EVALUATION OF C-REACTIVE PROTEIN IN PERITONEAL DRAIN FLUID FOR THE EARLY DETECTION OF ANASTOMOTIC LEAK

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ABSTRACT

BACKGROUND

Anastomotic leakage is the most dreadful complication of colorectal surgeries. It results in sepsis, entero-cutaneous fistula formation, leads to reoperation and permanent stoma and is associated with decreased survival and death. The clinical presentation may not be evident in the initial phase, when a timely intervention may save the life of the patient or could avoid a reoperation or a permanent stoma. The current study is to evaluate the diagnostic efficacy of peritoneal drain fluid CRP to predict anastomotic leakage in elective colorectal surgeries.

MATERIALS AND METHODS

50 patients with elective colorectal resection and primary anastomosis were studied. The selected patients were followed up from their preoperative admission in the ward till discharge. Demographic data of the patients, operative details, postoperative events and follow up data were obtained through a standardized case record form and were entered into a data base. In the postoperative period, drain fluid reservoirs were emptied 2 times a day within 12-hour intervals, under aseptic precautions. The evening collection was disposed off. CRP is estimated on postoperative day 3 and day 5. The values obtained were compared between the groups of patients without complications of surgery and in those with anastomotic leakage.

RESULTS

Clinically evident anastomotic leakage was observed in 7 patients (14%), in 3(6%) following right hemicolectomy and in 2(4%) following anterior resection and 2(4%) following left hemicolectomy. The mean value of CRP on postoperative day 3 was 48.41 in patients without anastomotic leakage and those with anastomotic leakage was 40.36 whereas, the postoperative day 5 CRP was 36.61 in patients without anastomotic leakage and 86.85 in those with leakage. On applying independent sample t test to day 5 CRP, it was found to be significantly elevated with a t value 9.45 and p value 0.001. To find out the cut off value of CRP in diagnosing those with anastomotic leak, an ROC curve was constructed. The area under the curve was 0.997 with a p value 0.001 and a confidence interval between 0.986 and 1.007. And it was found that with a cut off value of CRP 77.59, the sensitivity is 85% and specificity 100% in diagnosing anastomotic leakage.

CONCLUSION

Serial measurement of the drain fluid CRP can be reliably used in early detection of anastomotic leakage. It was found that CRP value on postoperative day 5 showed a progressive elevation from the day 3 CRP value. The mean CRP value on postoperative day 5 was 86.85 which is statistically significant with a sensitivity of more than 85% and with specificity of 100%.

KEYWORDS

Anastomotic Leakage, Enterocutaneous Fistula, Colorectal Surgeries, Anterior Resection, Right Hemicolectomy, Left Hemicolectomy, Stoma, Peritoneal Drain Fluid, CRP.

BACKGROUND

Anastomotic Leakage (AL) is a major life-threatening complication, after colorectal cancer surgerie.[1,2] Breakdown of anastomosis results in increased morbidity and mortality and adversely affects quality of life, duration of hospital stay and cost. The reported leak rate varies between 3% and 19%.[1,2,3,4]

Many previous studies have shown that elevated serum C-reactive protein (CRP) concentrations in the post-operative period may predict an increased chance of post-operative infection and AL. The CRP begins to increase before the occurrence of other signs and symptoms of post-operative infection like fever, tachycardia, and pain. Hence it is an ideal predictor of post-operative infectious complications. Since this is a non-selective marker of inflammation, it is necessary to exclude the infectious complications before diagnosing AL.

Peritoneal fluid is a filtrate of plasma and it is in equilibrium with serum and therefore our assumption is that the values of CRP in drainage fluid reflect values obtained in serum.

Aim of the Study

The aim of this study was to determine the sensitivity and specificity of CRP in peritoneal drainage fluid in the detection of AL in patients with elective colorectal resection.

MATERIALS AND METHODS

Hypothesis Statement

CRP in post op drain fluid can be used as a sensitive non-invasive screening tool for the detection of anastomotic leak and intra-abdominal infection following elective colorectal surgeries

Study Setting- Surgical wards, Government Medical College, Kottayam, Kerala.

Study Population- Patients admitted for elective colorectal surgery in Government Medical College, Kottayam for a time period of one year.

Type of Study- Descriptive study (Diagnostic test evaluation).

Period of Study- 12 months.

Location- Department of General Surgery, Government Medical College, Kottayam.

Sample Size- Sample size was calculated according to, n= Z2 1-α/ 2x specificity X (1-specificity) / d2 x (1- prevalence). Taking α= 0.05 and d as 0.1 estimated specificity as per the study by Ramos Fernandez et al as 0.895 and p as 0.14, and minimum sample size was calculated to be 44.

Inclusion Criteria

Patient undergoing-
1. Right hemicolectomy
2. Left hemicolectomy
3. Sigmoid resection
4. High anterior resection
5. Low anterior resection
6. Subtotal colectomy with ileorectal anastomosis
7. Resection for benign disease

Exclusion Criteria

1. Emergency operations
2. Patients under the age of 18 yrs.
3. Patients Not willing to participate in the study

Sampling Method

All patients admitted for colorectal surgery from September 1st, 2016 to 31st August 2017 satisfying the inclusion criteria were included in the study.

Study Tool

Semi Structured Performa

Study Procedure

After obtaining approval for the study from Institutional review Board, written informed consent was taken from 50 patients who were posted for elective colorectal surgery at the general surgery department in government medical college, Kottayam. Patients were followed up from their preoperative admission in the ward till discharge. Demographic data of the patients, operative details, postoperative events and follow up data were obtained through a standardized case record form and were entered into a data base. In the postoperative period drain fluid reservoirs were emptied 2 times a day within 12-hour intervals, under aseptic precautions. The evening collection was disposed off. The morning collection on postoperative day 3 and day 5 were sent for CRP estimation. Elevated CRP levels on post op days 3 and 5 were taken as an indicator of early anastomotic leakage/intra-abdominal infection. A progressive increase from day 3 to day 5 was considered with high chance of anastomotic leak or intra-abdominal Infection.

If Anastomotic leak or intra-abdominal infection was suspected- the postoperative day of diagnosis along with the manifestation, the diagnostic tool for detection of leak/infection and the treatment given were noted.

Study Variables used in the Study.

Anastomotic leak
Intra-abdominal infection
Other Co morbidities
CRP value of peritoneal drain fluid
Duration of hospital stay
Vital parameters of the patient during the follow up period.

Data-Analysis

The data was properly coded and entered into Microsoft excel after double checking. Further analysis was done using the software SPSS 16.6 Version. For finding out validity of CRP in diagnosing anastomotic leak- sensitivity, specificity, Positive and negative predictive values were used, to find out the cut off for CRP for diagnosing anastomotic leak ROC curves were constructed. The associations were tested using chi square and t test. The p value for significance was p <0.05.

RESULTS

A total of 50 patients with elective colorectal surgeries were studied. The average age of patients was 60.9 with a standard deviation of 11.40.
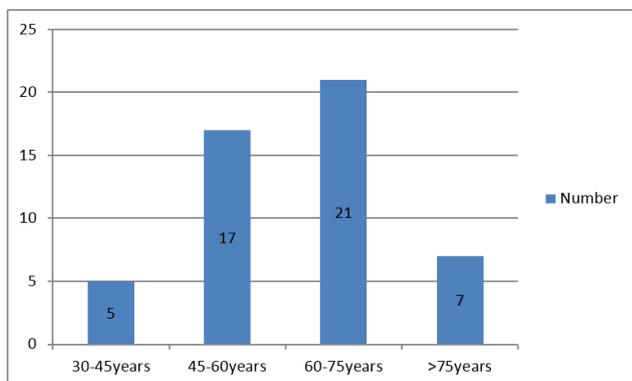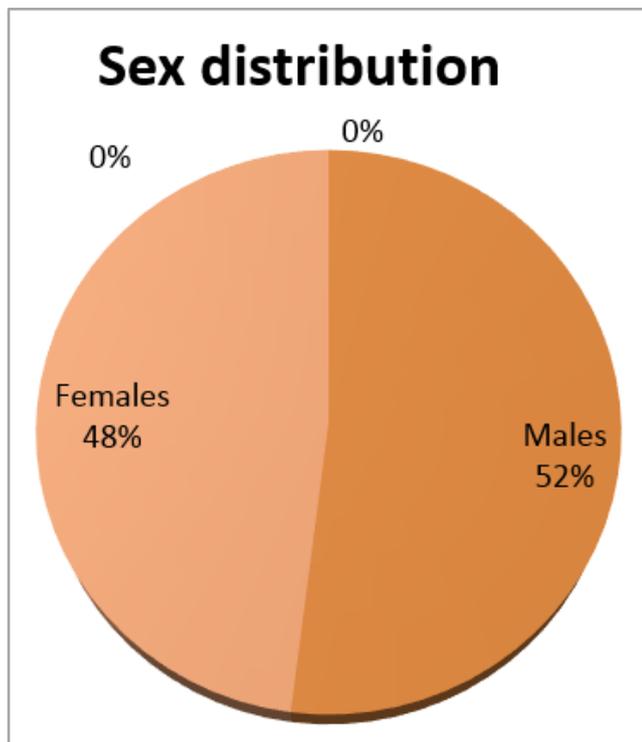
Diagram 1. Age Distribution

Type of Surgery	Frequency	%
Right Hemicolectomy	18	36.0
Left Hemicolectomy	4	8.0
Anterior Resection	18	36.0
Sigmoidectomy	7	14.0
Transverse Colectomy	1	2.0
Others	2	4.0
Total	**50**	**100.0**

Table 2. Distribution of Population According to Type of Surgery

Diagram 1. Sex Distribution

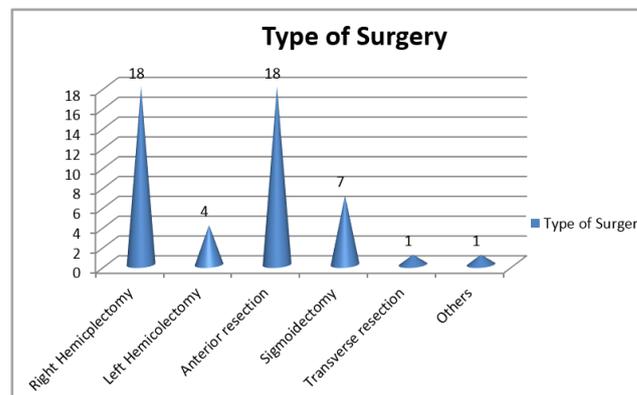*Diagram 3. Distribution of Patients According to Type of Surgery*
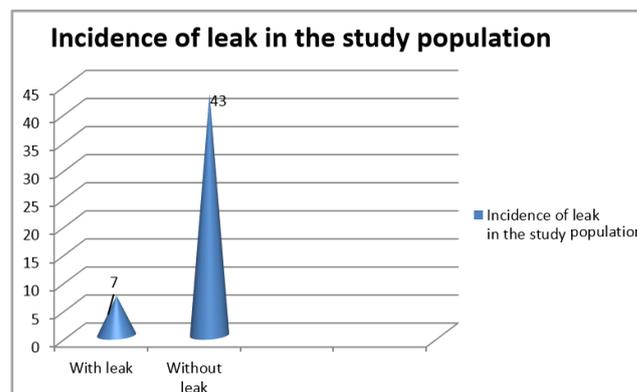
Diagram 4. Incidence of Leak in the Study Population

In the study population total number of male patients were 26 and females were 24 of which 5 were between the age 30 to 45 years (1 male and 4 female) 17 were between the age group of 45 to 60 (9 males and 8 females), 21 patients were between the age group of 60 to 75 (13 males and 8 females) and above 75 years there were 7 patients (3 males and 4 females).

In this study population 14% developed anastomotic leakage and underwent re- exploration. Out of which only 2 survived, all others expired either immediate postoperative period or during the hospital stay. All the patients developed leak after the 5th post-operative day with definite evidence of anastomotic leak either in the form of wound dehiscence or feculent drain.

Co-Morbidities	Percentage
DM	52%
HTN	50%
CAD	2%

Table 1. Distribution of Individual Comorbidities in the Study Population

Postoperative Day	Incidence of Anastomotic Leak
<3	0
3-5	0
>5	7

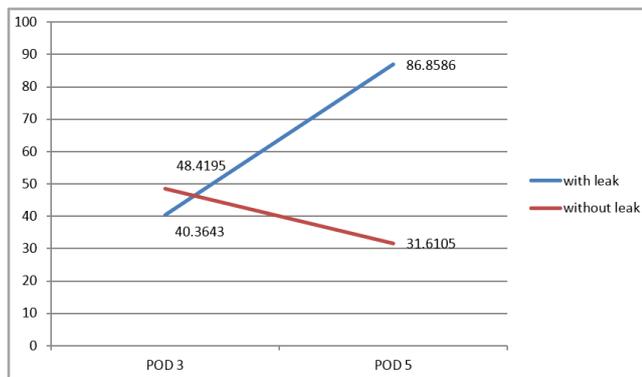*Table 3. Incidence of Anastomotic Leakage with Day of Presentation*

Diagram. 5 Comparison of CRP Value Levels in Patients Without Leak and with Leak on Day 3 and Day 5

In the study population it was observed that there is no significant difference in the mean value of CRP in patients with or without anastomotic leak on postoperative day 3. But in patients with anastomotic leak complications, CRP value was significantly elevated on postoperative day 5 whereas in patients without anastomotic leak CRP was declining. On applying independent sample T test to day 3 CRP values, it was found to be not significant with T value 0.787 and p value 0.435 and on applying independent sample test to day 5 CRP it was found to be significantly elevated with a T value 9.45 and p value 0.001.

| | | Levene's Test for Equality of Variances | | t-test for Equality of Means | | | | | | |
| | | F | Sig. | t | df | Sig. (2-tailed) | Mean Difference | Std. Error Difference | 95% Confidence Interval of the Difference | |
									Lower	Upper
d3crp	Equal variances assumed	.496	.485	-.787	48	.435	-8.05525	10.23979	-28.64372	12.53322
	Equal variances not assumed			-1.367	19.258	.187	-8.05525	5.89184	-20.37582	4.26533
d5crp	Equal variances assumed	.642	.427	9.452	48	.000	55.24811	5.84501	43.49592	67.00029
	Equal variances not assumed			7.735	7.171	.000	55.24811	7.14264	38.43994	72.05627
Table 4. Independent Samples Test										

Diagram 6. ROC Curve

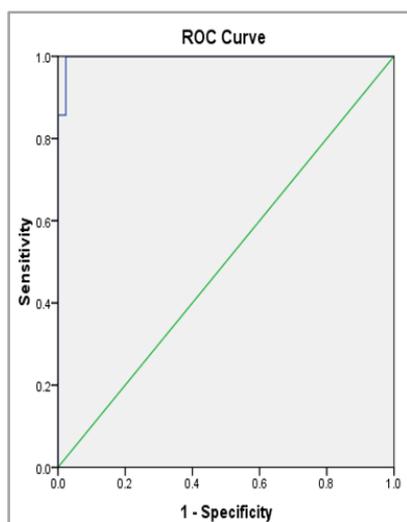| Area | Std. Error a | Asymptotic Sog.b | Asymptotic 95% Confidence Interval | |
			Lower Bound	Upper Bound
0.997	0.005	0	0.986	1.007
Table 5. Area Under the Curve				

Test Result Variable(s): d5crp
   a. Under the nonparametric assumption.
   b. Null hypothesis: true area=0.5

Area under the ROC curve on day 5.
To find out the cut off value of CRP in diagnosing those with anastomotic leak, ROC (Receiver Operating Characteristic) curve was constructed with sensitivity on Y axis and specificity on X axis. The area under the curve was 0.997 with a p value 0.001 and confidence interval (0.986-1.007). From this table it can found that sensitivity & specificity of CRP is 85% and 100% respectively with a cut off value 77.59.

Duration of Hospital Stay	No. of Patients	Mean
With leak	7	18.00
Without leak	43	13.40
Table 6. Comparison of Duration and Hospital Stay in Patients with Anastomotic Leak and Without Leak		

		Levene's Test for Equality of Variables			t- test for Equality of Means						
		F	Sig.	t	df	Sig(2-Tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference		
									upper	lower	
	Equal variances assumed	2.717	0.106	2.386	448	0.021	4.605	1.93	0.724	0.8485	
stay	Equal Variances not assumed			1.457	6.472	0.192	4.605	3.161	2.995	12.204	

Table 7. Independent Samples Test

By applying independent t test on the duration of the hospital stay in patients without anastomotic leak and with anastomotic leak the `t̒` was found to be 2.38 and p value 1.45. which was not significant, in 7 patients who developed leak 5 expired immediately after second surgery.

	value	df	Asymptomatic, Sig (2 Sided)	Exact Sig (2-sided)	Exact Sig (1 sided)
Pearson Chi-Square	2.860[a]	1	.091		
Continuity correction	1.604	1	.220		
Likelihood ratio	4.603	1	0.032		
Fischer's exact test				.168	.103
Linear-by- linear association	2.803	1	.094		
N of valid cases [b]	50				
a. 1 cells (25%) have expected count less than 5. The minimum expected count is 1.82					
b. Computed only for a 2*2 table					

Table 8. Chi-Square Test

In the study population in patients who developed anastomotic leakage 74% were with co morbidity and in those who did not develop complications the association of co morbidity was 26 percentage.

On applying Chi-square test it was found to be significantly different with Chi-square value 2.860 and p value 0.091.

DISCUSSION

Un-eventful healing of the intestinal anastomosis remains a challenge after colon and rectal resections.[5] Anastomotic leakage is the most dreaded complication and is a serious obstacle in the successful outcome of colon and rectal anastomotic surgeries. Incidence of anastomotic leak as per the current study was 14% which is comparable with previous studies.[5,6,7,8,9] The average age of the population was 60.9.1 (Fig. 1) it is evident that the study population includes patients from all age groups. A total of 26 males and 24 females were studied. 76% of the patients had co morbidities. The study population underwent right hemicolectomy, left hemicolectomy, anterior resection sigmoidectomy, transverse colectomy and colostomy reversal. Right hemicolectomy and anterior resection were the most common procedures underwent.

As a part of the study patients were monitored and evaluated from the time of preoperative period till discharge from the institution. All the patients were evaluated clinically, and peritoneal drain fluid CRP was measured on postoperative day 3 and 5.

In this study population, 7 patients developed anastomotic leak. One patient on postoperative day 6, other 3 on postoperative day 7 and the rest on day 8. All manifested either in the form of feculent discharge through abdominal drain or through the laparotomy wound.

The measured CRP value on day 3 showed a mean value of 48.41 in patients without anastomotic leak and in patients with anastomotic leak the mean CRP value on day 3 was found to be 40.36. On applying independent sample T test, it was found not significant, with T value 0.787 and p value 0.435. The mean value of postoperative day 5 CRP was found to be 86.85 in patients with anastomotic leak and in patients without leak it was found to be 31.61. On applying independent sample T test, it was found to be statistically significant with t value 9.45 and p value 0.001.

To find out the cut off value of CRP in diagnosing those with anastomotic leak a ROC (Receiver Operating Characteristic) curve was constructed with sensitivity on Y axis and specificity on X axis. The area under the curve was 0.997 with a p value 0.001 and confidence interval (0.986-1.007). From this table it was found that sensitivity & specificity of CRP is 85% and 100% respectively with a cut off value 77.59.

In the analysis of our patients we used exclusively the clinical and biochemical parameters to establish anastomotic leak, which was reported in 7 patients, in 3 patients following

Right Hemicolectomy (6%), and 2 patients (4%) after Left hemicolectomy and in 2 patients (4%) following anterior resection. The rate of post-operative mortality significantly increased after anastomotic leak, only 2 out of 7 patients who developed anastomotic leak survived.

Early detection of anastomotic leak would help us to make early and appropriate therapeutic measures to alleviate or eliminate adverse effects.

CRP is a widely available marker of acute inflammatory response. CRP serum concentration is determined by its synthesis rate and reflects the intensity of the stimulus for acute anti-inflammatory response. There are numerous studies on the significance of the serial measurement of CRP in detecting infectious complication of surgical treatment and anastomotic leak.

In our study we monitored the vital parameters of the patient in the post-operative period along with that we measured CRP values of the peritoneal drain fluid in the post-operative day 3 and day 5 and it was observed that there was no significant difference in mean value of CRP in peritoneal drain fluid in patients with or without anastomotic leak. In patients without complication after an initial rise of CRP values there was a gradual decline of CRP in POD5. In those with complications CRP values persisted or elevated significantly.

Analysis showed a highly statistically significant positive correlation between the measured values of CRP on POD5 with incidence of anastomotic leak with a cut off value of 77.59 which showed 85% sensitivity and 100% specificity with a P value <0.05.

CRP is a non-selective marker of inflammation and hence could be taken into consideration only within the clinical presentation context.

Summary

The study was to evaluate the sensitivity and specificity of peritoneal drain fluid CRP to predict anastomotic leakage in patients undergoing elective colorectal surgeries. 50 patients who developed anastomotic leakage were studied. All underwent re exploration, only two survived.

In those who developed complications CRP value of the peritoneal drain fluid were significantly elevated on postoperative day 5.

Our results indicate that measurement of CRP in the peritoneal drain fluid can be reliably used in early detection of anastomotic leakage. The CRP value on postoperative day 5 showed a cut off value off 77.59 specificity 100 % and sensitivity 85%.

Anastomotic leakage is a usual companion of colorectal resection. Its early detection is important as it allows early intervention and management which in turn reduces the adverse effects due to the same.

CONCLUSION

The results of our study indicate that measurement of CRP in peritoneal drain fluid can be reliably used in early detection of anastomotic leakage. It is found that the CRP value on the postoperative day 5 showed a persistent high value or progressive elevation from the previous CRP value. It is also found that the mean CRP value on the postoperative day 5 is 86.8586 which is statistically significant and has a sensitivity more than 85% and a specificity of 100%.

Limitations

Because of the smaller sample size, the results of the study could not be generalised to the population. To reduce the sampling error instead of colorectal anastomosis, all cases of bowel anastomosis may be included.

Recommendations

A study must be conducted in a high-volume centre in order to get a more accurate result that can be generalised.

Routine monitoring of peritoneal drain fluid CRP on post-operative day 3 and 5 can be adopted as an institutional policy.

In case of persistent high value of CRP on post-operative day 5 or a progressive elevation of CRP from post-operative day 3 -5, patient should be considered as high-risk and such patients should be monitored closely with prolonged NPO, higher antibiotics, keeping the abdominal drain for few more days and imaging.

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