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ESTIMATION OF C-REACTIVE PROTEIN ASSOCIATED WITH FRACTURES OF THE FACIAL SKELETON

Dental Science

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ABSTRACT

BACKGROUND- An elevated level of C-reactive protein (CRP), an acute phase protein, is one of the many downstream indicators of inflammation. CRP levels could predict septic complications before their clinical manifestation. This study was conducted to compare the pre-operative, first and seventh post-operative day CRP levels inorder to ensure uneventful healing post-operatively in fractures of the facial skeleton. Thirty adult patients in need of Open Reduction and Internal Fixation (ORIF) for fractures of mid-face and mandible and consented for the same were included in the study. Serum was collected to evaluate the pre-operative CRP level. The patients were operated under general anesthesia and ORIF was carried out. Serum was collected on the first and seventh post-operative day (POD) and levels were noted. In our study, CRP levels were compared at different time points in facial fractures. A significant difference was observed when pre-operative and POD-1 CRP levels were compared with POD-7 levels, showing that on POD-7 the levels decreased in all cases indicating normal healing. There were no studies or statistical analysis in literature to show the comparison of CRP levels in mid-face and mandible fractures. Our study showed that there is no significant difference in both of the above.

KEYWORDS

C-Reactive Protein, Facial Fractures, Open Reduction And Internal Fixation, Mandibular Fractures, Mid-face Fractures.

INTRODUCTION

C-reactive protein (CRP) was discovered in 1930 by William Tillett and Thomas Francis from the Rockefeller University. They described a third serologic fraction, or "fraction C," that could be isolated from patients infected with pneumococcus that was distinct from previously known capsular polysaccharide and nucleoprotein fractions detectable by specific antibody response. A decade later, Oswald Avery and Maclyn McCarty described CRP as an "acute-phase reactant" that was increased in serum of patients suffering from a spectrum of inflammatory stimuli, including myocarditis and the inflammation associated with rheumatic fever [1].

Maxillofacial surgeons encounter patients with facial trauma routinely. The sequel of facial fractures will invariably lead to swelling which may be just an inflammatory response or as a result of infection, prior to treatment or post-treatment which makes it difficult for a surgeon to differentiate between the two. Various laboratory investigations are available to evaluate the prognosis of healing. Inflammatory markers are routinely measured in frozen serum using standardized assays like C-reactive protein (CRP), interleukin (IL-6), Tumor necrosis factor (TNF), and soluble receptors (IL-2 sR, IL-6 sR, TNF sR1 and TNFsR2). White blood cell (WBC) count, absolute neutrophil count (ANC) and CRP estimations are the biomarkers that are considered. But CRP is gaining importance off late [2].

Bacterial infection is a particularly potent stimulus which causes marked elevation in serum CRP levels within a few hours. In the plasma, C-reactive protein appears as early as 2 hours after the trauma and it reaches its peak 48–72 hours after the injury. It returns to normal after 6–7 days in non-infected cases. However, its value rises when the healing is interrupted by a bacterial infection [2].

The routinely administered anti-bacterial prophylaxis may be terminated when plasma CRP level normalizes and hence avoids prolonged antibiotics [2].

METHODS

Thirty patients with fracture of the facial skeleton due to trauma were selected for our study. 15 patients had mid-face fracture (13 male and 2 female) and the other 15 patients had mandibular fracture (14 male and 1 female). Pre-operative radiograph was taken to assess the location of the fractures. Patients were operated under GA and ORIF was carried out in all the patients. CRP concentration was determined pre operatively, post-operative day one and on the seventh post-operative day. Patients with malnutrition, endocrinology ailments, immunology ailments, liver and cardiovascular disorders, patients having acute infection following trauma and those who have not consented for the study were excluded from the measurements. Informed consent was obtained from all individual participants included in the study.

MATERIALS

VITROS CRP Slides
VITROS 5600 Integrated System
VITROS Immuno-Wash Fluid
Syringe with hypodermic needle, alcohol swab

The cubital fossa was cleansed with antiseptic solution and venipuncture was done. A 23 gauge needle was used to draw 3 cc of blood without tourniquet stasis. Contracted clot was centrifuged.

A drop of patient serum sample was deposited on VITROS CRP slide and was evenly distributed by the spreading layer to the underlying layers. CRP in the sample binds to PC-linked capture beads and anti-CRP antibody labelled with horseradish peroxidase to form an insoluble sandwich complex.

The subsequent addition of 12µl of VITROS Immuno-Wash Fluid to the slide removes unbound materials from the read area, while also providing the hydrogen peroxide required for the enzyme-mediated oxidation of leucodye.

The reflection density of the dye was measured after the addition of VITROS Immuno-Wash Fluid. This reflection density is directly proportional to the concentration of CRP in the sample.

RESULTS

Our study included 15 cases of mid-face (13male and 2 female) and 15 cases of mandibular fractures (14 male and 1 female) that were treated with ORIF under GA.

The mean CRP values between different time points were compared of all the patients. And we observed that there was no significant difference in CRP values between pre-operative and POD-1 ($p=0.148$). There was a significant decrease in CRP levels on POD-7 when compared to the levels pre-operatively and on POD-1 ($p<0.05$), hence confirming normal healing pattern. (Tables 1,2).

Also, the CRP levels in mid-face fractures were compared. Here, we observed that there was no significant difference in CRP values between pre-operative and POD-1($p=0.077$). But when pre-operative

and POD-1 with POD-7 values were compared, we observed a significant decrease in CRP levels on POD-7 with p values 0.042 and 0.005 respectively, which is an indication that there was no sign of infection clinically as well as, in CRP values. (Tables 3,4)

The CRP levels in mandibular fractures were compared. We observed that there was no significant difference in CRP values between pre-operative and POD-1 (p=0.989). But when pre-operative and POD-1 with POD-7 values were compared, we observed a significant decrease in CRP levels on POD-7 with p values 0.028 and 0.013 respectively, which is an indication that there was no sign of infection clinically as well as, in CRP values. (Tables 5,6)

The C-reactive protein levels pre-operatively, on POD-1 and on POD-7 between mid-face and mandibular fractures were also compared. Here, we observed that there was no statistically significant difference in CRP values at any time points between mid-face and mandibular fractures which indicates that there is a similar pattern of changes in CRP levels in mid-face and mandibular fractures. (Table 7)

DISCUSSION

In 1930, Tillett and Francis discovered C-reactive protein as they were investigating serological reactions in pneumonia with various extracts of pneumococci and observed a non-specific somatic polysaccharide fraction, which they designated as "Fraction C", which were found to be precipitated by the sera of acutely ill patients. After the crisis, the capacity of the patient's sera to precipitate C-polysaccharide (CPS) rapidly disappeared and the C-reactive material was not found in sera of normal healthy individuals [2]. Avery et al characterized the C-reactive material as a protein which required calcium ions for its reaction with CPS and introduced the term 'acute phase protein' to refer to sera from patients acutely ill, with infectious diseases, which contains the CRP.

D.N Kiran et al [2] in 2012, studied 25 patients who underwent treatment for mandibular fractures with osteosynthesis by rigid fixation using AO/ASIF principles and correlated the prognosis of the convalescent period. They noticed that the CRP levels were high pre-operatively and an increase was noticed immediately after the surgery and after 24 hours of surgery. On the seventh day after the surgery, CRP levels were significantly decreased, indicating normal healing at the surgical site.

In both, mid-face and mandibular fractures, we have obtained a similar pattern of change in CRP levels where there was a statistically significant decrease in POD-7 values compared to pre-operative and POD-1 values. The values of mid-face and mandibular fractures were compared and has shown a similar pattern of change in CRP levels.

In our study, none of the cases showed an increase in CRP levels on POD-7. The levels of CRP decreased from POD-1 to POD-7 which is an indication that there was no sign of infection clinically as well as, in CRP values.

TABLE No.1 Comparison of CRP levels pre-operatively, at POD-1 and at POD-7

	Mean	N	Std. Deviation
CRP 1 (pre-operative)	15.183	30	13.2155
CRP 2 (POD-1)	20.467	30	15.9574
CRP 2 (POD-1)	20.467	30	15.9574
CRP 3(POD -7)	8.547	30	4.8815
CRP 1 (pre-operative)	15.183	30	13.2155
CRP 3(POD -7)	8.547	30	4.8815

TABLE No.2 Comparison of changes in CRP levels pre-operatively, at POD-1 and at POD-7

	Paired Differences					T	Df	p-value
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
CRP 1 (pre-operative) - CRP 2 (POD-1)	-5.2833	19.4722	3.5551	-12.5544	1.9877	-1.486	29	.148
CRP 2 (POD-1) - CRP 3(POD -7)	11.920	15.4838	2.8269	6.1382	17.7018	4.217	29	.000
CRP 1 (pre-operative) - CRP 3(POD -7)	6.6367	11.8116	2.1565	2.2262	11.0472	3.078	29	.005

***Paired Samples Test**

TABLE No.3 Comparison of CRP values (pre-operative, POD-1, POD-7) in mid-face fractures

	Mean	N	Std. Deviation
CRP 1 (pre-operative)	13.2267	15	13.05135
CRP 2 (POD-1)	23.7333	15	20.63903
CRP 2 (POD-1)	23.7333	15	20.63903
CRP 3(POD -7)	7.4600	15	2.82307
CRP 1 (pre-operative)	13.2267	15	13.05135
CRP 3(POD -7)	7.4600	15	2.82307

TABLE No.4 Comparison of CRP values (pre-operative, POD-1, POD-7) in mid-face fractures.

	Paired Differences					t	df	p-value
				95% Confidence Interval of the Difference				
	Mean	Std. Deviation	Std. Error Mean	Lower	Upper			
CRP 1 (pre-operative) - CRP 2 (POD-1)	-10.50667	21.30994	5.50220	-22.30772	1.29438	-1.910	14	.077
CRP 2 (POD-1) - CRP 3(POD -7)	16.27333	18.72361	4.83441	5.90454	26.64212	3.366	14	.005
CRP 1 (pre-operative) - CRP 3(POD -7)	5.76667	12.10016	3.12425	-.93418	12.46751	1.846	14	.042

a. Site = Midface

*Paired Samples Test

TABLE No.5 Comparison of CRP values (pre-operative, POD-1, POD-7) in mandibular fractures

		Mean	N	Std. Deviation
Pair 1	CRP 1 (pre-operative)	17.1400	15	13.53624
	CRP 2 (POD-1)	17.2000	15	8.86744
Pair 2	CRP 2 (POD-1)	17.2000	15	8.86744
	CRP 3(POD -7)	9.6333	15	6.23386
Pair 3	CRP 1 (pre-operative)	17.1400	15	13.53624
	CRP 3(POD -7)	9.6333	15	6.23386

TABLE No.6 Comparison of CRP values (pre-operative, POD-1, POD-7) in mandibular fractures

	Paired Differences					t	df	p-value
				95% Confidence Interval of the Difference				
	Mean	Std. Deviation	Std. Error Mean	Lower	Upper			
CRP 1 (pre-operative) - CRP 2 (POD-1)	-.06000	16.51782	4.26488	-9.20726	9.08726	-.014	14	.989
CRP 2 (POD-1) - CRP 3(POD -7)	7.56667	10.26837	2.65128	1.88023	13.25310	2.854	14	.013
CRP 1 (pre-operative) - CRP 3(POD -7)	7.50667	11.87245	3.06545	.93193	14.08141	2.449	14	.028

a. Site = Mandible

* Paired Samples Test

TABLE No.7 Comparison of CRP pre-operatively, at POD-1 & at POD-7 between mid-face and mandibular fractures

	S	Mean	Std. Deviation	t-statistic (df=28)	p- value
CRP 1 (Pre-operative)	Mandible	17.1400	13.53624		
	Mid-face	13.2267	13.05135	.806	.427
CRP 2 (POD-1)	Mandible	17.2000	8.86744	-1.126	.270
	Mid-face	23.7333	20.63903		
CRP 3(POD -7)	Mandible	9.6333	6.23386	1.23	.229
	Mid-face	7.4600	2.82307		

R. O. Niskanen et al [10] in 1995 conducted a review on serum C-reactive protein levels after total hip and knee arthroplasty. They noticed a rise in levels of C-reactive protein after infection and tissue destruction. And concluded that a pronounced rise of the CRP level on the second and third postoperative days after a major orthopedic operation is normal, but a further rise at one and two weeks suggests the presence of a serious complication. As the cases included in our study had a normal healing pattern with no post-operative infection or other complications in our clinical assessment, so the association of CRP in infections could not be made.

Pentti Kallio et al [6] in 1990, conducted a study on C-reactive protein in 42 cases with tibial fractures. They noticed that the timing of the CRP response was related to the timing of the treatment: the highest

values were usually recorded two days after admission or operation. The timing of the operation did not affect the degree of CRP response. Neither the site nor the age of the patient played any role and a late secondary rise in serial CRP values may indicate complications in healing.

From our study, we obtained similar results where the site (whether it is a mid-face or a mandibular fracture) and the age of patient did not bring any statistically significant difference in CRP levels. There was an increase in CRP levels on POD-1 which is in concordance with the above-mentioned study but it was not statistically significant. And this is in correlation with the study conducted by Iizuka et al [3].

In our study, the increase in CRP values pre-operatively compared to POD-7 may be because of the initial trauma. The increase in levels on POD-1 maybe because of surgical intervention and decrease in the levels on POD-7 maybe because of uneventful healing. Other factors that may raise the CRP levels maybe because of associated infections like pneumonia, urinary tract infection (UTI), thrombophlebitis, acute pancreatitis and myocardial infarction (MI) according to Tateyuki Iizuka et al [3]. These possibilities may make the interpretation of high serum CRP values in trauma patients difficult. In our study, there was no associated systemic complications/infections. There was a statistically significant decrease in the value of CRP levels from pre-operative to POD-7 as well as from POD-1 to POD-7. Hence, the increased CRP levels on POD-1 is solely due to surgical intervention. Our study signifies that the rapid rise and fall of CRP levels is because of inflammatory process, irrespective of whether it is an ORIF of mid-face or of the mandibular fracture.

There were no studies or statistical analysis in literature to show the comparison of CRP levels in mid-face and mandible fractures. Our study showed that there is no significant difference in both of the above. As in Pentti Kallio et al [6] study, the site of the fracture will not affect the degree of CRP response.

The estimation of CRP level though cannot be said as the only parameter for assessing the prognosis of the disease, but it certainly gives an indication of post-operative infection and healing. However, a bigger sample size may be required to draw a line on these conclusions we have made.

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