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C-REACTIVE PROTEIN AS AN INDICATOR TO DETERMINE THE TREATMENT OUTCOME IN MAXILLOFACIAL FRACTURES

Maxillofacial Surgery

Dr. Akshatha Kaniyoor* Lecturer, Department of Oral and Maxillofacial Surgery, Yenepoya Dental College. ORCID ID: 0000-0001-8109-8625 *Corresponding Author

Prof. (Dr.) B Rajendra Prasad Department of Oral and Maxillofacial Surgery, A B Shetty Memorial Institute of Dental Sciences, NITTE Deemed to be University, Mangalore, India.

Prof. (Dr.) Soumi Samuel Professor, Department of Oral and Maxillofacial Surgery, A B Shetty Memorial Institute of Dental Sciences, NITTE Deemed to be University, Mangalore, India.

ABSTRACT

Purpose: To evaluate levels of CRP with severity of maxillofacial trauma and to correlate it with the overall prognosis of the maxillofacial fractures after standardized surgical treatment. **Material And Methods:** A prospective study on C- reactive protein was conducted on subjects presenting with maxillofacial trauma reporting to the OPD-Department of Oral and Maxillofacial surgery, ABSMIDS for a period of 2 years. Patients with head injury, poly trauma, hepatocellular disease, cardiovascular disease, pneumonia or if the patient had a recent history of surgery in the past 1 month were excluded from the study after a detailed case history and clinical examination. A total of 119 subjects were included in the study and CRP levels were assessed preoperatively at the time of admission, post operatively after twenty four hours and on postoperative day four. **Results:** 106 patients included in the study reported within forty-eight hours of trauma and the levels of C- reactive protein in the body increased with the time elapsed since trauma, with the highest values at around forty-eight hours of trauma and lowest values when the patient reported immediately post trauma. 13 patients who reported after 48 hours of trauma were assessed separately. The fractures involving mandible showed significantly higher values of pre-operative CRP as compared to ZMC fractures ($p< 0.001$). On comparing the preoperative CRP values of fractures based on open (N=58; mean CRP- 22.75mg/L) or closed fractures (N=48; mean CRP -11.83), significant difference was found. Also on comparing between the single bone, two bone and multiple facial fractures statistically significant difference ($p<0.0001$, $p<0.002$, $p< 0.0001$ respectively) with a higher value on open fractures was seen. Irrespective of the approach used for a closed fracture, postoperatively the CRP values remained significantly lower as compared to the open fractures ($p<0.001$). Postoperatively on day four when CRP values were recorded the values reduced drastically beginning to normalize and we got a certain curve for CRP in maxillofacial trauma patients. This curve remained constant in open and closed fractures as well, with open fractures having a steeper curve and a longer period for CRP to normalize. **Conclusion:** The fractures of the facial skeleton is prone to infections due to the high bacterial flora present in the oral cavity. Awareness of the natural CRP responses after fractures may help in confirming the normal healing pattern for various bones, which can help us plan the correct treatment sooner thereby preventing the prolonged usage of antibiotics.

KEYWORDS

C- Reactive Protein, Maxillofacial trauma, Facial fractures, Treatment outcome

INTRODUCTION

Head injuries are the leading cause of death and major trauma for two and three wheeled motor vehicle users according to the WHO. India accounts for about 10% of the road crash fatalities worldwide. Among the injuries facial fractures is one of the common reason for presentation into the Accident and Emergency Departments.[1] Pedestrian, motorcycle or motor-vehicle accidents are most frequently implicated when compared to contact sports and recreational activities. Facial aesthetics is of utmost importance and failure to manage fractures of the facial skeleton can affect the quality of life of an individual.[2]

The sequel of a maxillofacial fracture will invariably lead to swelling which may be just an inflammatory response or as a result of infection, prior to treatment or post treatment. This makes it difficult for a surgeon to differentiate between the two since the latter can lead to complications. CRP is an acute-phase protein synthesized by the liver in response to a number of stimuli that involves tissue damage.[3,4]

CRP was first described in 1930 by Tillet and Frances in a patient with streptococcus pneumonia. They found a somatic polysaccharide which was nonspecific in nature and designated this as "Fraction C". Their study reported that this polysaccharide precipitated in the serum of acutely ill patients and it disappeared completely in about 3 days. Also the presence of this sera was not seen in healthy individuals.[5]

C-reactive protein now is considered a marker of inflammation and is superior to the conventional parameters (leukocyte counts, erythrocyte sedimentation rate) in detecting surgical complications with bacterial infection.[6,7] C-reactive protein is also considered to reflect the extent of surgical trauma.[8] It is sometimes difficult to differentiate between C-reactive protein elevation caused by post-operative infection and C-reactive protein elevation caused by surgery.[9] The maxillofacial fractures are often exposed to contamination by oral bacteria and therefore the possibility of infection always needs to be taken into account. It is important to know the kinetics of C-reactive protein post-surgery to identify deviations from the normal course in various fracture patterns so as to detect the infections early and provide a better outcome for patients.[10]

MATERIALS AND METHODS

Study Design

This prospective study on C- reactive protein was conducted on patients after obtaining informed consent from patients of all age groups presenting with maxillofacial trauma, reporting to the Department of Oral and Maxillofacial surgery, ABSMIDS, Mangaluru for a period of 2 years. This study was in accordance with with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and institutional ethical committee approval (ABSM/EC35/2017) for conducting the study was obtained. Patients with head injury, poly trauma, hepatocellular disease, cardiovascular disease, pneumonia, or if the patient had a recent history of surgery in the past 1 month were excluded from the study after a detailed case history and clinical examination.

Study Sample And Variables

A total of 119 patients (112 male and 7 female) after radiographic assessment for confirmation of the fractures were considered for surgical management. Patients included in the study belonged to all age groups with the maximum of 80 patients in the age group of 18-40 year old and road traffic accidents being the most common reason for the trauma. 106 patients mostly reported to our hospital within few hours or a day after trauma. About 13 patients reported to us after a few days after trauma and had already undergone primary management elsewhere. Among the 106 patients; single bone fractures were seen in 44 patients (closed fractures in 20 patients; open fractures in 24 patients) and 38 of them had mandibular fracture alone. Two bones were fractured in 12 patients (closed fractures in 7 patients; open fractures in 5 patients) and this was a rare scenario to be found. Multiple facial fractures was the most common finding in a road traffic accident with 50 patients (closed fractures in 21 patients; open fractures in 29 patients) fulfilling the study criteria. These multiple

facial fractures included zygomatico- maxillary complex fractures in 25 patients. Multiple facial fractures including the mandible was seen in 11 patients and 14 patients were admitted with comminuted or combination of multiple facial fractures except the mandible.

Treatment Protocol

The patients were operated under standard aseptic protocol of the department and after reduction of the fractures fixation was done using titanium miniplates and screws. Approach was extra-oral or intraoral or a combination of both depending on the fracture and also the existing laceration (contaminated/ clean –contaminated wounds) was explored whenever present. Patients were administered antibiotics as per standard regimen and analgesics for pain management.

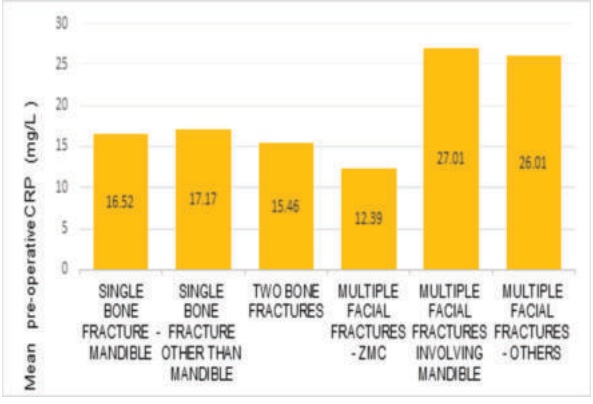
The CRP levels were assessed preoperatively at the time of admission, post operatively after twenty four hours and on post-operative day four. CRP levels were measured using the MISPA i2 from Agappe diagnostics which uses the latex enhanced nephelometry. The basis for the principle is that CRP samples bind to specific anti- CRP antibodies, which adsorb to the latex particles and agglutinates. The quantity of CRP in the sample was directly proportional to the agglutination.

Statistical Analysis

Statistical analysis was done using SPSS software where descriptive statistics is expressed in terms of percentage and frequency. Inferential statistics is dealt using Paired student T test, one way ANOVA and Pearson's analysis.

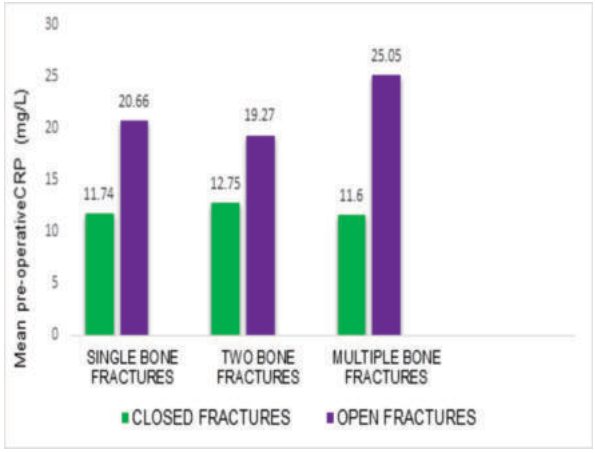
RESULTS

The patients who reported within forty-eight hours of trauma, the levels of C- reactive protein in the body increased with the time elapsed since trauma, with the highest values at around forty-eight hours of trauma and lowest values when the patient reported immediately post trauma. The pre-operative as well as 24 hour post-operative CRP between single bone, two bone and multiple facial fractures was found to be statistically insignificant. Pre-operative CRP values in single bone fracture of mandible ranged from 4.41mg/L to a highest value of 34.03mg/L with a mean of 16.52mg/L. Two bone fractures had a mean pre-operative CRP of 15.56 mg/L and had highest values in cases involving frontal bone fracture and mandibular fracture with 22.05mg/L and 23.5mg/L respectively. In the multiple facial fractures the zygomatico-maxillary complex fractures measured lowest CRP values with a mean of 12.39mg/L (Graph 1). The fractures involving mandible showed significantly higher values and was comparable with comminuted fractures with a mean of 27.01mg/L and 26.01mg/L respectively this was statistically significant as compared to ZMC fractures ($p < 0.001$).



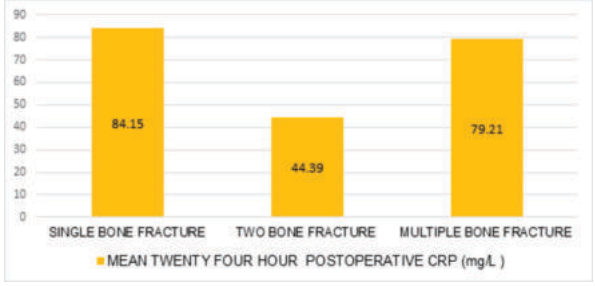
Graph 1: Mean pre-operative CRP for single bone, two bone and multiple facial fractures

On comparing the fractures based on open (N=58; mean CRP-22.75mg/L) or closed fractures (N=48; mean CRP-11.83), significant difference was found. Also on comparing within each group, statistically significant difference ($p<0.0001$, $p<0.002$, $p< 0.0001$ respectively) with a higher value on open fractures was seen (Graph 2). In single bone fracture, the highest CRP recorded was 34.03mg/L in an open mandibular para-symphysis fracture. Similarly two bone and multiple facial fractures also recorded 23.5mg/L and 42.51mg/L in open fractures involving mandible. But the highest value of 85.67mg/L was recorded in an open Lefort II fracture with NOE fracture and a mid-palatal split. Overall all the fractures with an open wound recorded comparatively higher values of CRP values irrespective of the bones involved.

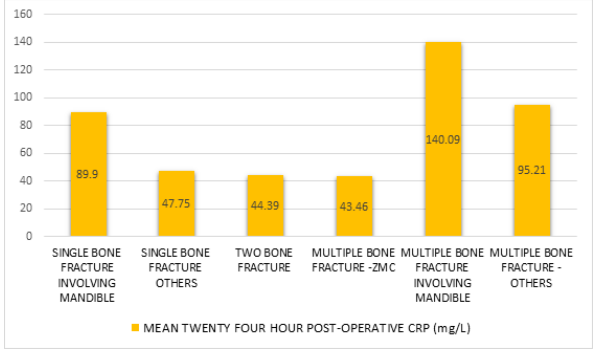


Graph 2 : Comparison of mean pre-operative CRP in closed and open fractures

Postoperatively after 24 hours, the single bone fractures recorded a mean CRP of 84.15mg/L and two bone fractures recorded a mean CRP of 44.39mg/L. The CRP values of single bone fractures postoperatively after 24 hours was comparable to the mean CRP recorded in case of multiple bone fractures measuring 79.21mg/L(Graph3) . Further, the multiple bone fractures involving the mandible had highest mean CRP values of 140.09mg/L with ZMC fractures recording a mean CRP value of 43.46mg/L and the comminuted multiple bone fractures recording mean CRP values of 95.21mg/L (Graph 4). This was found to be statistically significant ($p< 0.001$). The mean CRP values of the single bone fracture involving mandible was comparable with the comminuted multiple fractures of the face.



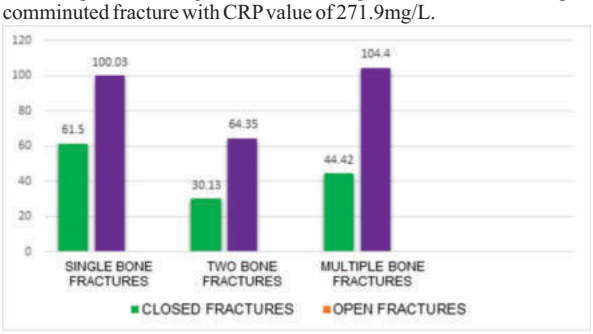
Graph 3: Mean twenty-four hour post-operative CRP



Graph 4: Mean twenty-four-hour post-operative CRP for single bone, two bone and multiple facial fractures

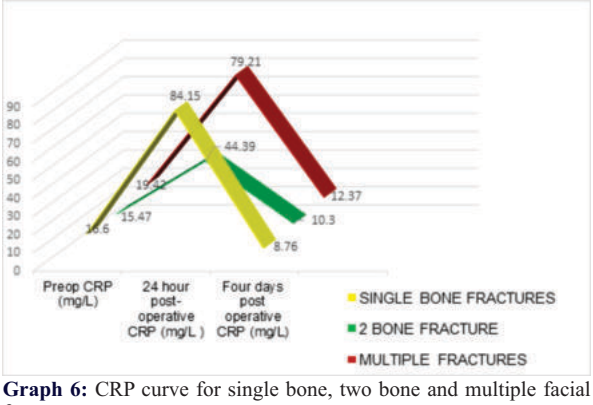
Irrespective of the approach used for a closed fracture i.e. an extra-oral skin incision or an intraoral vestibular incision the twenty four hour post-operative values of CRP consistently remained lower in single bone, two bone and multiple facial fracture groups (mean; 61.50mg/L, 30.13mg/L, 44.42mg/L respectively) as compared to the open fractures (mean; 100.03mg/L, 64.35mg/L, 104.40mg/L respectively)(Graph 5) and was found to be statistically significant ($p< 0.001$). In the open fractures, the single bone fractures recorded highest CRP value of 167.48mg/L in an open mandibular fracture, multiple facial fractures involving mandible recorded highest value of

188.59mg/L and the highest value in multiple fractures was in an open comminuted fracture with CRP value of 271.9mg/L.

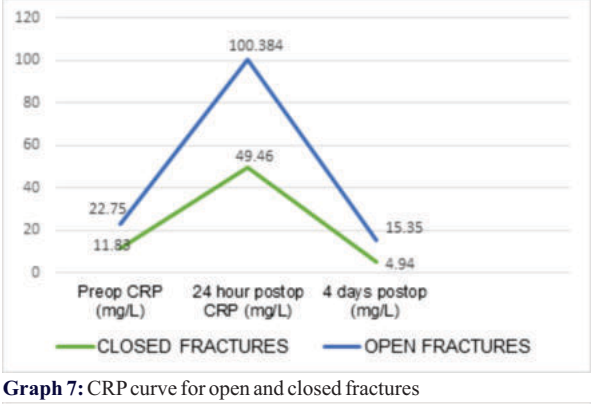


Graph 5: Comparison Of Mean Twenty-four Hour Post-operative CRP In Open And Closed Fractures

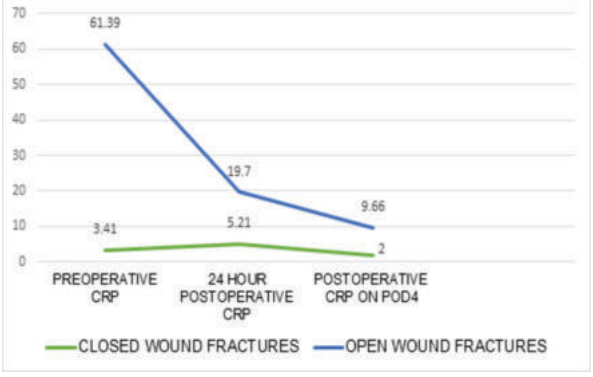
Postoperatively on day four when CRP values were recorded the values reduced drastically beginning to normalize. On comparing the preoperative, twenty-four hour post-operative and four days post-operative mean CRP values, we got a CRP response curve. (Graph6). This curve remained constant in open and closed fractures as well, with open fractures having a steeper curve and a longer period for CRP to normalize (Graph 7).



Graph 6: CRP curve for single bone, two bone and multiple facial fractures



Graph 7: CRP curve for open and closed fractures



Graph 8: CRP curve comparison in patients who reported after primary management.

Among the 13 patients who reported later, there were 5 patients with closed fractures and 8 patients with open fractures (Graph 8). On analyzing the CRP values in open fracture patients showed a different pattern with the values dropping drastically twenty-four hours post-surgery, indicating that removing the cause of infection with through debridement followed by fracture fixation is a key factor in the prognosis of open fractures. The CRP response curve for closed fractures in these patients followed the same curve as the one for patients who reported immediately, with no drastic rise in the CRP value postoperatively. In closed fracture patients who reported immediately, post-operatively low to moderate rise in CRP was seen as compared to the open fractures. This lead us to conclude that the bacterial flora communicating with the fracture causing infection is mainly responsible for the rise in CRP rather than the surgical trauma itself.

DISCUSSION

C-reactive protein is an acute-phase protein synthesized by the liver in response to a number of stimuli that involve tissue damage. Trace amount of CRP is present in healthy people in the blood serum. Stimulation of macrophage caused by tissue damage is necessary for CRP synthesis. Interleukin 6 (IL-6) is the most important factor that stimulates CRP synthesis as well as all other acute phase proteins.[11]

Previous studies have shown that the normal pre-operative CRP level after fracture is slightly increased. Patients treated conservatively never reach the CRP levels seen in patients after operative treatment.[12] The CRP response does not appear to be correlated with age, sex of the patient, amount of bleeding, transfusion, drugs administered, or the type of anesthesia.[13]

In the absence of infections, the increase was interpreted as being solely an effect of tissue damage during surgery. C-reactive protein levels reflect the extent of the surgical trauma, and the C-reactive protein value on the second post-operative day is a crude measure of the degree of operative trauma.[14, 15] *Also* previous studies showed that the increase in CRP depended not only on the amount of tissue injured but also on the type of tissue being damaged—such as bone, fat, or muscle.[13]

In our study, the CRP concentrations depended on the bone involved in the fracture, with mandibular fractures showing highest concentrations of CRP and found no correlation with the number of bone fractures on the face. This correlates with the findings of a previous study where they proposed that this may be due to the proportion of medullary cavity tissue damaged in the bone.[14] Macrophages, which are important in the development of acute-phase proteins such as CRP, are common in bone/marrow while being less prevalent in muscle tissue.[13] Another study substantiates similar findings with higher peak CRP levels in patients undergoing arthroplasty than in patients with dynamic hip screws suggesting that trauma to the bone marrow is crucial for the CRP response.[15]

C- reactive protein is considered to be superior to the conventional parameters (leukocyte counts, erythrocyte sedimentation rate) in detecting surgical complications with bacterial infection.[6] Sometimes it becomes difficult to differentiate between C-reactive protein elevation caused by post-operative infection and C-reactive protein elevation caused by surgery. To detect infections earlier, it is important to know the kinetics of C-reactive protein after surgery. Bacterial complications have been described as being accompanied by a rise of C-reactive protein values, but no characteristic behavior of serum levels relating to specific types of complications or cut-off levels are given.[5, 1] Studies have shown that a second rise of C-reactive protein values after the decline after the second post-operative day indicates a complication. The second rise in C-reactive protein level and the absolute numerical C-reactive protein values are important and related to the severity of the complication. [10] In our study we did not have any patient whose post-operative day four CRP was higher than the twenty- four-hour post-operative CRP. But the patients with open fractures took longer than the closed fracture patients for their CRP concentrations to normalize post-surgery.

Previous studies have proved that the second rise and a persistent elevation of C-reactive protein is a key indicator for post-operative infection. Having said that, C-reactive protein levels always must be correlated to the clinical situation because every bacterial inflammation can cause high levels of C-reactive protein (pulmonary

infection). No laboratory value alone can account for clinical decision making.[10]

CONCLUSION

In maxillofacial trauma, CRP can be used as a reliable tool for assessment of the regularity of ossification and correlating with the reparative processes. The fractures of the facial skeleton is prone to infections due to the high bacterial flora present in the oral cavity. When the bone healing takes place correctly the values of CRP is low. However, a rise in CRP is seen when bacterial infection interrupts the healing process. Awareness of the natural CRP responses after fractures may help in confirming the normal healing pattern for various bones, thereby diagnosing the post-traumatic and post-operative complications early. This can help us plan the correct treatment sooner and preventing the prolonged usage of antibiotics with a shorter hospital stay.

Consent For Publication:

All co-authors have reviewed the contents of the manuscript and agreed to submit the same for publication. This is an original study that has not been previously published and not under consideration for publication elsewhere.

Declaration of Interests: None

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