Analysis of C-reactive Protein Level as a Monitoring Tool in Patients with Odontogenic Space Infection: A Prospective Clinical Study

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Abstract

Aim: The aim of this study was to do analysis of C-reactive protein (CRP) level as an efficacy of treatment in odontogenic space infection in indoor patients to measure the severity of infection so that medicinal treatment response can be assessed and subsequently to avoid excessive postoperative antibiotic treatment given to the patients.

Materials and methods: A total number of 40 indoor patients of 17–50 years of age were analyzed for CRP levels as monitoring tools in odontogenic fascial space infection in the Department of Oral and Maxillofacial Surgery, PGIMS, in collaboration with the Department of Microbiology, PGIMS, to measure the severity of infection and to assess medicinal treatment response.

Results: The severity of infection and effectiveness of the treatment regime were determined using the correlation between clinical parameters and laboratory values of serum CRP, which explained the direct and linear relation between CRP and size of swelling, with CRP being a significant predictor of size of swelling ($p < 0.05$). The data for mouth opening explained an inverse relation between CRP and mouth opening.

Conclusion: The findings of this prospective analysis indicate that CRP can be served as effective markers for determining the severity of fascial space infections of odontogenic origin. Serum CRP reflects the immediate effect of the treatment and acts as a significant predictor of the severity of infection and effectiveness of the treatment regime, which can be incorporated as a monitoring tool for managing patients with fascial space infections of odontogenic origin.

Clinical significance: Looking at the scarcity of studies pertaining to CRP levels in odontogenic space infection patients, this prospective clinical study was conducted to monitor the levels of CRP level in odontogenic space infection patients to throw further light in this direction.

Keywords: Antibiotics, Broad spectrum, C-reactive protein, Inflammatory markers, Local anesthesia, Odontogenic space infection, Periodontal abscesses, Prospective clinical study, Research, Wide microflora.

Introduction

Fascial space infections have been documented in literature extensively. Earlier treatment of localized infection involved the opening of a bulging abscess using sharp stones or pointed sticks. Although today the principle behind the procedure remains alike, the technique has improved.¹ Infections originating from the tooth may vary from simple periapical abscesses to severe infections involving superficial and deep fascial spaces in the head and neck region, which may often lead to septicemia.²,³ These infections by virtue of their anatomical relation may range from low-grade, well-localized infections to severe life-threatening conditions. Henceforth, they include upper airway origin and may extend to potential spaces formed by fascial planes of the lower head and upper cervical area, i.e., buccal, sublingual, submandibular, temporal, masseteric, canine, and parapharyngeal, which further shows lethal complications like mediastinitis, cavernous sinus thrombosis, and brain abscess if left untreated.⁴–⁶

Despite great advancement in the orodental care and living in an era of antibiotics, odontogenic infections are still a major problem present with pain, erythema, active discharge, hoarseness of voice, swelling, and loss of function, which may be just an inflammatory response or a result of infection prior to treatment.⁷ The anatomic route of spread, involving the tooth, as well as complex microflora, determines the patient condition.⁸,⁹ Here, the primary treatment is incision and drainage, along which the knowledge of involved microorganisms and their sensitivity pattern also plays an important role.¹⁰ Sometimes, patient condition does not improve even after incision and drainage, possibly due to resistance in bacterial strains, thereby selection of wrong antibiotics.¹¹ The pathological process of odontogenic infection is polymicrobial, having a wide spectrum of facultative anaerobes, such as the Streptococci viridans group and the Streptococcus anginosus group, and strict anaerobes, especially anaerobic cocci and Prevotella and Fusobacterium species. The major

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isoles are strictly anaerobic gram-negative rods and gram-positive cocci. The microbiology of acute dental infections has been in the midpoint of many researches.

Pain, cellulitis, erythema, skin febrile on touch, and tooth sensitive to percussion by mouth mirror are the clinical features seen in patients with superficial infections, whereas signs such as abscess, swelling, rise in temperature and sometimes difficulty in swallowing, and difficulty in mouth opening are present in patients with deep infections. Infections caused by teeth may be sometimes confined to the alveolar ridge or tissues in close proximity but can spread into deep fascial spaces. If fascial spaces are involved, they may lead to cavernous sinus thrombosis, brain abscess, airway obstruction, mediastinitis, and endocarditis.12

Prognosis of odontogenic space infection can be determined to a great extent using laboratory investigations. Inflammatory markers hold great value and advantages for their usage in the diagnosis of these space infections.13 Quantitative determination of serum markers has proven to be effective in the determination of the efficacy of different treatment protocols.14 For early identification of these infections, there are some potential biological markers such as anti-inflammatory and proinflammatory cytokines, cellular markers, bioactive circulating molecules, etc. Acute-phase proteins such as C-reactive protein (CRP) and procalcitonin are released due to the activation of both IL-6 and the tumor necrosis factor (TNF-α).15

C-reactive protein is an acute-phase protein synthesized in the liver by hepatocyte cells and is normally present as a trace constituent of plasma or serum in diseased as well as otherwise healthy individuals. The value of CRP increases in infection or inflammatory processes. Elevated CRP goes hand-in-hand with traditional risk factors for heart disease, such as smoking, obesity, high blood pressure, or elevated cholesterol, and rarely occurs in their absence. Distinct treatment protocol’s therapeutic efficacy can be monitored by quantitatively analyzing the serum CRP as it is helpful in determining the antimicrobial efficacies and postoperative infections.16

C-reactive protein rise remarkably within 4–6 hours, attains peak value in 24–48 hours after acute infection occurs and declines quickly after inflammation resolves.17–19 Looking at the scarcity of studies pertaining to CRP levels in odontogenic space infection patients, this prospective analysis study was conducted to monitor the levels of CRP in odontogenic space infection patients to throw further light in this direction.

**Materials and Methods**

A prospective analysis of the assessment of quantitative serum CRP level as a monitoring tool in odontogenic space infection patients was carried out in this study in collaboration with the Department of Microbiology. A total number of 40 patients with space infections were included in the study, who reported and were admitted to the Department of Oral and Maxillofacial Surgery. The subjects were selected based on the inclusion and exclusion criteria.

The inclusion criteria were based on patient’s age, starting from 18 to 50 years, presented with any grossly decayed or periodontally compromised tooth as a source of infection, and radiographic evaluation reveals periapical changes. The exclusion criteria were based on the medically compromised condition of the patient, pregnant women, chronic alcoholic patients, and patients on steroid or on contraceptive therapy. The study was conducted according to the Guidelines of Good Clinical Practice of the Declaration of Helsinki (IDH-GCP).

All patients who fall under the inclusion criteria were examined by the same surgeon before the onset of treatment in the Department of Oral and Maxillofacial Surgery. A detailed case history was recorded on case history performance, and primary examination was done. A routine laboratory investigation was taken, besides airway evaluation.

During the treatment procedure, discharge, i.e., pus or serous fluid sample, was taken from the infectious site by sterile cotton swab stick and further sent for the culture and sensitivity test along with the blood sample for evaluating quantitative values of CRP in the Department of Microbiology.

**Principle and Procedure for C-reactive Protein Determination**

A sample of 3 mL of blood was collected from the cubital fossa of the left arm under an aseptic condition. Blood samples were taken on the 1st day before initiating treatment, 4th day of treatment, and 8th day of treatment. The collected sample was centrifuged immediately at 4000 rpm for 20 minutes at 4°C, and serum was gently pipetted off into a clean test tube using a glass Pasteur pipette. Serum collected was mixed with buffer and antibody and analyzed as per the instruction of the kit.

The CRP reagent kit is based on an immunological reaction between CRP antisera bound to biologically inert latex particles and CRP in the test specimen. When serum containing greater than 0.8 mg/dL CRP is mixed with the latex reagent, visible agglutination occurs.

The CRP latex slide test is used for the semiquantitative measurement of CRP. Semiquantitative test was done by taking a setup of at least five test tubes with 1:2, 1:4, 1:8, 1:16 dilution, etc. The sample was diluted with normal saline according to the dilution factor mentioned on each test tube.

One drop of each positive and negative control was put on separate slides. Place one drop of each dilution on the reaction slides. Gently resuspend the CRP latex reagent and add one drop to each test field. Mix well with a stir stick and rock the slide for 3 minutes and read immediately under direct light. The titer of the serum is the reciprocal of the highest dilution exhibiting a positive reaction multiplied by the concentration of the positive control.

**Interpretation**

Negative result indicated by a uniform milky suspension with no agglutination was observed with the CRP-negative control. Positive result was indicated by any observable agglutination in the mixture.

**Expected Values**

C-reactive protein in healthy individuals is approximately 0.02–1.35 mg/dL, and the mean value in adults is 0.047 mg/dL.

**Procedure**

An intravenous empirical antibiotic regime was started after stabilizing the central line for the infection control, and suitable analgesics were started for relief in pain. Before starting the procedure, extraction of the involved tooth was done if desired. The cleaning of the operating site by scrubbing with povidone-iodine was done, followed by giving a local anesthetic injection of 2% lidocaine with adrenaline 1:80,000 given to the incision site. A stab incision was made keeping into consideration the vital structures, esthetics and dependent part of swelling with no. 11 surgical blade (Fig. 1). Then, infected spaces were explored by using a curved artery (Hemostat), loci were breached if present, and thereby
decompression was achieved. Irrigation with metrogyl solution followed by normal saline was done twice a day. A corrugated rubber drain was placed and secured with silk suture and removed when there is no discharge. Even after the surgical intervention, if there was no relief or the infection spread increases, then the antibiotics must be substituted according to the culture report of the individual patient. Assessment of the patient was done on the basis of clinical parameters' evaluation on every 4th and 8th day associating with serum CRP values. Clinically, signs that are used were changes in swelling diameter, temperature, interincisal mouth opening (Fig. 2), tenderness, consistency, and any discharge.

Ethical and Human Considerations
Ethical clearance was sought from the Ethical Committee of the Institution, explaining the aim and importance of the study, and after approval, patients with fascial space infections reporting to the institution were taken in the study. Included patients are informed about the procedure prior to the examination and explained the treatment and research purpose with the provision to opt out of the study any time during the course of treatment without having to give any reason and then, a detailed informed written consent was taken from all interested patients in the presence of two witnesses. The study was conducted according to the Guidelines of Good Clinical Practice of the Declaration of Helsinki (IDH-GCP).

Results
A total of 40 patients with fascial space infections of odontogenic origin admitted to the dental ward were recruited to participate in this prospective clinical study. Male preponderance was found (male:female ratio 2.33:1) in the enrolled patients. The age-group most commonly involved was in the third and fourth decade of life, with the mean age-group being 34.65 years. Blood samples were taken and sent on the 4th day and 8th day of treatment and sent for quantitative analysis of serum CRP levels after the treatment begins. Extraction of the culprit’s tooth followed by incision and drainage with exploration was done nearly in all enrolled patients. Before giving an incision, aspiration using a needle was done, after that, the incision was placed and the sample was taken using swab stick that was further subjected to culture and sensitivity test. The severity of odontogenic infection in the form of swelling and the effectiveness of treatment protocol were analyzed by finding associations among clinical parameters and quantitative figures of serum CRP.

Data were entered into Microsoft Excel spreadsheet and were checked for any discrepancies. The data were analyzed by SPSS (21.0 version), Shapiro–Wilk test was used to check whether all variables were following a normal distribution (p-value < 0.05).

CRP Levels
The mean serum CRP titer: highest dilution at T1, i.e., preop day 1 was 113.80 (SD: 77.06, range: 8.0–256), T2, i.e., preop day 4 was 55.10 (SD: 37.69, range: 4.0–128.0), and T3, i.e., preop day 8 was 21.40 (SD: 20.14, range: 4.0–64.0) (Fig. 3). The mean serum CRP titer: highest dilution was compared by Friedman and this difference came out to be statistically significant within a group. The maximum serum CRP titer: highest dilution was seen at preop day 1, followed by preop day 4, and then least in preop day 8. The mean CRP levels were compared using repeated measures of ANOVA, and this difference came out to be statistically significant within a group. The CRP levels...
Analysis of CRP Level in Patients with Odontogenic Space Infection

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gradually decreased. On post hoc analysis, for pairwise comparison, significant differences were found between all time intervals. Hence, the CRP levels at postop day 8 were significantly lower than CRP levels at postop day 4 and CRP levels at preop day 1. Also, CRP levels at postop day 4 were significantly lower as compared with CRP levels at preop day 1.

Mouth Opening

The mean mouth opening at T1, i.e., preop day 1 (Figs 1B, 2B) was 16.05 (SD: 9.27, range: 42–6), T2, i.e., preop day 4 was 25.30 (SD: 7.47, range: 42–15), and T3, i.e., preop day 8 was 39.85 (SD: 4.24, range: 47–15) (Fig. 4). The mean for mouth opening was compared using repeated measures of ANOVA and this difference came out to be statistically significant within a group. It gradually increased. The minimum mouth opening was seen at preop day 1, and then it gradually increased at preop day 4 and maximum at preop day 8. The mean for mouth opening was compared using repeated measures of ANOVA, and statistically significant results were found within a group. It gradually increased. The minimum mouth opening was seen at preop day 1, and then it gradually increased at preop day 4 and maximum at preop day 8. Tukey’s post hoc analysis was done for intergroup comparison. The mean mouth-opening levels were compared using repeated measures of ANOVA, and this difference came out to be statistically significant within a group. On post hoc analysis, for pairwise comparison, significant differences were found between all time intervals. Hence, the mouth opening at postop day 8 was significantly higher than at postop day 4 and at preop day 1. Also, mouth opening at postop day 4 was significantly higher as compared with mouth opening at preop day 1.

VAS Scores

The mean VAS score at T1, i.e., preop day 1, was 6.07 (SD: 2.01, range: 8–2), T2, i.e., preop day 4, was 2.92 (SD: 1.93, range: 6–0), and T3, i.e., preop day 8, was 0.42 (SD: 0.90, range: 3–0). The maximum VAS scores were seen at preop day 1, and then they gradually decreased at preop day 4 and minimum at preop day 8.

The mean VAS score levels were compared using repeated measures of ANOVA, and this difference came out to be statistically significant within a group. They gradually decreased. On post hoc analysis, for pairwise comparison, significant differences were found between all time intervals. Hence, the VAS scores at postop day 8 were significantly lower than the VAS scores at postop day 4.
Analysis of CRP Level in Patients with Odontogenic Space Infection

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<th>Abbreviation</th>
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Figs 5A and B: Comparison of mean and standard deviation of swelling in study population

4 and VAS scores at preop day 1. Also, VAS scores at postop day 4 were significantly lower as compared with VAS scores at preop day 1.

**Swelling**

The mean swelling at T1, i.e., preop day 1, was 22.40 (SD: 10.66, range: 42–4), T2, i.e., preop day 4, was 17.17 (SD: 11.97, range: 36–0), and T3, i.e., preop day 8, was 0.25 (SD: 1.12, range: 6–0) (Fig. 5). The maximum swelling size was seen at preop day 1, and then it gradually decreased at preop day 4 and minimum at preop day 8. The mean swelling size was compared using repeated measures of ANOVA and this difference came out to be statistically significant within a group. The size of swelling decreases gradually. On post hoc analysis, for pairwise comparison, significant differences were found between all time intervals. Hence, the swelling at postop day 8 was significantly lower than swelling at postop day 4 and swelling at preop day 1. Also, swelling at postop day 4 was significantly lower as compared with swelling at preop day 1.

**Active Discharge**

The active discharge at T1, i.e., preop day 1, was present in 30 (75%) subjects and absent in 10 (25%) subjects, T2, i.e., preop day 4, was present in 7 (17.5%) subjects and absent in 33 (82.5%) subjects, and T3, i.e., preop day 8, was present in 2 (5%) subjects and absent in 38 (95%) subjects. The distribution of the study population according to signs: active discharge was compared using Chi-square, and came out to be significant. At postop day 8, subjects reporting active discharge were less as compared with preop day 1.

**Dysphagia**

The dysphagia at T1, i.e., preop day 1, was present in 21 (52.5%) subjects and absent in 19 (47.5%) subjects, T2, i.e., preop day 4, was present in 5 (12.5%) subjects and absent in 35 (87.5%) subjects, and T3, i.e., preop day 8, was present in 0 (0%) subjects and absent in 40 (100%) subjects. The distribution of the study population according to symptom: dysphagia was compared using Chi-square, and came out to be significant. At postop day 8, subjects reporting dysphagia were less as compared with preop day 1.

**Discussion**

Space infections in the oral and maxillofacial region are encountered quite frequently in the clinical practice. They have high mortality rate accounting for 10–40%. Odontogenic infection has haunted the humans since their existence. Odontogenic space infections being self-limiting in nature may occasionally involve the deep fascial spaces. Life-threatening infections of odontogenic or upper airway origin extend to potential spaces formed by fascial planes of the lower head and upper cervical area. Propagation of these infections occurs through various routes such as directly, by lymphatic routes, or by hematogenous routes. The impact of patient’s local and systemic factors may influence the method of propagation. Either a disruption of the normal flora or a propagation of the normal organisms to the site, where they are usually not seen, is contributory to these infections. A variation in presentation of these may be seen presenting as periapical infections or even as superficial to deep neck space infections. If ignored, they may transform into contiguous fascial spaces (namely sublingual, submandibular, temporal, masseteric, buccal, and canine and parapharyngeal) and contributing to additional complications. Mankind till date, despite all the efforts, has not been able to wipe out these infections. Hence, early diagnosis of these infections and adequate treatment is necessary for their management. Modern antibiotic therapy may be greatly effective in reducing the spread of these infections in the head and neck, but it still requires continuous monitoring by a surgeon. Other factors that can aggravate space infection are the latest dental treatment and systemic conditions like diabetes mellitus and compromised immune systems such as acquired immunodeficiency syndrome (AIDS).

These patients clinically present with toothache, reduced mouth opening, rise in temperature, malaise, erythema, hoarseness of voice, and difficulty in swallowing. If left untreated or delayed in the treatment plan, it may result in acute airway obstruction or multiorgan failure, leading ultimately to death. Due to the recent advances in sampling and culturing, bacterial specificity has been depicted easily. The major pathogens that are found are the streptococci and anaerobic bacteria, which are regarded as normal flora of the tooth and gingival crevice.
Laboratories on routine basis culture for anaerobic microorganisms in oxygen-free gas environments, which increases the growth of anaerobic bacteria in culture. The serum markers function as predictors for disease progression, which leads to the existence of various inflammatory markers.28

Promoters of inflammatory markers explained various advantages for their utilization.

Quantitative determination of serum markers has proven to be effective in the determination of the efficacy of different treatment protocols.

Thus, due to the various advantages of serum inflammatory markers, many authors advised the use of prealbumin and CRP for the assessment of infection.29 Serum CRP is nearly absent in healthy individuals and increases significantly when tissue damage occurs in acute infection, tissue injuries, or inflammation, and its production is proportional to the severity of tissue damage. For the initial diagnosis of septicemia, the serum concentration of these CRP levels is important as they are found to be high. Thus, based on this sensitive and quick response of the serum CRP markers, an attempt has been made in this study to use space infection patients.

In this study, we found that quantitative serum CRP levels had a high degree of correlation with the severity of infection having a p-value < 0.05 from day 0, day 4, and day 8, which shows that serum CRP level is directly proportional to hospital stay, that is, as the hospital stay increases, CRP levels are found to be raised. These results are congruent with the study done by Ylijoki et al.30 This study reported that these markers are valuable as their values fluctuate during infection and attained normal range on the 8th postoperative day. Thus, this study proved that serum CRP is a significant predictor of the severity of infection and efficacy of treatment regime.31,32

Conclusion

Spreading space infections of odontogenic origin of the maxillofacial region remains surprisingly common and represents a wide spectrum of disorders from simple harmless swelling to life-threatening, airway-compromising conditions. The results of this prospective clinical study clearly demonstrate that the assessment of serum CRP can be an effective inflammatory marker for deciding the seriousness of space infection and the efficacy of broad-spectrum antibiotics and subsequently shows the immediate effect of the prescribed treatment. Beyond doubt, the role of the principles of incision and drainage for diagnosed space infection cannot be overlooked, and this should be supported by intravenous broad-spectrum antibiotics treatment based on culture and sensitivity test reports. To conclude, serum CRP levels as an assessment tool should be considered and incorporated for management of patients with fascial space infections of odontogenic origin.

Acknowledgments

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Patients’ Consent Form

Patients were explained about the procedure prior to the examination and explaining the treatment and research purpose with the provision to opt out of the study any time during the course of treatment without having to give any reason and then, a detailed informed written consent was taken from all interested patients in the presence of two witnesses.

References
