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Original Research Paper

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POST-OPERATIVE SERUM C-REACTIVE PROTEIN (CRP) AS AN INDICATOR OF ANASTOMOTIC LEAK

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ABSTRACT **Introduction** Post-operative assessment of biomarkers has proven to be of crucial importance in the early detection of anastomotic leak. **Methods** Serum CRP was sent on post-operative days (POD) 1, 3, 5 and 7 in patients who underwent anastomosis during the study period of one year and variation in values were recorded in patients with and without leak. **Results** Serum CRP on POD 5 and 7 showed a continuous rise in patients with leak vs without leak ($p < 0.001$ and < 0.001 respectively) in whom the serum CRP values were on declining trend after post-operative day 3. **Conclusion** The fact that serum CRP remains elevated on early post-operative days before the clinical manifestation of anastomotic leak, makes it an ideal predictor of anastomotic leak.

KEYWORDS : C-reactive protein, anastomotic leak

INTRODUCTION

Despite recent advances, anastomotic leak remains the most physiologically significant and both psychologically and economically devastating complication following intestinal anastomosis.[1] Hence, it is important to probe the role of a cost efficient marker to predict anastomotic leak. C-reactive protein (CRP) is a capsular polysaccharide acute phase reactant displaying rapid and pronounced rise in concentration in response to infection and inflammation[2]. Therefore it is conveniently used for the assessment of inflammatory response during post-operative healing process. CRP plays a role in recognizing the pathogens and activating the complement system and phagocytic cells. It contributes to restoration of normal structure and function of injured tissues. CRP in serum and plasma has been used for a long time to objectify disease activity in infective or non-infective inflammatory states. CRP is one of the most popular and easily available biomarker of acute inflammatory response.[3] In 1976, Fischer et al. were the first to show the role of CRP in the prediction of postoperative inflammatory complications.[4] Consequently, several studies have documented the role of CRP in the prediction of post-operative complications including anastomotic leak. Hence, this study has been taken up to evaluate the significance of serial measurement of drain fluid CRP in the detection of anastomotic leak in the early post-operative period which will be helpful in the initiation of targeted treatment towards prevention of anastomotic breakdown and the related morbidity and mortality.

METHODS

A prospective, hospital based observational study was conducted in the premises of the department of general surgery, Assam Medical College and Hospital over a period of one year, on a total of 80 consecutive patients in whom any type of gastro-intestinal resection and anastomosis was performed on emergency or elective setup for a diverse diagnosis after excluding patients with any pre-operative infective condition, any known metabolic disease, inflammatory bowel disease.

All routine pre-operative investigations were carried out for all the patients including those to fulfill the inclusion and exclusion criteria. Preoperative diagnosis was made on the basis of clinical parameters, radiological and endoscopic investigations which were carried out on admission with minimal investigation done for emergency case as time permits. All the patients were subjected to same pre-operative preparations which are followed in our institution. The surgical procedure was according to the surgeon's discretion as the operative procedure varied for different diagnosis and also for different intra-abdominal findings on laparotomy.

Serum was collected in a clot vial on POD 1, 3, 5 and 7 and sent for CRP estimation[5,6]; values were rounded off to the nearest integer. Serum CRP was measured by the method- Fixed Point Immuno Rate[7-9]. The immuno-rate format for CRP is based on an enzymatic heterogeneous, sandwich immunoassay format. VITROS CRP slides and VITROS chemical products were used.

Patients were closely observed for any complications most importantly for the occurrence of anastomotic leak which was defined in 2010 by the International Study Group of Rectal Cancer as a defect at the anastomotic site leading to communication between the intraluminal and extraluminal compartmentsl which was clinically suspected on the appearance of fever, tachycardia, pain abdomen, diffuse peritonitis and also from the volume and nature of the drain fluid. In case of indecisiveness, radiological investigation (CT scan) was performed to aid in the diagnosis. On suspicion of anastomotic leak, patient was resuscitated with conservative management and if not controlled with conservative measures, decision of re-exploration with creation of diverting proximal enterostomy or takedown of the old anastomosis and re-doing of new anastomosis was taken.

Data were analysed using appropriate statistical measures and considering p-value of less than 0.05 as significant.

RESULTS

The study was conducted in 80 consecutive patients, who underwent any type of gastro-intestinal anastomosis, of which 47 were male and 33 were female.

Table 1: Demographic profiles

Main parameters	Sub-parameters	Values
Total no of cases		80
Cases with leak	As a whole	13(16.25%)
	Male	7/47(14.89%)
	Female	6/33(18.18%)
Average age of participants		50.43±7.95 years
Maximum leak	41-50 years	21.87%

Leak rate according to site	Upper GI tract	3.13%
	Small bowel	20.00%
	Colorectal	26.32%

Table 2: Mean serum CRP values

Post operative day	Mean serum crp value (mg/L)		p-value
	With Leak	Without Leak	
POD 1	81.38±5.97	77.16±11.18	0.190
POD 3	98.31±8.20	62.71±9.20	<0.001
POD 5	78.08±8.71	43.42±4.73	<0.001
POD 7	86.00±8.93	35.24±5.11	<0.001

Table 3: Cut-off values of serum CRP

Post-operative day	Cut-off value of serum CRP (mg/L)
POD 1	70
POD 3	82
POD 5	64
POD 7	71

Highest serum CRP value was found on POD 3 with an average of 98.31 mg/L for patients with leak. In the patients with leak, serum CRP was found to be towards higher range on POD 5 and 7 though not continuously increasing; but in the patients without leak, serum CRP was found to be on sharply decreasing trend on POD 3, 5 and 7. No patients were found to have anastomotic leak below the values mentioned in table 3. Highest number leak had occurred during POD 6 to 10. Out of 13 patients with leak, 8 presented with generalized peritonitis and 5 with localized intra-abdominal abscess; 2 patients had expired during the follow up period of 30 days with a mortality rate of 5.38%.

DISCUSSION

Incidence of leak: Buchs NC et al (2008)10 recorded a incidence of anastomotic leak of 3.8%, which is lowest of all the reviewed literatures. Highest incidence of anastomotic leak among the literatures is 19.2% recorded by Matthiessen P et al (2007)11. Kostic Z et al (2016)6 found it as 10%. The incidence in our study was towards the higher range because of late presentation of patients, poor nutritional status and also due to unavailability of advanced technical facilities.

Site of highest leak rate: Rullier E et al (1998)12 stated that anastomotic leak rate was on increasing trend with the site of anastomosis being more closer to anal verge with highest leak rate when anastomosis was done within 5 cm from anal verge. Karanjia ND et al (1994)13 recorded higher leak rates with low anterior resections. All these literatures including our study depicted a higher incidence of leak rate in colorectal and sigmoid resection and anastomosis.

Post-operative serum CRP: In our study, though the serum CRP values were recorded to be in gradually decreasing trend on POD 5 and 7 in patients with leak, they remained towards the higher range of values; whereas the serum CRP values in patients without leak were on sharply decreasing trend on POD 5 and 7 ($p < 0.001$ and < 0.001 respectively). Kostic Z et al (2016)6 recorded the maximum value of serum CRP on POD 3 similar to our study; they also concluded that the values of serum CRP on POD 5 and 7 were maintained towards higher range in patients with leak with high statistical significance (p-value < 0.001 and < 0.001 respectively) in comparison to patients with no leak. Benoit O et al (2019)14 recorded high values of serum CRP on early post-operative days (POD 1 to 5) in patients with leak with significant difference in comparison to patients with no leak. The findings of these studies conform to the findings of our study.

Cut-off values of serum CRP for leak: Kostic Z et al (2016)6 found that anastomotic leak was not observed in patients with serum CRP below 77 mg/L and 90 mg/L on POD 5 and 7 respectively and in patients with drain fluid CRP below 53 mg/L and 42 mg/L on POD 5 and 7 respectively. Benoit O et al (2019)14 concluded that serum CRP values of >100 mg/L on POD 1-4 were associated higher post-operative complications including anastomotic leak. These studies comply with the observations recorded in our study.

CONCLUSION

After analysing the observations of our study, it can be clearly commented that the serial measurement of serum CRP is a most valuable predictor of anastomotic leak mostly the values on post-operative days 5 and 7 which showed a persistently high values indicating the presence of an ongoing inflammatory process in comparison to those without leak in whom the serum CRP values were on declining trend after post-operative day 3 indicating the subsidence of inflammation. Although our study is limited by time frame and small sample size, the observations comply with various relevant literatures.

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