RESEARCH PAPER

To Compare the Efficacy of C-Reactive Protein and Total Leucocyte Count as Markers for Monitoring the Course of Odontogenic Space Infections

Rishi Bali¹ · Parveen Sharma¹ · Priya Ghanghas¹ · Niti Gupta¹ · Jay Dutt Tiwari¹ · Abhiroop Singh¹ · Nitin Sapra¹ · Disha Goyal¹

Received: 5 April 2016 / Accepted: 11 October 2016 / Published online: 21 October 2016
© The Association of Oral and Maxillofacial Surgeons of India 2016

Abstract

Objective To compare the efficacy of CRP and TLC as markers for monitoring the course of odontogenic space infections (OSI) in 50 patients.

Methods A Clinical severity scale (CSS) was developed to grade the severity of infections in patients. Blood samples were taken preoperatively and postoperatively at day 1, day 2, day 3 and day 7 for measuring the levels of CRP and TLC. The trends of CRP and TLC were analysed against the CSS. The data was subjected to paired “t” test, ANOVA, Spearman rank correlation, Pearson’s bivariate correlation as appropriate.

Results The CRP values were elevated in all 50/50 (100 %) patients as compared to TLC which were elevated in 32/50 (64 %) patients only. The CSS displayed a high

internal consistency and reliability (Cronbach $\alpha = 0.748$). A significant strong positive correlation ($\rho = 0.754$) was found between CRP and CSS as compared to a moderate correlation ($\rho = .607$) between TLC and CSS.

Conclusion CRP displayed a more consistent relation with clinical severity of the infection than TLC. Hence it could be more reliably employed to judge the progress in a patient with OSI.

Keywords Odontogenic space · Infection · CRP · TLC · Laboratory markers

Introduction

Patients with fascial space infections of odontogenic origin are at significant risk from life threatening complications due to anatomical connectivity of potential spaces to vital structures. These can be anticipated and avoided by keeping a strict vigil on the clinical/laboratory parameters of such patients.

The clinical signs may sometimes appear late or may be insufficient to give precise assessment of an infectious process. Many laboratory markers have been used to predict the severity and course of infections, thereby avoiding the potential risk of patients slipping into further complications. These include TLC, DLC, ESR, Pre-albumin, Procalcitonin and C-reactive protein (CRP). Quantitative determination of serum markers can help in determining therapeutic efficacy of different treatment regimes of infection, for monitoring post operative infections, for investigating levels of infections and appropriate use of antibiotics [1–3].

Both CRP and TLC have been known to rise in an infectious process. TLC represents the cellular arm of immunity whereas CRP is the humoral component. Rise in

✉ Rishi Bali
rshbali@hotmail.co.uk

Parveen Sharma
parveen66@yahoo.co.uk

Priya Ghanghas
priyaghangas24@gmail.com

Niti Gupta
neeti0@gmail.com

Jay Dutt Tiwari
jdtewari@gmail.com

Abhiroop Singh
abhiroop.pratap@gmail.com

Nitin Sapra
nitinsapra1987@gmail.com

Disha Goyal
drdg09@hotmail.com

¹ Department of Oral and Maxillofacial Surgery, D.A.V (C) Dental College and Hospital, Yamunanagar, India

serum CRP concentration is seen up to 1000-fold within few hours of severe infections [3, 4]. Also CRP has a very short half life of 5–7 h [1, 2, 4] as compared to a life span of 5–6 days for leucocytes. This short half life makes it a more sensitive indicator of infection.

Serial CRP and TLC measurements have been effectively utilized as a marker to judge infection in many disciplines. We designed a study to compare the efficacy of CRP and TLC as markers for monitoring odontogenic fascial space infections. Additionally, values of DLC were also recorded.

Patients and Methods

A prospective cohort study was done during October 2013–October 2015 in 50 patients of odontogenic space infections. Pregnant and medically compromised patients were excluded.

Design of Clinical Severity Scale (CSS)

A consolidated Clinical Severity Scale (CSS) that could truly represent the severity of infection in the patient was developed for the study.

The selection of Loco regional parameters was done by a group of four senior maxillofacial surgeons whereas the Systemic parameters were modified from the popular APACHE-II in consultation with senior specialists from Medicine, Pathology and microbiology departments. The scoring of the selected parameter was done in consultation with Mr Varun Arora, an expert in Biostatistics and Epidemiology. The scale included Nine clinical indicators—Six Loco-regional (swelling, pain, pus, associated symptoms, associated signs and mouth opening) and three systemic (temperature, heart rate and respiratory rate) parameters as the indicators of clinical profile of a patient. For each clinical indicator, a scoring between 0 and 4 was done in proportion to the severity of derangement. For pus, associated signs and symptoms a weighted binary scoring system was used i.e. score 0 represented absence and score 4 represented the presence of the sign/symptom. For temperature, the scoring was done as 0, 1, 3 and 4 considering the irrelevance of the score 2. For pain too, scores allocated were 0, 1, 2 and 4, considering the irrelevance of score 3. Similarly, for heart rate scoring was done as 0, 2, 3 and 4 considering the irrelevance of score 1.

Further based on the cumulative scores, grades were assigned by the team of consultants. It was decided that a score of 0 indicates a NORMAL clinical profile, a score between 1 and 8 MILD clinical impact of infection, a score between 9 and 16 MODERATE and above 16 STRONG indicator of clinical impact of infection (Table 1).

Table 1 Clinical severity scale

Parameters	Criteria	Score
<i>Loco-regional parameters^a</i>		
Swelling	Baseline score (at admission)	4
	<25 % reduction from baseline	3
	25–50 % reduction	2
	50–75 % reduction	1
	>75 % complete resolution	0
Pain	No pain	0
	Mild pain	1
	Moderate pain	2
	Severe pain	4
Pus	Absent	0
	Present	4
Associated symptoms ^b	Absent	0
	Present	4
Associated signs ^c	Absent	0
	Present	4
Mouth opening	<9 mm	4
	9–17 mm	3
	18–26 mm	2
	27–35 mm	1
	>35 mm	0
<i>Systemic parameters^d</i>		
Temperature	36–38.4 °C	0
	38.5–38.9/34–35.9 °C	1
	30–31.9/39–40.9 °C	3
	≤29.9/≥41 °C	4
	70–109	0
Heart rate	55–69/110–139	2
	40–54/140–179	3
	<40/≥180	4
	12–24	0
	10–11/25–34	1
Respiratory rate	6–9	2
	35–49	3
	<5/≥50	4

Grades of Infection as per CSS Score: >16 = severe; 9–16 = moderate; 1–8 = mild; 0 = normal

^a Loco regional parameters

^b Associated symptoms—Dyspnoea, Dysphagia, Dysphonia

^c Associated signs—Uvula deviation, obliteration of nasolabial fold/ vestibule, Ocular signs

^d Systemic criteria (modified from: APACHE II)

Investigations and Management

Patients were asked to undergo routine blood investigations including evaluation of CRP, TLC and DLC prior to initiating antimicrobial treatment. Empirical antibiotics including I.V Amoxicillin 1000 mg/clavulanate 200 mg

Table 2 Clinical severity grades in patients ($n = 50$) at different intervals

	Grading	Severe	Moderate	Mild	Normal
Days	0 (Baseline)	5/50 (10 %)	45/50 (90 %)	0 (0 %)	0 (0 %)
	Day 1	1/50 (2 %) ↓8 %	39/50 (78 %) ↓22 %	10/50 (20 %) ↑20 %	0 (0 %) ↔
	Day 2	0/50 (0 %) ↓2 %	14/50 (28 %) ↓50 %	36/50 (72 %) ↑52 %	0 (0 %) ↔
	Day 3	0 (0 %) ↔	3/50 (6 %) ↓22 %	47/50 (94 %) ↑22 %	0 (0 %) ↔
	Day 7	0 (0 %) ↔	0 (0 %) ↓6 %	37/50 (74 %) ↓20 %	13/50 (26 %) ↑26 %

↓: Decrease in patient count since last observation

↑: Increase in patient count since last observation

↔: Count remains the same

12-hourly together with Metronidazole 500 mg 8-hourly were initiated in all patients [5, 6]. Incision and drainage along with removal of the focus of infection was carried out under appropriate anaesthesia. Drainage was maintained with a corrugated rubber drain and regular copious betadine, saline irrigations were carried out. Patients were monitored on the basis of clinical signs (which were recorded as per CSS) and laboratory findings (Table 2).

Collection of Data

Patients' age, sex, focus of infection, and number and type of spaces involved were recorded. Various clinical variables of clinical severity scale including change in degree of swelling (measured by thread and scale), changes in the amount of pain (measured by verbal pain scale), presence or absence of pus, improvement in mouth opening and dysphagia or dyspnoea (if symptoms were present) were scored.

Improvement in systemic variables including heart rate, body temperature, and respiratory rate were assessed using the criteria adopted from APACHE II [7]. A cumulative score was calculated to grade the clinical severity of odontogenic infection at all intervals. CRP and TLC values were recorded pre-operatively, after 24, 48, 72 h and on 7th day. Values of these biomarkers were then correlated with CSS at various study intervals to compare their efficacy in monitoring the odontogenic space infections.

Analysis of Data

A database was constructed using Microsoft Excel (Microsoft, Redmond, WA). The statistical analysis was done with help of SPSS software (Statistical Package for Social Sciences) Version 15.0 statistical Analysis Software. The significance of differences was assessed using Paired “*t*” test, ANOVA, Spearman rank correlation, Pearson's bivariate correlation, as appropriate.

Results

Validation of Scale: The CSS was evaluated and validated in the present study on 50 patients with maxillofacial space infections, by evaluating it against the established inflammatory markers CRP, TLC and DLC. There was very highly significant correlation between the markers and CSS except monocytes and eosinophil. The scale indicated a strong correlation with these inflammatory markers and hence was found to be validated (Table 3).

Internal Consistency and Reliability: The scale was assessed using Cronbach alpha estimation and Inter-item correlation matrix. The Cronbach alpha value was calculated as 0.748, thus indicating that the scale was internally consistent and showed a high reliability.

The CRP showed a significant strong positive correlation ($\rho = 0.754$, $p = 0.000001$) as compared to TLC which showed a moderately positive correlation ($\rho = 0.607$, $p = 0.000001$) with clinical severity of infection as per CSS.

At admission, 45 (90 %) patients had *Moderate* and 5 (10 %) had *Severe* clinical infection whereas at day 7, 13 (26 %) patients had *Normal* and 37 (74 %) had *Mild*

Table 3 Correlation of CRP and TLC with CSS

Lab parameter	Correlation (ρ)	Significance (p value)
CRP	0.754	0.000001
TLC	0.607	0.000001
N	0.744	0.000001
L	0.746	0.000001
M	-0.148	0.019
E	-0.061	0.340

Spearman rank correlation value (ρ) $\rho < 0.3$: weak/no correlation, $\rho = 0.3$ to 0.5 : mild, $\rho = 0.5$ to 0.7 : moderate, $\rho = 0.7$ to 0.9 : strong, $\rho > 0.9$: very strong to perfect

Fig. 1 Trend of mean CSS values at various study intervals

Fig. 2 Trend of mean CRP values at various study intervals

Fig. 3 Trend of mean TLC values at various study intervals

clinical infection as per CSS, thus showing a significant difference from baseline ($p < 0.001$). CSS scores ranged from 12 to 23 with a mean value of 14.58 ± 2.42 .

The CRP values were increased in all 50 (100 %) patients as compared to TLC values which were increased only in 32 (64 %) patients at the time of admission.

The mean values of CSS (Fig. 1), CRP (Fig. 2) and TLC (Fig. 3) showed a decline from admission to day 7, except CRP which showed an increase at day 2.

Discussion

Appropriate and early timely intervention in an infectious process can help to minimize the morbidity and mortality in surgical practice. In patients with infections the signs and symptoms alone, may not always be sufficient to judge the severity of infectious process and its clinical impact. Both clinical parameters and inflammatory markers have been employed in tandem to monitor patients with infections.

Owing to the close proximity of fascial spaces to vital structures, it is important to be highly vigilant regarding the clinical status of OSI patients.

Various inflammatory markers have been used to aid in judging the clinical severity of infection. CRP and TLC are one of the most readily available economic markers employed for this purpose. To be able to objectively compare the two, a clinical scale named Clinical severity scale was developed for this study. Against this Clinical Severity Scale (CSS) efficacy of CRP and TLC were evaluated.

CRP is an acute-phase protein produced by the liver in response to inflammation and infection and is a valuable marker of infection [8].

CRP rises within 4–6 h of injury and peaks in 24–48 h, then falls rapidly once the inflammation resolves. This rapid rise and fall of CRP makes it a more sensitive marker than WBC [9].

Normal plasma concentration of CRP is below 10 mg/L [10, 11].

Advantage of having short half lives of 5–7 h makes serum CRP a sensitive indicator of infection as well as a definitive aid in the early diagnosis of septicemia [12].

At baseline (admission), the mean value of CRP was 95.40 mg/L (Fig. 2). These values correlate well with the previous studies [13–15]. On day 1 (postop), mean value of CRP was higher (100.72) than preoperative value (95.40) (Fig. 2). This can be partly attributed to the surgical manipulation caused by incision and drainage resulting in higher postoperative values [16]. On the day 2 and day 3, a decline in the mean CRP levels was evident. On day 7, mean CRP levels decreased significantly approaching towards normal values (mean = 11.82 mg/L) (Fig. 2). This correlates well with the clinical improvement and responsiveness to the therapy as proved by other studies [2, 12, 15]. Between baseline and day 1 a (5.32/95.4) 5.58 % increase in mean CRP levels was observed. However, at day 2 onwards a declining trend in CRP values was observed. At day 2, day 3 and day 7 intervals mean decline was (−39.18/95.4) 41.07 %, (−62.74/95.4) 65.77 % and (−83.58/95.4) 87.61 % respectively.

CRP had a high degree of correlation with clinical severity of infection which is in correlation with the studies of various authors [2, 13].

In the study, there was decline in Clinical Severity Scale (CSS) score from baseline (admission) to day 7, which signifies that clinical condition of the patient was improving. Decline in CRP levels from baseline to day 7 was in direct relation with CSS score except on day 2 which can be attributed to surgical manipulation.

Total and the differential leucocyte counts have been used for the past 95 years to help evaluate infectious diseases. The specific findings are neutrophilia and generalized leukocytosis [17].

Normal value of TLC ranges from 4000–11,000 mm^{-3} and the normal neutrophil count range from 48 to 72 % in a healthy adult.

WBCs produce, transport and distribute antibodies as a part of the immune response. In response to acute infection or inflammation, the number of WBC's increases [18]. Neutrophils are short-lived cells that usually die while performing their antimicrobial function.

At admission mean TLC was 12446 ± 2824 which declined to reach at 7454 ± 1571 at day 7 (Fig. 3). Mean % decline in TLC was (–1364/12,446) 10.96 %, (–3084/12,446) 24.78 %, (–4172/12,446) 33.52 % and (–4992/12,446) 40.11 % respectively at days 1, 2, 3 and 7 respectively (Fig. 3).

The TLC showed a consistent decline unlike CRP which peaked on first postoperative day and then declined. This also indicates that CRP more accurately reflects the surgical insult than TLC.

In all the 50/50 (100 %) patients, the values of CRP were raised above the normal values at the time of admission. While TLC was raised above the normal only in 32/50 (64 %). Neutrophil count was raised in 49/50 (98 %) patients.

According to Boucher et al. [19] the WBC may react slowly to bacterial infections. Clearly the WBC at admission is normal or only slightly increased in many patients with odontogenic infection. This findings correlate well with the present study. Heimdahl and Nord [20] concluded that the WBC is of minor importance when judging the severity of orofacial infections, a view that the present study would support. The WBC is perhaps more useful in assessing a patient's response to therapy.

Comparing CRP and TLC, various studies support the fact that CRP is a better indicator of an infectious process because the CRP level rises faster than WBC in odontogenic infections [12, 21, 22].

In the entire study, CSS scores from the time of admission, showed a declining trend representing an overall improvement of clinical profile of patient. At baseline CSS severity score was 14.58 ± 2.42 which declined to 1.18 ± 0.96 at day 7 (Fig. 1). Percent decline in CSS score was (–3.04/14.58) 20.85 %, (–7.58/14.58) 51.99 %, (10.72/14.58) 73.53 % and (–13.40/14.58) 91.91 % at day 1, day 2, day 3 and day 7 intervals. At all

the follow up intervals, mean CSS scores were significantly lower as compared to baseline, indicating improvement in the clinical profile of the patient.

Association between Clinical Severity Scale (CSS) grades and laboratory parameters was assessed and it was found that mean values of CRP, TLC and Neutrophil showed a significant incremental trend with increasing Clinical Severity Scale (CSS) grade ($p < 0.001$).

On overall evaluation between Clinical Severity Scale (CSS) score and different biomarkers, a significant and strong positive correlation was observed with CRP and neutrophil count ($p > 0.7$; $p < 0.001$). The correlation between TLC and CSS was positive moderate and significant ($p = 0.607$; $p < 0.001$).

In conclusion, CRP was found to be a more consistent indicator for monitoring the patients of OSI. It displayed a more consistent relation with the clinical status of the patient as compared to TLC. In addition, the differential neutrophil count was found to have better correlation with the clinical severity of OSI than TLC.

Acknowledgments I thanks Mr. Varun Arora, Bio-statistician for his assistance with the statistical analysis of my research study.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Statement Obtained for experimentation with human subjects from patients as well as from ethical committee.(F/Ethical/1593). The study design was approved by the Board of Studies of the University.

Informed Consent An informed consent was obtained from all the patients.

References

1. Ylyjoki S, Suuronen R, Somer HJ, Meurman JH, Lindqvist C (2001) Differences between patients with or without the need for intensive care due to severe odontogenic infections. *J Oral Maxillofac Surg* 59:867–872
2. Ren YF et al (2007) Rapid quantitative determination of C-reactive protein at chair side in dental emergency patients. *J Tripleo* 104(1):49–55
3. Sganga et al (1985) Hepatic protein reposition after trauma and sepsis. *J Surg* 120:189–199
4. Sabel KG, Wadsworth C (1979) C-reactive protein in early diagnosis of neonatal septicemia. *Acta Paediatr Scand* 68:825–831
5. Bali R, Sharma P, Gaba S (2015) Use of metronidazole as part of an empirical antibiotic regimen after incision and drainage of infections of the odontogenic spaces. *Br J Oral Maxillofac Surg* 53(1):18–22. doi:10.1016/j.bjoms.2014.09.002
6. Bahl R, Sandhu S, Singh K, Sahai N, Gupta M (2014) Odontogenic infections: microbiology and management. *Contemp Clin Dent* 5(3):307–311

7. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) APACHE II: a severity of disease classification system. *Crit Care Med* 13(10):818–829
8. Póvoa P (1998) C-reactive protein as an indicator of sepsis. *Intensive Care Med* 24(10):1052–1056
9. Barreto VT, Isaac A, Bhimidi P, Nguyen C, Jones G (2013) Trends of C-reactive protein laboratory values with white blood cell count levels in maxillofacial infections. *J Oral Maxillofac Surg* 71(9):e31–e32
10. Vigushin DM, Pepys MB, Hawkins PN (1993) Metabolic and scintigraphic studies of radioiodinated human C-reactive protein in health and disease. *J Clin Invest* 91:1351–1357
11. Pepys MB, Baltz ML (1983) Acute phase proteins with special reference to C-reactive protein and related proteins (pentaxins) and serum amyloid A protein. *Adv Immunol* 34:141–212
12. Ylijoki S, Suuronen R, Jousimies-Somer H, Meurman JH, Lindqvist C (2001) Differences between patients with or without the need for intensive care due to severe odontogenic infections. *J Oral Maxillofac Surg* 59(8):867–872
13. Seppänen L, Lauhio A, Lindqvist C, Rautemaa R (2008) C-reactive protein in predicting the need for reoperation in odontogenic maxillofacial infections requiring hospital care. In: 18th European congress of clinical microbiology and infectious diseases. Barcelona, Spain
14. Bakathir AA, Moos KF, Ayoub AF, Bagg J (2009) Factors contributing to the spread of odontogenic infections. *Sultan Qaboos Univ Med J* 9(3):296–304
15. Sharma A, Gokkulakrishnan S, Shahi AK, Kumar V (2012) Efficacy of serum CRP levels as monitoring tools for patients with fascial space infections of odontogenic origin: a clinico-biochemical study. *Natl J Maxillofac Surg* 3(2):148–151
16. Chang J-S, Yoo K-H, Yoon SH, Ha J, Jung S, Kook M-S et al (2013) Odontogenic infection involving the secondary fascial space in diabetic and non-diabetic patients: a clinical comparative study. *J Korean Assoc Oral Maxillofac Surg* 39:175–181
17. Travis RT, Steinle CJ (1984) The effects of odontogenic infection on the complete blood count in children and adolescents. *Pediatr Dent* 6(4):214–219
18. Aminzadeh A, Parsa E (2011) Relationship between age and peripheral white blood cell count in patients with sepsis. *Int J Prev Med* 2(4):238–242
19. Boucher NE, Hanharan JJ, Kihara FY (1967) Occurrence of C-reactive protein in oral diseases. *J Dent Res* 46(3):624–627
20. Heimdahl A, Nord CE (1983) Orofacial infections of odontogenic origin. *Scand J Infect Dis* 39(Suppl):86–91
21. Kallio LU, Kallio MJ, Peltola H, Eskola J (1994) Serum C-reactive protein, erythrocyte sedimentation rate, and white blood cell count in acute hematogenous osteomyelitis of children. *Pediatrics* 93(1):59–62
22. Clyne B, Olshaker JS (1999) The C-reactive protein. *J Emerg Med* 17(6):1019–1025