International Surgery Journal
Caparlar MA et al. Int Surg J. 2021 May;8(5):1418-1423
http://www.ijsurgery.com
pISSN 2349-3305 | eISSN 2349-2902

DOI: https://dx.doi.org/10.18203/2349-2902.isj20211804

Original Research Article

Procalcitonin: the ideal predictor of anastomotic leakage. But, when?

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Received: 03 January 2021
Revised: 14 February 2021
Accepted: 15 February 2021

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ABSTRACT

Background: Rectal cancer ranks 3rd among the most common malignancies in both sexes. Abdominal infections that can be seen after rectal cancer surgery are the most feared postoperative complications, as they can also be the harbinger of anastomotic leakage. According to its localization, the rate of anastomotic leak varies between 4% and 29.5%. Procalcitonin (PCT) is an increasing parameter in bacterial infections and sepsis. Therefore, it is used to monitor the infection and the effectiveness of the treatment. Our study we aimed to evaluate the effect of PCT on early diagnosis of anastomotic leakage in rectal surgery and the correlation between PCT and CRP and WBC levels.
Methods: File records of 50 patients who were operated on for rectal cancer and had anastomosis between 2016 and 2019 were retrospectively analyzed. Demographic features, operation information, preoperative and postoperative clinical features of the patients were recorded. The WBC, CRP and procalcitonin values of the patients were measured on the preoperative and postoperative 1st and 5th days. Patients were divided into two groups as PC values<2 ng/ml and ≥2 ng/ml. Patients with surgical site infections were found. The relationship between hospital stay and PCT levels and those with surgical incision site infection and those with intra-abdominal infection was examined. The correlation between PCT values and CRP and WBC values of the patients was evaluated.
Results: There was no significant difference in PCT values in infections at the surgical incision site. However, it was observed that the PCT values of patients with surgical infection in the abdomen were significantly higher than those without (p=0.005). It was observed that the PCT level was high and the duration of hospital stay was observed to be prolonged in patients with infections in the surgical incision area and in the abdomen.
Conclusions: PCT can be used as a biochemical parameter in terms of abdominal infection and anastomotic leaks. It is recommended to be checked especially on the fifth postoperative day and to investigate for anastomotic leakage if it is seen to reach the highest value.

Keywords: Anostomotic leakage, Procalcitonin, Rectal

INTRODUCTION

Rectum cancer is the third most commonly diagnosed cancer in both genders. A total of 44180 new cases was diagnosed in 2018.[1] Abdominal infections are the most feared postoperative complications because they are also the precursors of anastomotic leakage. According to its localization, the anastomotic leakage rate differs between 4% - 29.5%.[2,3] The patients are discharged in the early postoperative period due to ERAS protocols, which have gained popularity. Postoperative complications are sometimes diagnosed lately and cause prolonged treatments and unplanned hospital admission, causes and economic burden and increased work in the health

system.[4-6] There are always diagnostic tolls required in the early postoperative period, which indicates complications, including anastomotic leakage and abdominal infections.

Procalcitonin is a 116 amino acid protein and the prohormone of calcitonin. It is produced by the parafollicular C cells of the thyroid gland. The basal blood level is usually lower than 0.1 ng/ml. PCT increases bacterial infections and sepsis. Therefore, it is used to follow the infection and the treatment's effectiveness.[7,8] PCT is a marker used for early diagnosis of complications after abdominal surgery.[9,10]

The study aimed to evaluate PCT's effect on the early diagnosis of rectal surgery and anastomotic leakage and the correlation between PCT and CRP and WBC levels.

METHODS

File records of patients whose data were operated rectum cancer and anastomosis patients (abdominoperineal resection, ultra-low anterior resection, Hartman procedure, and trans anal excision were excluded) between 2016 and 2019 years were examined retrospectively. There were a total of 50 patients. All patients were included in the study. Demographic information such as age, gender, body mass index (BMI), type of operation, presence of comorbidity, smoking, alcohol use, and ASA score was analyzed. (Table 1)

Patient's preoperative, postoperative 1st and 5th days WBC (in Sysmex XN1000 device), CRP (Roche CRP kit and Roche Cobas6000 device), and PCT (Roche brand kit and Roche Cobas E411 brand device) values were determined. Patients were grouped as PCT values <2 ng/ml and 2 ng/ml (Table 2). Patients with infections in the surgical incision and those with infections are superficial (skin, subcutaneous) or deep (fascia and muscle), intraabdominal or pelvic abscesses were examined in patients with surgical site infec-tion and infection the abdomen. Cardiovascular and respiratory complications developed after surgery were excluded (Table 3). The relationship between the median value of PCT and infection status at the surgical incision and surgical infection in the abdomen was examined (Tables 4, 5). The relationship between the duration of hospitalization and PCT levels, surgical incision infection and surgical infection status in the abdomen was ex-amined (Table 6). Correlation between patients' PCT values with CRP and WBC values was evaluated (Table 7). The relationship between infection status of the incision site in the abdomen, PCT levels, tumor size according to pathology re-ports, lymph node involvement, neurovascular invasion, serosal invasion, and pathologic stage were examined (Table 8). Research data were evaluated using the Statistical package for social sciences (SPSS) 15.0 statistical package program. Descriptive statistics are presented as frequency distribution and percentage. The variables' compliance to normal distribution was examined by visual (histogram) and analytical methods (Kolmogorov-Smirnov / Shapiro-Wilk). Chi-square, Mann Whitney U test and Spearman test were used as statistical methods. Statistical significance value was accepted as $p < 0.05$.

RESULTS

Thirty (60%) of the patients were 65 years old and under, 20 (40%) of them were over 65 years old, thirty-two (64%) of the study participants in the study were male, and 18 (36%) were female.

Table 1: Distribution of some descriptive characteristics of the individuals participating in the study, Ankara, 2019.

	Number	Percentage
Age groups (n=50)		
65 years and below	30	60.0
Above 65 years	20	40.0
Gender (n=50)		
Male	32	64.0
Female	18	36.0
Body Mass Index (BMI) (n=50)		
<18,5 kg/m^2	1	2.0
18,5-24,99 kg/m^2	23	46.0
25-29,99 kg/m^2	18	36.0
30-34,99 kg/m^2	6	12.0
≥35 kg/m^2	2	4.0
Type of operation (n=53)		
Operated out of GIS	16	37.0
Operated for GIS	9	20.9
No operation	18	41.9
Comorbidity**		
HT-CVS	21	42.8
DM	4	8.1
Other	14	28.5
No	24	48.9
Smoking (n=45)		
Yes	17	37.8
No	28	62.2
Alcohol use (n=45)		
Yes	5	11.1
No	40	88.9
ASA Score (n=50)		
ASA I	7	14.0
ASA II	32	64.0
ASA III	11	22.0

ASA=American Society Anaesthesiology, *percentage of %column, **: More than one option has been marked.

When the body mass index (BMI) was examined, it was observed that only 1 (2%) patient was underweight (BMI below 18.5), 23 (46%) patients were normal (between 18.5-24.9), 18 (36%) patients were overweight (be-tween 25-29.9), 6 (12%) patients were 1st degree obese

(between 30-34.9), 2 (4%) patients were 2nd degree obese (BMI 35 and above) (n = 50).

Table 2: Distribution of procalcitonin values of the study participants, Ankara, 2019.

	N	(%)*
PCT preoperative (n=50)		
<2 ng/ml	45	90.0
≥2 ng/ml	5	10.0
PCT postoperative 1st day (n=50)		
<2 ng/ml	31	62.0
≥2 ng/ml	19	38.0
PCT postoperative 5th day (n=50)		
<2 ng/ml	38	76.0
≥2 ng/ml	12	24.0

*percentage of %column

Table 3: Distribution of the characteristics of the surgical complications of the study participants, Ankara, 2019.

	N	(%)*
Infection status in surgical incision (n=50)		
No	38	76.0
Yes	12	24.0
Those who had infection in surgical incision		
Superficial	11	91.7
Deep	1	8.3
Surgical site infection status in abdomen (n=50)		
Yes	6	12.0
No	44	88.0
Deep infection localization (n=6)		
Intraabdominal	2	33.3
Pelvic abscess	4	66.7
Presence of cardiovascular complications (n=50)		
Yes	1	2.0
No	49	98.0
Presence of respiratory complications (n=50)		
Yes	1	2.0
No	49	98.0

*percentage of %column

When the files of the patients were examined, it was seen that 18 patients (%41,9) had not operated on at all, 9 patients (20.9%) were operated on related to the gastrointestinal system (GIS), and 16 patients (37%) were operated on out of the gastrointestinal system (GIS) (n = 53). When comorbidities were examined, it was observed that 24 patients (48.9%) had no additional disease, 21 (42.8%) patients had hypertension or cardiovascular system disease, 4 (8.1%) patients had diabetes, 14 (28.5%) patients had other diseases. 28 patients (62.2%) did not smoke, 17 patients (37.8%) used it; It was observed that 40 patients (88.9%) did not use alcohol, 5 (11.1%) used it (n = 45). In terms of ASA score, 7 (14%) patients were ASA1, 32 (64%) patients were ASA II, 11 (22%) patients were ASA III (n = 50) (Table 1).

Table 4: Distribution of the characteristics of the postoperative 5th day of the study participants, Ankara, 2019.

	Postoperative 5th day PCT median (min-max)	U Value	P*
Surgical site infection status in abdomen			
No	0,55(0,02-5,97)	38,000	0,005
Yes	7,86(0,27-35,3)		

Mann-Whitney U Test was used. * p<0.05 was considered significant.

When PCT values were divided into as<2 ng/ml and≥2 ng/ml, it was observed that 5 patients (10%) were pre-operative, 19 patients (38%) were on the postoperative first day, and 12 patients (24%) were on postoperative 5. day had the value of 2 and above 2 (N=50) (Table 2).

When the characteristics of the patients' surgical complications were examined, it was observed that 12 patients (24%) patients had an infection at the surgical incision site as 11 patients of them were the superficial infection and one patient was in a deep area. It was observed that 12 patients (24%) had surgical site infection in the abdomen, and two patients (60%, n=5) had an intraabdominal abscess, and four patients (40%, n=5) had a pelvic abscess. It was observed that cardiovascular complications developed in 1 patients (2%, n=50), respiratory complications in 1 patients (2%. n=50) (Table 3).

There were no significant differences in PCT values in infection at the surgical incision site (Table 4).

However, it was observed that PCT values of patients with surgical infection in the abdomen were significantly higher than those without infection (p = 0.005) (Table 5).

It has been observed that the duration of hospitalization was prolonged for those with high PCT levels, those with infections at the surgical incision, and those with surgical site infections in the abdomen (p=0.004; p=0.016; p=0.002, respectively) (Table 6).

When the relationship between PCT, CRP, and WBC values was examined, there was a low level of correlation between PCT and CRP (correlation coefficient 0.290) at postoperative (PO) first day, and this was statistically significant (p<0.05). There was a moderate correlation (correlation coefficient 0.479) between PCT and CRP, and this was statistically significant (p<0.05) at PO 5th day. It was observed that there was a low-moderate correlation (correlation coefficient 0.341) between PCT and WBC at PO 5. day, which was statistically significant (p<0.05) (Table 7).

PCT values were higher in patients with surgical site infection in the abdomen (p=0.024). It was also observed that lymph node involvement and neurovascular invasion were significantly higher in patients with infections (p=0.001; p=0.026) (Table 8).

Table 5: The relationship between PCT values and infection in surgical incision of the study participants, Ankara, 2019.

Infection in Surgical Incision				
	No	Yes		
	Median (Min-Max)	Median (Min-Max)	U Values	P
PCT Preoperative	0.05 (0.01-15.08)	0.04 (0.02-6.1)	202.000	0.567
PCT Postoperative 1st day	0.91 (0.05-44.29)	1.74 (0.16-5.78)	203.000	0.570
PCT Postoperative 5th day	0.42 (0.04-35.3)	0.99 (0.02-6.76)	165.000	1.152

Mann-Whitney U Test was used. p<0.05 was considered significant.

Table 6: Distribution of the characteristics affecting the length of hospitalization of the study participants, Ankara, 2019.

	Duration of Hospitalization Median (min-max)	U Values	P*
PCT postoperative 5th day			
<2ng/ml	9 (2-25)	99.500	0.004
≥2ng/ml	15 (8-21)		
Surgical Site Infection			
No	10 (5-21)	119.000	0.016
Yes	14,5 (2-25)		
Surgical site infection status in abdomen			
No	10 (2-25)	28.500	0.002
Yes	20 (11-21)		

Mann-Whitney U Test was used. p <0.05 was considered significant.

Table 7: Correlation status of procalcitonin values of the study participants with CRP and WBC values, Ankara, 2019.

	Spearman's Rho	P değeri
Preop PCT- Preop CRP	0.149	0.301
Preop PCT - Preop WBC	0.283	0.049
PCT 1- CRP 1	0.290	0.041
PCT 1- WBC 1	0.164	0.255
PCT 5- CRP 5	0.479	0.001
PCT 5- WBC 5	0.341	0.015

Spearman test was used. p <0.05 was considered significant.

Table 8: Distribution of the surgery site infection in abdomen according to some characteristic's individuals of the study participants, Ankara, 2019.

	Surgery site infection in abdomen			
	No		Yes	
	N	(%)*	N	(%)*
PCT Postoperative 1st day (n=50)				
0.5 ng/ml	14	93.3	1	6.7
<0,5 and <2 ng/ml	15	93.8	1	9.3
<2 and <10 ng/ml	14	87.5	2	12.5
>10	1	33.3	2	66.7
χ^2=9,399 p=0,024				
PCT Postoperative 5th day (n=50)				
<2 ng/ml	36	94.7	2	5.3
>2 ng/ml	8	66.7	4	33.3

Continued.

	Surgery site infection in abdomen			
χ^2= 5,746 p=0,017**				
Lymph node involvement (n=50)				
No	36	97.3	1	2.7
Yes	8	61.5	5	38.5
χ^2= 10,175 p=0,001**				
Neurovascular invasion (n=50)				
No	28	96.6	1	3.4
Yes	16	76.2	5	23.8
χ^2= 4,940 p=0,026				

*percentage of %column, Fisher's was used.

DISCUSSION

Anastomotic leak and subsequent infection are among the most feared complications in patients undergoing surgery for rectal cancer. When it is noticed late, it causes peritonitis and sepsis, increases morbidity and mortali-ty, may cause an increase in local recurrence, and increase the duration of hospitalization and cost.[10-13]

In recent years, the ERAS protocol has been increasing after colorectal surgery. These practices aiming at early discharge and decrease postoperative problems.[14,15] However, these protocols may be disadvantageous in the early diagnosis of anastomotic leak and subsequent sepsis. Consequently, it causes a severe increase in mortali-ty, morbidity, and costs.[16,17]

Infections involving the skin and subcutaneous tissues, which can be treated with much simpler applications, can be frequently seen in patients with contaminated surgeries such as colorectal surgery.

These two conditions can be distinguished from each other by clinical, laboratory, and imaging methods. An application that can differentiate between abdominal and superficial subcutaneous infections and provide us with a prediction about abdominal sepsis early is significant for patient health and survival.18 PCT is a 116 ami-no acid protein that is the prohormone of calcitonin produced in parafollicular C cells in the thyroid gland, and basal levels in the blood are less than 0.05 ng / ml. In the case of bacterial sepsis, the blood level rises rapidly within two to three hours and can reach 700 ng/ml levels in the case of sepsis.[7,8]

Contrary to CRP, the severe bacterial infection is not considered at values below 0.5 ng/ml of PCT, which increases not only in inflammatory processes but only in the case of a bacterial infection, but it is necessary to be alert about severe sepsis and septic shock at values above 2 ng / ml.

In a study by Legoutte et al PCT's cut-off value was taken as 0.068 ng/dl, and 70% specificity and sensitivity were determined. On the other hand, Garcia Granero et al found that when they took the cut-off value of PCT as 0.31ng / ml, it showed abdominal infection with 100% sensitivity and 72% specificity.

Based on this information, we found that when the cut off value of PCT was taken as 2 ng/ml, it was significantly higher in patients with the abdominal infection on the postoperative 5th day. There was no significant difference in skin and subcutaneous infections in our study.

Since PCT's blood value increases before clinical findings appear and additions not only in the inflammatory process but only in bacterial infections, it is an early warning for abdominal sepsis and leakage. It promises as a predictor factor.

We observed that abdominal infection was more common in those with a PCT value of 2 and above on PO first and 5th days. Although publications are emphasizing that the PCT value due to bacterial translocation from the colon may be higher with the effect of PO first day surgery and this should be neglected, we think that patients with PCT values above 2 ng/ml on the postoperative first day should be followed up closely, and abdominal infection and leakage should be clarified with diagnostic radio diagnostic methods. Thus, an advantage in terms of morbidity, mortality, and cost should be achieved.

In terms of hospitalization duration, we have observed that those with PC values 2 ng/ml and above on PO 5th day were hospitalized longer. We think that this may be caused by an anastomotic leak, bacterial infection, and sepsis. These showed us that high PC values could guide the early detection of complications and develop appropriate treatment strategies. We also noticed that it was a harbinger of long-term hospitalization and high patient costs. We considered that early and appropriate antibiotic therapy would reduce morbidity, mortality, and consequently, costs.

In particular, in clinics such as ERAS protocol, where early discharge is applied, PCT examination on the fifth postoperative day and, if high, advanced examination and early treatment will protect both patients and healthcare providers in terms of patient health, medico-legal processes and costs.

The high degree of correlation between PCT and CRP on the postoperative 5th day reminded us that although we accept procalcitonin's superiority, we can also benefit from CRP and WBC for leakage and abdominal infection are not able to look at it.

The limitations of the study are its retrospective nature and the small number of patients.

CONCLUSION

PCT can be used as a biochemical predictor parameter in terms of abdominal infection and leaks. Especially on the fifth postoperative day, it should be determined, and leaked research should be done at its height. Its correlation with CRP and WBC is an indication that although they are not alternatives to each other, they should be more alert about leaks in case of their height.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Çaparlar MA, Uçar Y, Dokcu S, Hasırcı I, Ulutaş ME, Erşen O. Procalcitonin: the ideal predictor of anastomotic leakage. but, when? Int Surg J 2021;8:1418-23.