Efficacy of Serum Prealbumin and CRP Levels as Monitoring Tools for Patients with Fascial Space Infections of Odontogenic Origin: A Clinicobiochemical Study

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Received: 3 November 2011 / Accepted: 21 March 2012 / Published online: 12 May 2012
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Abstract

Objectives Study includes 20 patients with diagnosis of fascial space infections of odontogenic origin to assess efficacy of serum prealbumin and CRP levels as monitoring tools for determining severity of infections, nutritional status, hospital stay and efficacy of treatment.

Methods Blood samples taken on day 0, 4, and 8 for measuring serum levels of markers. Simultaneously clinical parameters like swelling size, pain etc., were also recorded on day 0, 4, and 8 and appropriate treatment given to each patient. Correlation between markers and parameters was found using regression and paired *t* test.

Results Statistical analysis found strong correlation between laboratory values of markers and parameters used to measure severity of infection also. Prealbumin and crp are significant markers for hospital stay ($p < 0.01$). Prealbumin also found to be a sensitive indicator of nutritional status ($p < 0.001$).

Interpretation and Conclusion Prospective analysis indicates prealbumin and crp are effective markers for determining severity of infection, treatment efficacy and hospital stay. Prealbumin is also sensitive marker for nutritional status. Duration of antibiotic usage, intensive unit care, use of nutritional supplements becomes more rationale. Markers also make treatment cost effective and help protecting patients from side effects of excess drug usage.

Keywords Prealbumin · C-reactive protein · Odontogenic space infection

Introduction

Patients with fascial space infections of odontogenic origin are at high risk for life threatening situations due to anatomical connectivity of potential spaces to one another. Lethal complications may become inevitable making vigilant scrutiny and monitoring of such patients a necessity.

Although, conventional measures to estimate infections such as WBC count and ESR values are valuable in determining state of patient at testing time, the predictability of these is limited [1]. The desirability of serum derived surrogate predictor behavior and outcome cannot be under estimated, arousing interest in identifying substances which could function as prospective monitor of disease progression. Thus, various inflammatory markers came into existence [1, 2].

Advocates of inflammatory markers narrate numerous advantages for their usage. According to them, quantitative determination of serum markers can be used for determining therapeutic efficacy of different treatment regimes of infection, for monitoring post operative infections, for investigating levels of infections, use of prophylactic antibiotics and duration of antibiotic usage becomes more appropriate [1–3]. Thus, keeping various advantages of serum inflammatory markers in mind, many authors advised use of prealbumin and CRP in assessment of infection [3].

Quantitative determination of serum prealbumin levels are between 14 and 36 mg/100 ml with mean values around 22 mg [3, 4]. Prealbumin levels vary in physiological conditions (like sex and pregnancy) and pathological conditions (like viral hepatitis and Laennec's cirrhosis and other non

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thyroidal conditions) [3, 4]. Low prealbumin levels are common in stress, inflammation, infection, malnutrition and trauma [3, 4].

C-reactive protein (CRP) was discovered in 1930 in pneumococcal pneumonia patients [1]. CRP is present only in small amounts in normal healthy individuals and is involved in the process of innate immune system with functions of compliment activation, antigen clearance and mediation of phagocytosis by activation of neutrophils [1, 2, 5, 6]. In severe infections or inflammatory reactions, striking rise in serum concentration of CRP is seen up to 1,000-fold within few hours of clinical symptoms [3, 6].

Prealbumin has a half life of 1.9 days and value of prealbumin decreases with infection making it a negative acute phase reactant [4, 5]. On other hand CRP concentration raises with infection making it a positive acute phase reactant with a very short half life of 5–7 h [1, 2, 6]. Thus, advantage of having short half lives makes serum prealbumin and CRP levels as sensitive indicators of infection [3, 5, 6].

So in the present study, we assessed the efficacy of serum prealbumin and CRP levels as monitoring tools in 20 patients with fascial space infections of odontogenic origin, for determining severity of infections, nutritional status, length of hospital stay and efficacy of treatment regime.

Materials and Methods

The prospective study was conducted on patients visiting Department of Oral and Maxillofacial Surgery, Government Dental College and Research Institute, Bangalore with diagnosis of fascial space infections of odontogenic origin. All the patients were treated on in-patient basis. Inclusion criteria was patients with in age group of 17–57, any carious or periodontally involved tooth correlated as foci of infection on clinical examination and radiographic evidence of periapical changes. Medically compromised patients, pregnant females, chronic alcoholics, patients on steroid therapy and on contraceptives were excluded from the study. The facial spaces involved in the study were buccal, canine, sublingual, submandibular, submental, submassetric, pterygomandibular, superficial temporal, deep temporal, parotid, lateral pharyngeal and retropharyngeal spaces (Table 1). All patients were treated and observed by the same surgeon. Routine laboratory investigations were done along with airway assessment.

At the onset of treatment, discharge samples from infectious site was collected and sent for culture sensitivity. Blood samples of all the patients was taken to evaluate prealbumin and crp levels at, T1—before starting any treatment, T2—4th day of treatment and T3—8th day of treatment.

Table 1 Spaces involved in each subject

S. no	Name of the spaces
1	Left submandibular
2	Right submandibular
3	Left temporal
4	Right buccal
5	Right submandibular, right pterygomandibular, right lateral pharyngeal, retropharyngeal, submental, right sublingual
6	Left buccal, left temporal, left canine, left submandibular, left submassetric, left sublingual
7	Left submandibular, submental
8	Left submandibular
9	Right pterygomandibular, right submandibular
10	Left pterygomandibular, left retropharyngeal, left lateral pharyngeal
11	Right submandibular, right pterygomandibular
12	Right temporal, right buccal
13	Left infra orbital, left temporal
14	Right pterygomandibular, right lateral pharyngeal
15	Left submassetric, left submandibular
16	Right buccal, right canine, right submandibular, right deep temporal, right submassetric, right parotid
17	Left submandibular, left pterygomandibular
18	Right submandibular, right submassetric
19	Left pterygomandibular, left lateral pharyngeal
20	Right submandibular, right pterygomandibular, right lateral pharyngeal

Empirical antibiotic regime was started to control infection and appropriate analgesics were given for pain relief. In the empirical antibiotic regime patients were given intravenous amoxicillin with clavulanic acid 1.2 g bd and metronidazole 500 mg tid. For pain control intramuscular diclofenac sodium 75 mg bd was given. If pain persisted then injection tramadol 50 mg was further given.

Extraction of offending tooth was done if indicated. Incisions were placed keeping facial esthetics, vital structures and dependent part of swelling into consideration. Infected spaces were explored, locules were broken if present and decompression done. Irrigation with antibiotic solution was done and continued daily. Penrose drain was placed until discharge stopped. If infection subsided no further surgical intervention was done and empirical antibiotic therapy continued. But if infection increased or fail to subside further surgical intervention was done and antibiotic regime changed according to culture and sensitivity reports.

Assessment of patients was done based on various clinical parameters on every 4th day and correlated with laboratory values of serum prealbumin and CRP. Clinical parameters to assess infection were divided into signs and

symptoms. Signs used were change in size of swelling (using thread and scale), mouth opening (measuring central incisor distance), active discharge (one if present and zero if absent) and number of spaces involved (using clinical observation and CT scan). Symptoms recorded were pain (visual analog scale), dysphagia (one if present and zero if absent) and hoarseness of voice (one if present zero if absent).

Serum prealbumin level below 16 mg/dl depicts definite malnutrition and infection [7]. Similarly serum CRP levels above 11 mg/dl depict definite infection. Treatment regime was considered effective if laboratory values of both inflammatory markers and clinical parameters showed improved condition of patients. Patients were followed up for a period of 1 month (Figs. 1, 2, 3, and 4). Statistical package used in this study was paired *t*-test and regression analysis.

Results

This was a prospective study conducted on 20 patients with diagnosis of fascial space infections of odontogenic origin. The patients were within age group of 17–57 years with 90 % males and 10 % females (Graph 1). The mean age of

Fig. 1 Preoperative picture of Rt buccal space infection

Fig. 2 Post-treatment photograph of patient

Fig. 3 Preoperative picture of Lt submandibular and submental space infection

males was 40.78 ± 8.41 and that of females was 40 ± 15.56 years (Table 2). Mandible was involved in 16 patients (80 %) and four patients (20 %) had infection of

Fig. 4 Post-treatment photograph of patient

maxillary origin (Graph 2). Laboratory values of serum prealbumin and CRP on day 0, 4, and 8 was recorded (Tables 3, 4) and correlated with clinical parameters.

Day 0

The regression equation on day 0 explained inverse relation between prealbumin and size of swelling. Prealbumin was found to be a significant predictor of swelling size ($p < 0.01$). Contrary to swelling, mouth opening was directly proportional to prealbumin which was found to be a significant predictor of mouth opening ($p < 0.05$). But number of fascial spaces involved was inversely proportional to prealbumin values and regression equation for it

Table 2 Age group of study population (age in years)

Males	Females
41	29
21	51
40	
51	
48	
42	
39	
32	
47	
50	
34	
42	
26	
42	
38	
43	
45	
53	
Mean	
40.78	40.00
SD	
8.41	15.56

implied that with every one unit increase in prealbumin, there was a decrease of 0.64 units in number of spaces and 57.79 % of the variation in number of fascial spaces was explained by prealbumin values. Similarly regression equation for pain showed inverse relationship with prealbumin and with every one unit increase in prealbumin; there was a decrease of 0.19 units in pain and 17.52 % of variation.

The relation of CRP with the clinical signs and symptoms was also evaluated using the same method. On day 0,

Graph 1 Gender distribution in the study population

Graph 2 Site distribution in the study population

Table 3 Prealbumin levels of patients on day 0, 4, and 8

Prealbumin value (mg/dl)			
S. no	Day 0	Day 4	Day 8
1	9.1	17	19.2
2	8.4	13	17.2
3	9.2	13	18
4	6.9	13.4	18
5	3.4	4.1	
6	4.1	7.4	13
7	7.4	11.2	17
8	8.5	11	14
9	6	13.3	17.2
10	3	7	13
11	4.2	9.2	18
12	8.4	12	15.3
13	6.4	11	14.2
14	7	13.4	17
15	7.4	11.2	16.1
16	4	10.3	14.2
17	6.3	11.4	18.5
18	6.8	13.3	17.2
19	6	11.4	16
20	4.3	7.4	11

the regression equation explained the direct and linear relation between CRP and size of swelling with CRP being significant predictor of size of swelling ($p < 0.01$). The data for mouth opening explained an inverse relation between CRP and mouth opening. Regression also proved CRP being a significant predictor of mouth opening ($p < 0.01$). Number of fascial spaces involved was directly proportional to CRP values. The regression equation implied that for every one unit increase in CRP, there was an increase of 0.04 units in number of spaces and 56.2 % of the variation in number of fascial spaces was explained by

CRP values. Similarly regression equation for pain showed direct relationship with CRP. With every one unit increase in CRP, there was an increase of 0.01 units in pain and 12.03 % of the variation in pain could be explained by CRP values. The analyzed data also showed that 20 patients (100 %) included in study had discharge present on day 0. Dysphagia was seen in 13 patients (65 %) and eight patients (40 %) had hoarseness of voice.

Day 4

The values obtained on day 4 were again evaluated using the same method. The regression equation explained the inverse relation between prealbumin and swelling, prealbumin being significant predictor of swelling size ($p < 0.05$) and 27.7 % variation in size of swelling could be explained by changes in prealbumin values. But mouth opening was directly proportional to prealbumin and prealbumin was found to be a significant predictor of mouth opening ($p < 0.05$) with R value of 26.52 %. And number of fascial spaces involved was inversely proportional to prealbumin values. The regression equation implied that for every one unit increase in prealbumin, there was a decrease of 0.37 units in number of spaces and 53.59 % of the variation in number of spaces was explained by prealbumin values. Similarly regression equation for pain showed inverse relationship with prealbumin. With every one unit increase in prealbumin, there was a decrease of 0.28 units in pain and 41.65 % of the variation in pain could be explained by prealbumin values.

The regression equation explained the direct and linear relation between CRP and size of swelling, CRP being significant predictor of size of swelling ($p < 0.01$) having R values of 35.94 %. The data for mouth opening explained an inverse relation between CRP and mouth opening. Equation proved that CRP was a significant predictor of mouth opening ($p < 0.01$) having R values of 47.71 %.

Table 4 CRP levels of patients on day 0, 4, and 8

CRP values (mg/dl)			
S. no	Day 0	Day 4	Day 8
1	39	19.8	7.4
2	40	21.3	7
3	43	20	8
4	41	22.4	13
5	130	122	
6	92	30	18
7	80	41	13
8	43	21.2	10
9	69.3	23	10.2
10	109	40	17
11	58.4	28.6	7.1
12	78	40.3	9
13	63.2	20.3	15
14	80.4	33.3	13
15	42	23.4	12
16	101	42.3	15
17	64.3	31.1	10.2
18	78.5	45	9.4
19	94	47	10
20	121	78.6	34.2

Contrary to mouth opening number of fascial spaces involved was directly proportional to CRP values. The regression equation for number of spaces implied that for every one unit increase in CRP, there was an increase of 0.04 units in number of spaces and 53.28 % of the variation in number of spaces was explained by CRP values. Similarly regression equation for pain showed direct relationship with CRP. With every one unit increase in CRP, there was an increase of 0.03 units in pain and 4.73 % of the variation in pain could be explained by CRP values. The data also showed that 75 % of patients included in study had discharge present on day 4. Dysphagia was seen in 30 % of patients and 15 % of patients had hoarseness of voice.

Day 8

The regression equation on day 8 explained the inverse relation between prealbumin and swelling, prealbumin being significant predictor of swelling size ($p < 0.01$) and 43.61 % variation in size of swelling could be explained by changes in prealbumin values. Mouth opening was directly proportional to prealbumin but data obtained was not found to be significant ($p > 0.05$) with R value of 5.7 %. Number of spaces involved was inversely proportional to prealbumin values. The regression equation implied that with every one unit increase in prealbumin, there was a decrease

of 0.27 units in number of spaces and 44 % of variation in number of spaces could be explained by prealbumin values. Similarly regression equation for pain showed inverse relationship with prealbumin with every one unit increase in prealbumin. There was a decrease of 0.16 units in pain and 8.58 % of the variation in pain could be explained by prealbumin values.

The regression equation explained direct and linear relation between CRP and size of swelling, but CRP was not a significant predictor of size of swelling ($p > 0.05$) having R values of 17.9 %. The data for mouth opening explained an inverse relation between CRP and like swelling size CRP was also not a significant predictor of mouth opening ($p > 0.05$) having R values of 19.2 %. Number of spaces involved was directly proportional to CRP values. The regression equation implied that for every one unit increase in CRP, there was an increase of 0.10 units in number of spaces and 49.82 % of the variation in number of spaces was explained by CRP values. Similarly regression equation for pain showed direct relationship with CRP. With every one unit increase in CRP, there was an increase of 0.05 units in pain and 8.1 % of the variation in pain could be explained by CRP values. The data showed that none of patients included in study had discharge present on day 8. Dysphagia was seen in four patients (20 %) and one patient (5 %) had hoarseness of voice.

The above statistical analysis finds strong correlation between laboratory values of markers with clinical parameters used to measure severity of infection. The analysis also proved that values of markers significantly changed and moved towards normal as the condition of patient improved with effective treatment. On the other hand there was minimal change in the values of markers for the patient whose condition did not improve and patient died on 6th day. The values of markers remained significantly deranged than the normal values. Patient at the time of admission was suffering from right submandibular, right pterygomandibular, right lateral pharyngeal, retropharyngeal, right sublingual and submental spaces. Patient further developed mediastinitis and severe pneumonia which lead to respiratory complications causing death.

Thus, study proved that CRP and prealbumin are significant predictors of severity of infection and effectiveness of treatment regime.

Analysis of hospital stay

From the obtained data, we noticed that prealbumin was a significant predictor for hospital stay ($p < 0.01$). The regression equation showed that there was an inverse relationship between prealbumin and hospital stay, i.e., higher the prealbumin level, lower was the hospital stay (no. of days). $R^2 = 0.4059$ implies that, 40.59 % of the variation in hospital stay could be explained by prealbumin levels (Graph 3).

Similarly, we noticed that CRP was also a significant predictor for hospital stay ($p < 0.001$). The regression equation shows that there was a linear relationship between CRP and hospital stay, i.e., higher the CRP level, higher was the hospital stay. $R^2 = 0.4011$ implies that, 40.11 % of variation in hospital stay was explained by CRP (Graph 4).

Assessment of Nutritional Status

Mean value of prealbumin at day 0 was found to be 6.34 ± 1.94 . The mean values of prealbumin obtained on day 4 and 8 were 11.05 ± 2.91 and 16.01 ± 2.22 mg/dl, respectively. Comparison of prealbumin levels between day 0 and 4, day 0 and 8 as well as that between day 4 and 8 were found to be statistically significant ($p < 0.001$) (Table 5). The results obtained when compared with the clinical condition of the patient suggested that prealbumin levels are closely related to general condition of the patient and reflect nutritional status of the patient.

Discussion

The acute phase response is a complex set of systemic and metabolic reactions elicited by infections or other causes of injury. Besides other physiological, metabolic and

biochemical changes, the acute phase response is characterized by alterations in the hepatic synthesis and serum levels of some proteins. Thus, while the levels of positive acute phase proteins like CRP, complement 3, serum amyloid A, alpha-1 and glycoprotein, etc. increase due to stimulation of hepatic synthesis, depression of hepatic production of visceral transport proteins (negative acute phase proteins) like albumin, transferring, thyroxin binding prealbumin (TBPA) and retinol binding proteins (RBP) etc. occurs [8].

Several reports have indicated that visceral transport proteins, mainly those with a low turnover rate, like TBPA, RBP are useful to evaluate protein and protein energy under nutrition as well as to monitor nutritional recovery during nutrient repletion. However, the presence of infection results in depression of their hepatic production as well as increased passage to the extra vascular space, consequently diminishing their serum levels making them markers for acute phase conditions [8].

Similarly CRP, which is present in only small amounts in healthy individuals, is involved in several processes of the unspecific immunologic defense. In severe infections or inflammatory reactions a striking rise in the serum concentration is often seen. This suggests the possibility that rise of CRP is sufficiently rapid and specific to serve as a definitive aid in the early diagnosis of septicemia [6]. Thus,

Graph 3 Relationship between prealbumin and hospital stay

Graph 4 Relationship between CRP and hospital stay

Table 5 Assessment of nutritional status in relation to prealbumin

Prealbumin	Baseline (mean $\pm$ SD)	Mean difference	<i>t</i>	<i>p</i> value
Comparison of prealbumin at day 0 and 4				
Day 0	6.34 $\pm$ 1.94	−4.710	−11.935	<0.001*
Day 4	11.05 $\pm$ 2.91			
Comparison of prealbumin at day 0 and 8				
Day 0	6.34 $\pm$ 1.94	−9.557	−15.317	<0.001*
Day 8	16.01 $\pm$ 2.22			
Comparison of prealbumin at day 4 and 8				
Day 4	11.05 $\pm$ 2.91	−4.763	−6.584	<0.001*
Day 8	16.01 $\pm$ 2.22			

* Denotes a significant difference

based on these properties of the markers attempt has been made to use them in patients with fascial space infections [2, 4].

In this study, the prealbumin concentrations of patients admitted for treatment were significantly lower than the concentrations considered being clinically normal. Low concentrations of prealbumin seemed to result from the anorexia and malnutrition associated with trismus, pain, discomfort due to swelling, hoarseness of voice, dysphagia, and discharge in addition to systemic effects of infection. The number of fascial spaces involved in odontogenic infections is also an indicator of infection and prealbumin was significantly lower than normal clinical values when number of spaces involved were more than two. The results go well with the study conducted by Cunningham et al. [4] on patients with deep space infections.

In the present study, we found that prealbumin and CRP had a high degree of correlation with severity of infection having *p* value <0.01 from day 0 to 4. These results were similar to study conducted by Pinilla et al. [9], where they found statistically significant correlation between prealbumin and CRP at 2nd day ($R = 0.45$, $p < 0.01$) and 5th day ($R = 0.53$, $p < 0.01$) in infection patients.

CRP levels were found to be significantly high ($p < 0.01$) in most of the patients of space infections of odontogenic origin. Similar results were obtained by Ren et al. [2] and Ylyjoki et al. [1] where CRP levels declined significantly when effective treatment was given to the patient.

From this study, we noticed that prealbumin was a significant predictor for hospital stay ($p < 0.01$). The regression equation showed that there was an inverse relationship between prealbumin and hospital stay, i.e., higher the prealbumin level, lower was the hospital stay. These results are in concurrence with the study of Cunningham et al. [4]. They also found statistically significant

relationship between prealbumin concentration and length of hospital stay ($p < 0.38$). Logistic regression analysis used in their study showed that length of hospital stay was negatively related to prealbumin concentrations.

In this study, CRP was also a significant predictor for hospital stay ($p < 0.001$). The regression equation shows that there was a linear relationship between CRP and hospital stay, i.e., higher the CRP level, more was the hospital stay. These results go well in accordance with study of Ylyjoki et al. [1]. They also found CRP to be a significant predictor for hospital stay ($p < 0.001$).

For assessment of nutritional status, prealbumin levels were used. Mean value of prealbumin at day 0 was found to be 6.3 ± 41.94 . The mean values of prealbumin obtained on day 4 and 8 were 11.05 ± 2.91 and 16.01 ± 2.22 mg/dl, respectively. Comparison of prealbumin levels between day 0 and 4, day 0 and 8 as well as that between day 4 and 8 were found to be statistically significant ($p < 0.001$). The results match with study done by Ingenbleek [10]. In their study mean plasma prealbumin value was 6.37 ± 1.89 on day 0, rose to 13.06 ± 3.75 after 7 days and increased further to 19.46 ± 5.36 on day 15. Comparison of prealbumin levels on day 0, 7, 15 were found to be statistically significant ($p < 0.001$), similar to present study and that of Cunningham et al. [4].

Conclusion

The findings of this prospective analysis indicate that prealbumin and CRP can be effective markers for determining severity of infection, efficacy of treatment regime and length of hospital stay for patients with fascial space infections of odontogenic origin. Prealbumin having additional advantage of being a sensitive marker for nutritional status of the patient. Serum CRP reflects immediate effect of the treatment whereas prealbumin levels give further prognostic information. The duration of antibiotic usage, need for intensive care, and use of additional nutritional supplements becomes more rationale if these measurements are incorporated in clinical decisions. Thus, we conclude that prealbumin and CRP should be incorporated as monitoring tools for managing patients with fascial space infections of odontogenic origin.

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