ISSN- O: 2458 - 868X, ISSN –P: 2458 - 8687

International Journal of Medical Science and Innovative Research (IJMSIR)

IJMSIR : A Medical Publication Hub

Available Online at: www.ijmsir.com

Volume – 3, Issue –1, February - 2018, Page No. : 86 - 93

To Evaluate The Efficacy of Serum C-Reactive Protein As Inflammatory Marker In Oral And Maxillofacial Surgeries

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Type of Publication: Original Research Paper

Conflicts of Interest: Nil

Abstract

Purpose: To evaluate efficacy of the serum C-reactive protein as an inflammatory marker in Oral and Maxillofacial Surgeries.The objective of the study was to determine the CRP levels preoperatively, immediate postoperatively, 3rd, 5th and 7thpost-operative days in 30 patients who underwent Maxillofacial Surgical procedures.

Materials and methods: A 23 gauge needle was used to draw 2 cc of blood initially with tourniquet stasis to identify the vein, and tourniquet was removed once the blood started to flow into the syringe to qualitatively assess the CRP levels preoperatively, immediate postoperatively, 3rd, 5th and 7th post operative days. Additional clinical parameters such as the pain, swelling, mouth opening, treatment efficacy and hospital stay were also noted.

Results: the CRP levels increased by the end of 3rd day, which is due to initial immediate inflammation and soft tissue injury caused by the surgery. The additional clinical parameters which were observed such as pain and swelling were more in the first 3 days with the reduced mouth opening. Gradually mouth opening increased with decreased pain and swelling by the end of 7 days. The decrease in CRP levels after the 3rd postoperative day indicated that prognosis for the treatment was good (Treatment efficacy).

Conclusion: It can be concluded that C- reactive protein an inflammatory marker is a reliable, consistent and simple prognostic tool to evaluate post operative inflammation, treatment efficacy and hospital stay.

Key words: Serum C-reactive protein, pain, swelling, mouth opening, treatment efficacy, hospital stay, inflammatory markers.

Introduction

The stimulation of a variety of inflammatory mediators takes place immediately after trauma or surgical procedures. At the molecular level, a variety of inflammatory mediators has been implicated in the pathogenesis of inflammation. Serum markers of immune reactivity can be selectively grouped into markers of acute phase reactants (lipopolysaccharide-binding protein, C-reactive protein, procalcitonin), mediator activity {TNF (Tumor necrosis factor), IL-1(interleukins-1), IL-6, IL-10, IL-18}, cellular activity (TNF-RI, TNF-RII, IL-1R-I) [1].

C-reactive protein (CRP) was discovered in Oswald Avery's laboratory during the course of studies of patients with Streptococcus pneumonia infection. Sera obtained from these patients during the early, acute phase of the illness were found to contain a protein that could precipitate the "C" polysaccharide derived from the pneumococcal cell wall. C-reactive protein is one of the common test parameters used in clinical practice to diagnose and assess the prognoses of inflammation, tissue injury and infection. CRP is phylogenetically a highly conserved plasma protein, with homolog in vertebrates and many invertebrates that participates in the systemic response to inflammation. Its plasma concentration increases during inflammatory states, a character that has long been employed for clinical purposes. CRP is produced in many sites within the human body. It is produced in the liver in response to release of pro-inflammatory cytokines like IL-6. It is also produced in very limited concentration by non-hepatic cells like neurons, atherosclerotic plaques, monocytes, kupffer cells and lymphocytes[2]. As serum C-reactive protein levels increase in response to inflammation in the postoperative period of Oral and Maxillofacial Surgeries, this study was undertaken to know its efficacy as an inflammatory marker and prognosis of the treatment. In this study other observations such as pain, swelling, mouth opening, treatment efficacy and hospital stay were also observed. A total number of 30 patients who underwent Maxillofacial Surgeries are included in this prospective study.

Materials and methods

Source of data

This prospective study was carried out in a total number of 30 patients, who reported to the Department of Oral and Maxillofacial Surgery, GITAM Dental College and Hospital, Visakhapatnam. Patients with maxillofacial trauma and pathological lesions who are fit to undergoing the surgical procedures were included in the study.

The institutional review board with ethical clearance was taken before the study. A thorough clinical history was taken followed by detailed clinical and radiological examination. The major surgical procedure investigations done preoperatively were complete hemogram, bleeding time, clotting time, viral screening, serum urea, serum creatine, routine urine analysis, chest x – ray, ECG and qualitative analysis of CRP. The written informed consent for the study and laboratory procedure was obtained.

Inclusion criteria

- Patients who are fit to undergo major surgical procedures.
- Patients willing to participate in the study.

Exclusion criteria

- Medically compromised patients who are not fit for major surgical procedures.
- Syndromic patients.
- Patients who are not willing to participate in the study.
- Patients under steroid therapy.

Methods

C-reactive protein (CRP) is a sensitive marker for inflammation, infection and tissue damage, and also

contributes to the host defense against infection by activating the compliment pathway. C-reactive protein (CRP) is an acute phase reactant produced by liver under the control of cytokines, especially by interleukin-6. CRP is commonly measured as a acute phase protein in inflammatory, infectious and neoplastic cases and in tissue damage for a long time. Under aseptic conditions, initially hands should be cleaned and absolute alcohol applied to hands before wearing gloves to prevent contamination to the operator from patient's blood. The site of the proposed venipuncture i.e. brachial vein in the antecubital fossa or forearm should be wiped with an alcohol swab. After cleansing, skin must not be touched. Apply a tourniquet medial to selected site. Fix the vein by applying pressure to skin over the vein, approximately two inches below venipuncture site. Approach the skin, with needle bevel uppermost at an angle of 35-45 degrees, when the needle has penetrated the skin, realign it with the vein and reduce the angle to about 15 degrees. As soon as blood starts to flow into the tube, remove the tourniquet. When blood flow ceases and 2ml blood taken, withdraw the needle from vein. The blood sample was transferred to plain sterile glass test tubes. Contracted clot is centrifuged at 4000 rpm for 20 min at 4 degree Celsius and the top layer of clear serum in the tube was separated with the help of a micropipette. Serum collected was mixed with buffer and antibody. CRP in the sample combines specifically with anti-human CRP in the reagent to yield an insoluble aggregate that causes increased turbidity in the solution. The degree of turbidity of the solution was measured optically which is proportional to the amount of CRP in the patient's sample.

Principle: Serum C-reactive protein (CRP) causes agglutination of the latex particles coated with anti-human C-reactive protein. The agglutination of the latex particles is proportional to the CRP concentration and can be measured by turbidimetry.

Reagent 1: Glycine buffer ≤ 0.15 mol/L, Sodium azide ≤ 0.99 g/L, pH 8.6.

Reagent 2: Suspension of latex particles coated with antibody CRP,

Sodium azide <0.99 g/L.

Pain was evaluated subjectively by Faces pain rating scale (VAS). This scale combines pictures and numbers to allow pain to be rated by the patient. The faces range from smiling face to sad and crying face. A numerical rating has been assigned to these faces, ranging from 0 to 10 in ascending order, proportionate to increase of pain. The patient is asked to rate his or her pain using appropriate picture. Swelling was assessed with a five-line measurement using a standard plastic tape measure (accuracy ± 0.5 mm) placed in contact with the skin preoperatively, immediate postoperative, 3rd, 5th and 7th post operative days.

Line a: Most posterior point of the tragus to most lateral point of the lip commissure.

Line b: Most posterior point of the tragus to pogonium.

Line c: Most posterior point of the tragus to lateral canthus of the eye.

Line d: Lateral canthus of the eye to most inferior point angle of the mandible.

Line e: Most inferior point angle of the mandible to middle of the nasal bone.

Marking endpoints for subsequent tape measurements were drawn, using a fine water-proof tip pen. Maximal mouth opening was recorded measuring the maximum inter-incisal distance using callipers.

In this study statistical analysis was done by using **paired t test.**

Results & Discussion

Efficacy of CRP as an inflammatory marker in Oral and Maxillofacial Surgical procedures was done by measuring CRP levels in 30 subjects preoperatively, immediate postoperatively, 3rd, 5th and 7thpost operative days. Additional clinical parameters such as pain, swelling, mouth opening, treatment efficacy and hospital stay were also noted. The comparison of CRP levels between preoperative and immediate post operative, 3rd, 5th and 7th postoperative days is illustrated in the Table 1 shows, values of which are 1.12, 1.39, 1.89, 0.91 and 0.68 respectively. Comparison between preoperative to immediate and 3rd postoperative day was statistically highly significant (p<0.01). Comparison of preoperative to 5th and 7th postoperative days were statistically non significant (p<0.51, 0.16 respectively). It can be inferred that CRP levels increased till the 3rd postoperative day and then decreased by 7th postoperative day, which can be attributed to the initial inflammation present immediately post surgery due to tissue injury caused while surgery, which gradually decreases by the end of 7th day.

Parameters	Time	Mean	SD	P-Value	Inference
CRP	Pre OP	1.12	1.85	<0.01	HS
	Immediate	1.39	1.90		
	Pre OP	1.12	1.85	<0.01	HS
	3rd Day	1.89	1.71		
	Pre OP	1.12	1.85	0.51	NS
	5thDay	0.91	0.42		
	Pre OP	1.12	1.85	0.16	NS
	7th Day	0.68	0.38		

Table 1: Comparison of CRP levels between preoperative and immediate post operative, 3rd, 5th and 7th postoperative days.

The comparison of pain between preoperative and immediate post operative, 3rd, 5th and 7th postoperative days is illustrated in the Table 2 shows, values of which are 2.53, 3.07, 3.33, 2.33 and 1.33 respectively. The comparison between preoperative to immediate, 3rd and 5th day postoperative day was statistically Non Significant (p<0.07, 0.09, 0.55 respectively). Comparison of preoperative to 7th postoperative days showed statistically Highly Significant (p<0.01). It can be inferred that pain is more for the first3 days, which could be because of presence of immediate post operative inflammation. Pain decreased by the end of one week, when compared to preoperative value, as the inflammatory phase gradually decreases by time.

Parameters	Time	Mean	SD	P-Value	Inference
Pain	Pre OP	2.53	1.81	0.07	NS
	Immediate	3.07	0.87		
	Pre OP	2.53	1.81	0.09	NS
	3 Day	3.33	1.45		
	Pre OP	2.53	1.81	0.55	NS
	5 Day	2.33	0.71		
	Pre OP	2.53	1.81	<0.01	HS
	7 Day	1.33	0.80		

Table 2: Comparison of Pain between preoperative and immediate post operative, 3rd, 5th and 7th postoperative days. The comparison of swelling between preoperative and immediate post operative, 3rd, 5th and 7th postoperative days is illustrated in the Table 3 shows, values of which are 12.20, 12.55, 12.71, 12.48 and 12.30 respectively. The comparison between preoperative to immediate, 3rd, 5th day postoperative days was statistically Highly Significant (p<0.01). Comparison of preoperative to 7th postoperative days showed statistically Non Significant (p<0.18). It can be inferred that swelling is more in the first 5 days, which can be attributed to the initial inflammation present immediately post surgery due to tissue injury caused during surgery, which decreases by time that is by the end of seven days when compared to preoperative values.

Parameters	Time	Mean	SD	P-Value	Inference
Swelling	Pre OP	12.20	0.73	<0.01	HS
	Immediate	12.55	0.78		
	Pre OP	12.20	0.73	<0.01	HS
	3 Day	12.71	0.88		
	Pre OP	12.20	0.73	<0.01	HS
	5 Day	12.48	0.84		
	Pre OP	12.20	0.73	0.18	NS
	7 Day	12.30	0.83		

Table 3: Comparison of swelling between preoperative and immediate post operative, 3rd, 5th and 7th postoperative days.

The comparison of mouth opening between preoperative and immediate post operative, 3rd, 5th and 7th postoperative days is illustrated in the above Table 4 shows, values of which are 29.50, 24.93, 30.57, 33.77 and 35.80 respectively. The comparison between preoperative to immediate, 3rd, 5th day postoperative days were statistically Non Significant (p<0.07, 0.62, 0.06). Comparison of preoperative to 7th postoperative days were statistically Highly Significant (p<0.01). It can be inferred that mouth opening is decreased in immediate postoperative day, which can be attributed to the initial inflammation present immediately post surgery due to tissue injury caused during surgery. At the end of seven days mouth opening gradually increased.

	Time	Mean	SD	P-Value	Inference
Mouth opening	Pre OP	29.50	12.76	0.07	NS
	Immediate	24.93	8.13		
	Pre OP	29.50	12.76	0.62	NS
	3 Day	30.57	7.49		
	Pre OP	29.50	12.76	0.06	NS
	5 Day	33.77	7.30		
	Pre OP	29.50	12.76	<0.01	HS
	7 Day	35.80	8.54		

Table 4: Comparison of Mouth Opening between preoperative and immediate post operative, 3rd, 5th and 7th postoperative days.

Based on the statistical observations it can be understood that the CRP levels increased by the end of 3rd day, which is due to initial immediate inflammation and soft tissue injury caused by the surgery. The additional clinical parameters which were observed such as pain and swelling were more in the first 3 days with the reduced mouth opening. Gradually mouth opening increased with decreased pain and swelling by the end of 7 days. The decrease in CRP levels after the 3rd postoperative day indicated that prognosis for the treatment was good (Treatment efficacy). Out of 30 patients in this study, 27 patients had been admitted in the hospital for 5 days and 3 patients for 3 days .

Maxillofacial Surgeons routinely encounter patients with facial trauma and pathological lesions. The sequel of Maxillofacial Surgical procedures will invariably lead to swelling and pain which can be attributed to inflammatory response. The acute-phase response (APR) is critical to the body's ability to successfully respond to injury. It normally lasts only few days; however, the acute phase response may contribute to the development of chronic inflammatory states, tissue damage and disease[3]. The acute phase response is typically characterized by fever and changes in vascular permeability, along with profound changes in the biosynthetic profile of various acute phase proteins[4]. Acute phase proteins (APP) are an evolutionarily conserved family of proteins produced mainly in the liver in response to inflammation. There are many laboratory investigations to evaluate the prognosis of healing by using inflammatory markers such as interleukins (IL) 1-17, interferons, tumor necrosis factor (TNF), fibrinogen, serum amyloid A (SAA),

ceruloplasmin, alpha$_1$ - antichymotrypsin (A_1CT), alpha$_1$ - antitrypsin (A_1AT) and C-reactive protein (CRP).

Out of various acute phase proteins, C- reactive protein is very consistent in response. Therefore, it is the most satisfactory single screening test for an acute phase reactant and a useful marker for the amount of tissue injury and inflammation. So this study was undertaken to evaluate the efficacy of serum C- reactive protein as inflammatory marker in Maxillofacial Surgeries. Among all the pro-inflammatory markers C- reactive protein is an inexpensive and simple test to assess inflammation[5].

Serum CRP is nearly absent in healthy individuals and increases significantly when tissue damage occurs during inflammation and tissue injuries. CRP is one of the most sensitive acute phase reactants. It increases rapidly in response to many disease conditions[6.] Various factors known to effect the level of C – reactive protein were anaesthetic technique, stress, increases with ageing, increased blood pressure, smoking, coffee, alcohol consumption, decreased physical activity ,raised levels of triglycerides, insulin resistance[7], diabetes, high protein diet, chronic tiredness, suffering from sleep disturbances and depression,obesity, physical inactivity. In this study CRP levels were assessed at time intervals of 24 hrs 3, 5 and 7 days post operatively which is similar to the time interval in the study done by Ohzato et al[8] and Giannoudis PV et al[9] in trauma victims. Lizuka[10] carried out a study on 80 patients who underwent treatment for mandibular fracture with osteosynthesis by rigid fixation using AO/AISF principles in which the levels of CRP were assessed. It correlates with this study where the CRP levels showed a gradual increase.

This increase in CRP value can be attributed to surgical trauma. On the seventh day, CRP levels decreased indicate normal healing at surgical site in both the studies. Another study with similar findings was reported by Werner[11] which stated that the levels of beta globulins including CRP increased in response to trauma as well as surgery which were raised in serum after initial trauma.The marked rise in CRP levels from day 1-3 followed by its decline on day 8 as observed in this study is in coherence with the previous study by Claudia et al[15]. The maximal generation of CRP on the third day can be linked to high levels of circulating IL-6 release which evidently precedes the equivalent production of CRP by at least 12 hours.

Schentaget al.[5], noted that patient with abdominal sepsis who could not be treated by antibiotics alone and needed surgery and antibiotics had a higher CRP level preoperatively indicating infection. CRP levels raised after surgery and reduced to normal after the seventh post-operative day indicating normal healing at the surgical site. In this study the patients included were the ones with pathological lesions for whom no prior antibiotics were given and trauma patients who required a prior dose of antibiotics preoperatively, the CRP levels raised after surgery due to surgical trauma in both groups of patients. Normal CRP levels after the seventh day postoperatively indicating normal healing at the surgical site.

In this study C-reactive protein (CRP) had a high degree of correlation with severity of inflammation having P value <0.01 from Day 1 to Day 3. These results were similar to those found in a study conducted by the Ren et al[6] CRP levels increased till the 3rd postoperative day and then decreased by 7th postoperative day. From the above observations this study suggests that the C-reactive protein is a good pro-inflammatory marker.

The increase in the C- reactive protein levels in the first 3days can be attributed to the increase in pain and swelling immediate post operatively and decrease in mouth opening. So this study suggests that C- reactive protein is good indicator of inflammation post operatively.

Additional parameters being hospital stay and treatment efficacy was also observed. It was seen in this study that C- reactive protein was also significant predictor for hospital stay as most of the patients were discharged at the end of five days when there was a significant decrease in the level of C- reactive protein compare to the first few days of the operation. The regression equation shows that there was a linear relationship between CRP and hospital stay i.e. higher the CRP level more was hospital stay. According to Yeh Edward T et al.[12] C-reactive protein is not only a marker but also an amplifier of inflammation. Since inflammation is believed to have a role in the pathogenesis of post-operative events, measurement of inflammatory markers has been proposed as a method to improve the prediction of the risk of these events.

In this study the concentrations of CRP are significantly high with severity of inflammation. CRP has direct and linear relationship with size of swelling and pain; it is inversely related to the mouth opening. These results are in accordance with the results obtained by Ylyjokiet al[13] and Ren FY et al[14], who along with these parameters found CRP to be a significant predictor for hospital stay and assessment of treatment efficacy.

According to the above observations made in this study it can be concluded that C- reactive protein is a good inflammatory marker post Maxillofacial Surgeries which can be helpful in the assessment of treatment efficacy and also the hospital stay.

Further studies can be done to establish the significance of serum C- reactive protein as an inflammatory marker in Maxillofacial Surgery with few additional parameters such as duration of surgery, preoperative inflammatory condition, type of anaesthesia, measurement of amount of stress preoperatively, intraoperatively and postoperatively and assessment of amount of tissue injury. It was suggested that further studies with large sample size and inclusion of the above parameter should be carried out for establishment of C- reactive protein as an inflammatory marker and good prognostic tool in Maxillofacial Surgeries.

Conclusion

In this study the clinical parameters such as pain, swelling, mouth opening, treatment efficacy and hospital stay were in correlation with the CRP levels. Increased CRP levels were noticed in the initial inflammatory phase i.e. first three post operative days where there is increased pain and swelling with decreased mouth opening. At the end of 5th day with decreased inflammatory signs there were decreased CRP levels, which determined the treatment efficacy. Most of the patients were discharged at the end of 5th day with decreased CRP levels which can be attributed to the treatment efficacy and thus determining the length of hospital stay. It can be concluded that C-reactive protein an inflammatory marker is a reliable, consistent and simple prognostic tool to evaluate post operative inflammation, treatment efficacy and hospital stay.

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