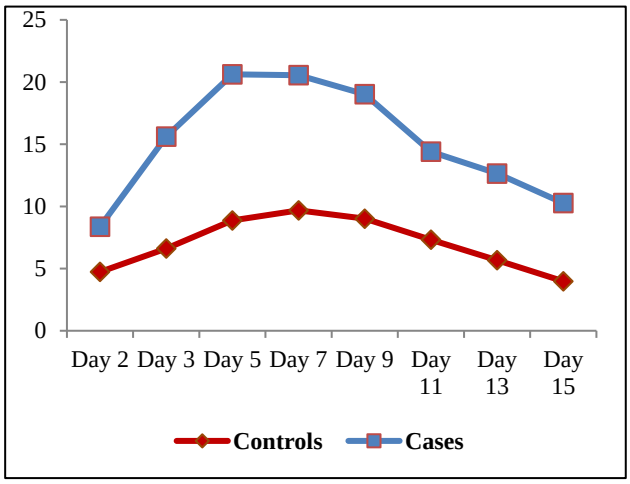

Figure 3: Mean CRP levels in all patients in relation to sepsis.

Table 3: Efficacy of CRP in predicting sepsis.

CRP status	Number of patients	
	Septic	**Non septic**
CRP rise	28 (47%)	6 (10%)
No CRP rise	2 (3%)	24 (40%)
CRP status	**Number of patients**	
	Dead	**Alive**
CRP rise	12 (20%)	22 (37%)
No CRP rise	8 (13%)	18 (30%)

Thus it is evident that septic patients had steeper rises in CRP as well as earlier rises in CRP, especially when the involved BSA was more than 50%. Out of the 34 patients with significant increase in CRP values, 12 patients died, indicating a death rate of 35%. Among the patients with no increase in CRP, 8 patients expired.

Serum CRP level predicted sepsis with an efficacy of 87%. The sensitivity was found to be 93% while the specificity was 80%. This was found to be statistically significant, with an Odds ratio of 56 (95% Confidence Intervals between 10.3263 to 303.6915). The z statistic was found to be 4.667 and p value much less than 0.001. CRP level was able to predict sepsis about 2 days before the onset of clinical features. Out of the 34 patients with increased CRP levels, the death rate was moderate, at 35%, which might be explained by the fact that they went through rigorous antibiotic therapy. CRP was not found to predict death, the Odds ratio being low at 1.22 and the p value being not significant, at 0.71.

DISCUSSION

The results of the present study coincide with that of other similar studies in establishing the efficacy of CRP in predicting the onset of sepsis in thermal burns. CRP measurement is cheap and rapidly available, but increases of CRP levels are claimed to be unspecific, since they can be observed after surgery or trauma.[11] High CRP levels correlate with disease severity and are discussed to represent the effectiveness of antimicrobial therapy. As per one clinical study, the authors showed that a rise in CRP serum levels significantly predicted the incidence of major infection around 2.3 days before sepsis occurred. Also, the same authors found that a rise in CRP of 1.5 mg/dl indicated sepsis and a rise of 3 mg/dl indicated severe bacterial or fungal infection.[12] In a large cohort study, the authors determined that CRP has significant correlations to burn size and mortality but the changes of CRP values did not reflect and hence do not predict the incidence of major infection or sepsis.[13]

Specific work with patients with burn injuries has been done by Daniels et al. and Faymonville et al. who documented a raise in CRP after a burn.[14,15] Gottschlich and his study group, who examined CRP levels between days 7 and 10 showed that a raise in CRP was associated with infection and death.[16] Pruchniewski and his colleagues measured CRP serum level at a variety of times after burn and found that in general, CRP levels increased in serum 48 hours after a burn and preceded sepsis.[17] Neely AN et al. in a similar study in burned children showed that when sepsis occurred it was preceded by increased CRP and the increment occurred around 2.3 days before clinical sepsis.[18] Yentis SM et al and Ellis S et al showed that measurement of CRP can be used to monitor the antibiotic therapy and that successful antibiotic therapy lowered CRP levels.[19,20]

As a summary, this study has thrown up positive results regarding the utility of CRP in burn patients. The CRP values correctly predict sepsis in majority of the patients. Also, rise in the serum levels of CRP can give sufficiently early warning regarding onset of sepsis and is able to prompt the initiation of appropriate antibiotic treatment. However, the study does have its own drawbacks in that the sample size was not very high and hence may not be representative enough. However, the results obtained, though small, are significant, particularly in view of obtaining such a strong statistical association.

CONCLUSION

The authors would like to state that CRP is an effective predictor of sepsis in burns patients with a prediction window of 48 hours. Of course, the biomarker result should not be the only trigger for a decision to treat or not, but should be combined with the presence of clinical signs heralding infection. We recommend that CRP be routinely tested in all burn patients and that those with a rise in CRP should be closely watched for features of sepsis. Aggressive monitoring and appropriate antibiotics as per culture reports in these patients can alleviate development of sepsis and thus save precious lives.

ACKNOWLEDGEMENTS

Authors are thankful to Dr. Nizarudeen A., Professor, Department of General Surgery, Government Medical College, Thrissur, for supervising the study. The authors also thank the Department of Epidemiology and Statistics, Government Medical College, Trivandrum, for helping with the statistical analysis of this study.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee

REFERENCES

1. Mathers C, Fat DM, Boerma J. The global burden of disease: 2004 update. Geneva: World Health Organization; 2008.
2. Williams FN, Herndon DN, Hawkins HK. The leading causes of death after burn injury in a single pediatric burn centre. Crit Care. 2009;13(6):183.
3. Fournier PE, Drancourt M, Colson P, Rolain JM, Scola BL, Raoult D. Modern clinical microbiology: new challenges and solutions. Nature Reviews Microbiology. 2013;11:574-85.
4. Kumar A, Ellis P, Arabi Y. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. Chest. 2009;136(5):1237-48.
5. Hogan BK, Wolf SE, Hospenthal DR. Correlation of American Burn Association sepsis criteria with the presence of bacteremia in burned patients admitted to the intensive care unit. J Burn Care Res. 2012;33(3):371-8.
6. Modi S, Rashid M, Malik A, Shahid M. Study of complement activation, C3 and interleukin-6 levels in burn patients and their role as prognostic markers. Indian J Med Microbiology. 2014:32(2):137-42.
7. Lanser ME, Saba TM, Scovill WA. Opsonic glycoprotein (plasma fibronectin) levels after burn injury. relationship to extent of burn and development of sepsis. Ann Surg. 1980;192(6):776-82.
8. Li HX, Liu ZM, Zhao SJ, Zhang D, Wang SJ, Wang YS. Measuring both procalcitonin and C-reactive protein for a diagnosis of sepsis in critically ill patients. J Int Med Res. 2014;42:1050-9.
9. Vigushin DM, Pepys MB, Hawkins PN. Metabolic and scintigraphic studies of radioiodinated human C-reactive protein in health and disease. J Clinical Investigation. 1993;91(4):1351-7.
10. Schmit X, Vincent JL. The time course of blood C-reactive protein concentrations in relation to the response to initial antimicrobial therapy in patients with sepsis. Infection. 2008;36:213-9.
11. Clyne B, Olshaker JS. The C-reactive protein. J Emerg Med. 1999;17:1019-25.
12. Neely AN, Smith WL, Warden GD. Efficacy of a rise in C-reactive protein serum levels as an early indicator of sepsis in burned children. J Burn Care Rehabil. 1998;19(2):102-5.
13. Jeschke MG, Finnerty CC, Kulp GA, Kraft R, Herndon DH. Can we use C-reactive protein levels to predict severe infection or sepsis in severely burned patients? Int J Burn Trauma. 2013;3(3):137-43.
14. Daniels JC, Larson DL, Abston S, Ritzmann SE. Serum protein profiles in thermal burns II: protease inhibitors, complement factors and C-Reactive proteins. J Trauma. 1974;62:140-53.
15. Faymonville ME, Micheels J, Bodson L, Jacquiemin D, Lamy M. Biochemical investigations after burning injury complement system, protease antiprotease balance and acute phase reactants. Burns. 1987;13:26-33.
16. Gottschlich MM, Baumer T, Jenkins M, Khoury J, Warden GD. The prognostic value of nutritional and inflammatory indices in patients with burns. J Burn Care Rehab. 1992;13:105-13.
17. Pruchniewski D, Pawlowski T, Morkowski J, Mackiewicz S. C-reactive protein in management of children's burns. Ann Clin Res. 1987;19:334-8.
18. Neely AN, Warden GD, Rieman M, Friedberg DL, Holder IA. Components of the increased circulating proteolytic activity in pediatric burn patients. J Trauma. 1992;33:807-12.
19. Yentis SM, Soni N, Sheldon J. C-Reactive protein as an indicator of resolution of sepsis in the intensive care unit. Intensive Care Med. 1995;21(7):602-5.
20. Ehl S, Gering B, Bartmann P, Hogel J, Pohlandt F. C-reactive protein as useful marker for guiding duration of antibiotic therapy in suspected neonatal bacterial infection. Pediatrics. 1997;99:236-21.

Cite this article as: John J, Chisthi MM, Kuttanchettiyar KG. C-reactive protein: an early predictor of sepsis in patients with thermal burns. Int Surg J 2017;4:628-32.