

Original Research Article

Can analysis of drain fluid biomarkers predict anastomotic leak?

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ABSTRACT

Background: Anastomotic leak is a major complication often leading to significant morbidity and mortality. A method to predict leaks in the early postoperative period will help in better management and outcome. Though serum biomarkers like C-reactive protein and procalcitonin levels are often used to predict chances of developing complications, they are nonspecific and suggest mainly ongoing sepsis in general. Detection and assessment of the presence of these biomarkers at the local milieu is an alternate non-invasive option as they are produced at the injury site and increase in anastomotic leaks. If measured serially, can guide to a strong suspicion of a leak before the clinical signs are evident.

Methods: Forty-eight patients who underwent intestinal anastomosis for various indications were included. Serial measurement of drain fluid C-reactive protein and procalcitonin were measured on postoperative days 3, 5 and 7.

Results: 7 patients developed leaks with two deaths. CRP and procalcitonin levels were higher on all days in comparison with the no leak group. CRP had the highest sensitivity on day 5 with 85.71% and 97.56% specificity on day 7. The sensitivity and specificity of procalcitonin were 71.43% and 97.56% on day 5 and day 7. Accuracy was 93.7% for CRP and 87.5% for procalcitonin on the seventh day.

Conclusions: Serial analysis of drain fluid CRP and procalcitonin showed persistently increased levels in patients with an anastomotic leak. Correlation of the levels in patients with anastomotic leak suggests the possibility of their utility in the early detection of leaks.

Keywords: Anastomotic leak, Drain fluid, C-reactive protein, Procalcitonin

INTRODUCTION

Anastomotic leak is a poorly understood complication of gastrointestinal surgeries. Incidence of anastomotic leak ranges from 2.4 to 19% with a mortality rate of 15%.¹ Existing screening and diagnostic methods detect anastomotic leaks around 6-13 days.² Clinical features, serum C-reactive protein and leucocytosis are nonspecific indicators and suggest ongoing inflammation and confirmation of sepsis with contrast CT scan is often done when the patient is severely ill which delays the diagnosis and increases mortality.

Surgical trauma and infections initiate inflammatory changes with an increase in the various cytokines levels in the peritoneal fluid within few hours of surgery and decrease after 24 hours in uncomplicated recovery.³⁻⁵ The levels increase or remain high if there is an anastomotic leak.^{6,7}

Procalcitonin is one such biomarker found in peritoneal fluid. Procalcitonin is involved in calcium metabolism, cytokine network and modulation of nitric oxide synthesis with a half-life of 30 hrs. Increase procalcitonin levels in the peritoneal fluid are suggestive of sepsis and progression of sepsis.⁸ Peritoneal fluid also shows

increased levels of C-reactive protein, a pentameric protein produced in response to a rise in cytokine levels with a half-life of 19 hours.⁹ Higher levels of CRP in drain fluids are present in the postoperative period in patients with an anastomotic leak.¹⁰

Detection of the presence of biomarkers in drain fluids may suggest the possibility of the anastomotic leak earlier. Attempts have been made to correlate the levels of these cytokines. This study is an attempt to analyze the drain fluid for procalcitonin and C-reactive protein postoperatively and to correlate the levels with an anastomotic leak in patients undergoing intestinal anastomosis.¹¹⁻¹³

METHODS

The was an observational cross-sectional study conducted in a teaching hospital in a semi-urban area between September 2016 to August 2018, after obtaining Institutional Ethical Committee clearance and informed consent of participants. The sample size was calculated by the convenience sampling method. Forty-eight patients who underwent small and large bowel anastomosis as elective or emergency procedures were included in the study. Patients who underwent diversion procedures were excluded.

All 48 patients received standard care as needed with post-operative antibiotic therapy and intraabdominal closed drainage was kept in the vicinity of anastomosis for seven days post-operatively. Drain fluid receptacles were emptied twice daily with a gap of 12 hours. The morning samples of drain fluid were collected with aseptic measures and analyzed for CRP and procalcitonin levels on postoperative days 3, 5 and 7. The levels were assessed using MINIVIDAS BLU with the chemiluminescence immunofluorescent assay method.

Statistical analysis was done using SPSSV 23.0 and Microsoft office 2007. Mean and standard deviation for a descriptive summary, Chi-square for the association, and Wilcoxon unpaired T-test were applied for variables. Sensitivity, Specificity was calculated and a p value<0.05 was considered significant.

RESULTS

Among 48 patients 37 were males and 11 were females. The majority of the patients ranged between 41-50 years

(45.5%) and 51-60 years (29.7%) age group. Anastomotic leak developed in 7 (14.7%) patients. 5 patients were managed conservatively and two underwent surgery. There were two mortalities. The details of the procedures, complications, and management in all patients are depicted in Table 1.

As noted in Table 2, drain fluid procalcitonin and CRP levels were lower on all 3 days in patients who recovered uneventfully compared to patients with an anastomotic leak. Similarly, there was a statistically significant elevation of procalcitonin levels on all three postoperative readings in patients with an anastomotic leak.

Figure 1 depicts the serial drain fluid levels of C-reactive protein and procalcitonin levels in patients with anastomotic leak.

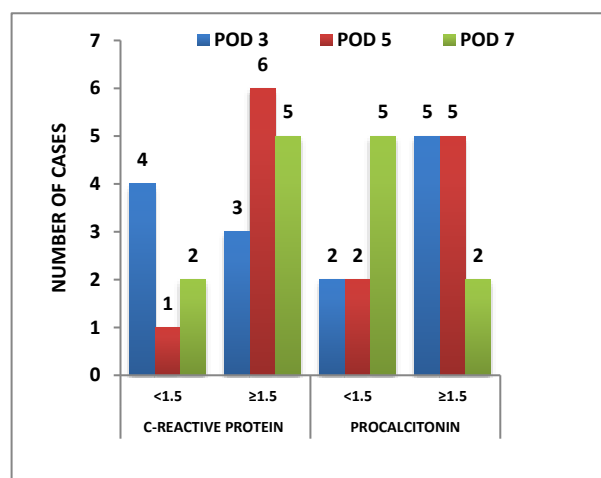


Figure 1: Drain fluid levels of C-reactive protein and procalcitonin levels in patients with anastomotic leak.

Table 3 shows sensitivity, specificity, positive and negative predictive values of both biomarkers on postoperative days three, five, and seven. It is observed that the sensitivity and specificity of CRP are maximum on day five and the negative predictive value is high on day five. Analysis of drain fluid procalcitonin showed the highest specificity on day seven but sensitivity was poor. The negative predictive value was 94.74% on day five and reduced later.

However overall accuracy was 93.75% on a post-operative day seven for C reactive protein and 87.5% for procalcitonin on a postoperative day seven respectively.

Table 1: Details of patients who underwent anastomosis.

No. of patients	Gender	Diagnosis	Procedure	Anastomotic leak
16	11 Males 5 Females	Intestinal obstruction	Exploratory laparotomy with ileoileal resection and anastomosis.	Yes (1/16)
1	Male	Penetrating injury of the abdomen with jejunal tears	Exploratory laparotomy with resection and jejunojejunal anastomosis.	-

Continued.

No. of patients	Gender	Diagnosis	Procedure	Anastomotic leak
1	Male	Gastric outlet obstruction	Roux-n-Y retrocolic, iso peristaltic end to side gastro jejunostomy with jejuno-jejunostomy.	-
1	Female	Large duodenal perforation	Exploratory laparotomy with the closure of the perforation.	Yes
18	13 Males 5 Females	Ileal perforation	Exploratory laparotomy with resection and ileoileal anastomosis.	Yes (4/18)
1	Male	Carcinoma stomach stage II	Subtotal gastrectomy with gastrojejunostomy.	Yes
1	Male	Ileal perforation	Exploratory laparotomy with ileoileal anastomosis.	-
2	Male	Gastric outlet obstruction	Truncal vagotomy with retrocolic gastro jejunostomy.	-
1	Male	Penetrating abdominal trauma with jejunal, ileal perforations and mesenteric injury	Exploratory laparotomy, primary closure of jejunal injury, resection and anastomosis of ileum.	-
1	Male	Ileoileal intussusception with mobile caecum	Exploratory laparotomy with resection and anastomosis of ileum with ceacopexy.	-
1	Male	Caecal perforation	Exp lap with loop ileostomy with ileoileal anastomosis.	-
1	Male	Gastric Outlet Obstruction	Exp lap with gastrojejunostomy with colocolic anastomosis with appendectomy.	-
1	Male	Blunt abdominal trauma	Exploratory laparotomy with resection of jejunum and anastomosis with mesenteric injury repair.	-
1	Male	Blunt abdomen trauma	Exp lap with Roux-en-y anastomosis with feeding jejunostomy.	Yes
1	Male	Mesenteric cyst of the mesocolon	Exp lap with resection of mesenteric cyst with a segment of transverse colon with end-to-end colocolic anastomosis.	-

Table 2: Mean C-reactive protein and procalcitonin according to anastomotic leak.

Parameters	Day	Anastomotic leak				P value
		Yes		No		
		Mean	SD	Mean	SD	
C-reactive protein	POD-3	2.66	2.77	1.08	0.40	0.001*
	POD-5	2.84	2.77	0.84	0.48	<0.001*
	POD-7	2.83	3.06	0.59	0.31	<0.001*
Procalcitonin	POD-3	3.19	2.95	1.17	0.61	<0.001*
	POD-5	1.62	0.65	0.98	0.61	0.015*
	POD-7	1.07	0.79	0.67	0.41	0.046*

* significant at 5% level of significance (p<0.05).

Table 3: Sensitivity, specificity, positive predictive value and negative value of biomarkers.

	C-reactive protein			Procalcitonin		
	POD-3(%)	POD-5(%)	POD-7(%)	POD-3(%)	POD-5(%)	POD-7(%)
Sensitivity	42.86	85.71	71.43	71.43	71.43	28.57
Specificity	73.17	82.93	97.56	73.17	87.80	97.56
Positive predictive value (PPV)	21.43	46.15	83.33	31.25	50.00	66.67
Negative predictive value (NPV)	88.24	97.14	95.24	93.75	94.74	88.89
Accuracy	68.75	83.33	93.75	72.92	85.42	87.50

DISCUSSION

C-reactive protein and procalcitonin are common acute phase reactants produced by the liver or at the site of injury or inflammation. There is a mild physiological rise in serum levels of CRP and procalcitonin on first and second postoperative days due to transient bacterial contamination and response to injury and are not significant in suggesting leak.¹⁴ Management of anastomotic leaks is a therapeutic challenge. Early detection improves the management and in turn reduces morbidity and mortality.

This study supports the other studies where, the adequate blood supply of the anastomotic edges, the level of anastomosis, use of staples, adverse effect during the operation, lack of bowel preparation and prophylactic antibiotic therapy, blood loss and blood transfusions during operation, and patient-related risk factors including hypertension, tobacco and alcohol use, chronic obstructive pulmonary disease, obesity, and malnutrition have been associated with a higher risk of anastomotic leaking.¹⁵⁻¹⁸

Modern surgical techniques and perioperative care have improved a lot, anastomotic leak remains one of the most serious and important complications in patients after colorectal surgery. The leakage rate varies from 3% to 21% and the mortality rate associated with symptomatic leaks is 6-22% which is in line with our study 14%.¹⁹

Few other studies support this observation, where different variables were correlated with major anastomotic leaks.²⁰⁻²² CRP and procalcitonin were shown to be reliable predictors of anastomotic leak on day 3 and 5 with 100% sensitivity, 72% specificity, 100% negative predictive value but the positive predictive value was poor.²³

The role of mechanical bowel preparation and prophylactic antibiotic therapy remains unclear despite few studies suggesting reduced leaks.²⁴⁻²⁶ Any modality of investigation for early detection aids better management. A non-invasive reliable method is always preferred. Serum levels of biomarkers like CRP and procalcitonin may not suggest an anastomotic leak and even if raised, only suggest sepsis or ongoing inflammation. An increase in the levels of these markers from drain fluid is more specific in suggesting leak.

Serial changes in levels can add significantly towards accurate diagnosis.

Limitation of this study was small sample size is the limitation of our study.

CONCLUSION

Evaluation of C-reactive protein and procalcitonin in drain fluid on pod 3, 5 and 7 were found to be associated with higher than normal values in anastomotic leakage patients. Therefore, serial measurement of procalcitonin and

C-reactive protein from drain fluid helps to detect anastomotic leaks early with likely reduction in morbidity.

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