RESEARCH ARTICLE

Acidic Pelvic Drainage as a Predictive Factor For Anastomotic Leakage after Surgery for Patients with Rectal Cancer

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Abstract

Purpose: To demonstrate the value of sequential determinations of pelvic drainage in the identification of increased risk of anastomotic leakage (AL) after anterior resection for rectal cancer with a double stapling technique. Patients and Methods: Between January 2004 and December 2011, data for the daily postoperative pH of pelvic drainage fluid in 753 consecutive patients with rectal cancer who initially underwent anterior resection with a double stapling technique were reviewed. All patients experienced a total mesorectal excision. Patients with anastomotic leakage (Group AL, n=57) were compared to patients without leakage (Group nAL, n=696). Patients with perioperatively abdominopelvic implants that were likely to affect pH value (determined at 25 °C) other than leakage were excluded. Mean postoperative values were compared. Results: Anastomotic leakage was noted in 57 (7.6%) of 753 patients with rectal cancer. The diagnosis of AL was made between the 6th and 12th postoperative day (POD; mean 8th POD). There was no significance of the daily average values of pH on POD1 & 2 in group AL while a significantly sharp decline mean pH value reached its diagnostic point of AL ($p<0.001$) on POD3. A cut-off value of 6.978 on the 3rd POD maximized the sensitivity (98.7%) and specificity (94.7%) in assessing the risk of leakage. Conclusion: According to these results, an early and persistent decline of pH value of pelvic drainage fluid after rectal surgery with anastomosis, is a marker of AL. A cut-off value of 6.978 determined at 25°C on POD3 maximizes sensitivity and specificity.

Keywords: Rectal cancer - anastomotic leakage - pH value - pelvic drainage - anterior resection

Asian Pac J Cancer Prev, **14 (9)**, 5441-5447

Introduction

It has been found that colorectal cancer (CRC) is the third commonest cancer in males and the second in females. In 2008, more over 1.2 million new CRC cases and 608.700 deaths were reckoned to be occurred (Ahmedin et al., 2011). With the advent of stapling devices, surgical operation combining with preoperative chemo-radiation therapy (PCRT) and by means of total preventive ileostomy rate of anal sphincter preservation in present days (Tjandra et al., 2005). Nevertheless, patients with rectal cancer undergoing anterior resection can develop various postoperative complications. It is quite obvious that AL is the severest and most morbid complication.

Anastomotic leak after rectal cancer surgery has been reported to range between 5% and 25% of patients (Mileski et al., 1988; Fazio et al., 2007; Veenhof et al., 2007). Not only, the instant clinical consequences, but also AL carries long-term outcome, such as intra pelvic infection, peritonitis, sepsis, longer hospital stay, considerable extra cost, increased in-hospital morbidity and mortality, impaired pelvic organ function (Eriksen et al., 2005; Law et al., 2007; Lee et al., 2008; Riss et al., 2011).

Although there are multiple risk factors, such as being male, advanced age, severe obesity, lower tumor site (less than 4cm from the anal verge) and the reduction of TSGF in POD5, which are associated with anastomotic leakage have been reported in our previous study (Yang et al., 2013), it is difficult to predict this complication in individual patients on account of the absence of a diagnostic test and the difficulty with identifying AL at a early stage.

The diagnosis of AL should be as early as possible for the sake of reducing its associated morbidity and mortality (Doeksen et al., 2007). Many studies on anterior resections regarding AL come from multi-center and different surgeons. A variety of factors predisposing to AL have been reported in the previous investigations. However, lack of data about the risk factors and incidence associated with AL from a single-institute of one team of doctors.

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In addition, a great deal previous studies are repetitive works and duplicated effforts because of the limited power of innovative thinking. The pathophysiological character of AL is acute inflammation. In view of the essential role that neutrophils play in acute inflammatory processes and considering that interstitial acidic pH characterizes most inflammatory microenvironments, the notion that extracellular acidosis may intensify the acute inflammatory responses by enhancing neutrophil activity and extending its functional lifespan (Trevani et al., 1999; Martínez et al., 2006). The acidic microenvironments and acute inflammatory promote mutually so that AL is developing and the pelvic draining is becoming acidic, which is the main theoretical foundation for the present research. This study aimed to evaluate the utility of sequential postoperative pelvic drainage determinations of pH value in the identification of the increased likelihood of AL after anterior resection of rectal cancer, which has not been reported ever before.

Materials and Methods

Between January 2004 and December 2011, 753 consecutive patients with rectal cancer underwent anterior resection with double stapling anastomosis for primary rectal cancer at Colorectal Cancer Center, the Affiliated Jiangsu Cancer Hospital of Nanjing Medical University & Jiangsu Institute of Cancer Research, Nanjing, China. The medical notes of all patients were reviewed in detail. Eligibility criteria included rectal cancer, phrase I to III of TNM stage, histologically proven adenocarcinoma, open and laparoscopic surgery with pelvic drainage, all patients with 12 postoperative determinations of pH value, and antibiotics using for 7 PODs. Exclusion criteria were as follows: Hartmann's and Miles' procedure, phrase IV of TNM stage, colon cancer, hand-sewn anastomosis and perioperatively abdominopelvic implants that might be affect pH value, ongoing infection before surgery or an acquired infection in the postoperative period other than leakage. Rectal cancer was classified according to the distance from the anal verge, as determined by rigid sigmoidoscopy. Total mesorectal excision was adopted as the standard surgical technique according to tumor location. The Ethics Committee of Science approved data collection in the register.

All the patients were assigned to one of two groups according to the presence or absence of AL: with AL (Group AL, n=57), without AL (Group nAL, n=696). The two groups were compared according to the following characteristics: median age, gender, physical status (ASA score), the alcohol and tobacco abuse, tumor site, TNM stage, preoperative BMI, preventive ileostomy, surgical approach (laparotomy vs. laparoscopy), diabetes mellitus (DM), neoadjuvant chemoradiotherapy that was defined as a regimen of oral chemotherapy (carmofur or capecitabine) combined with radiotherapy (45 Gy), sequential postoperative pelvic drainage determinations of pH value that was determined by the pH meter, pp-15 (Sartorious Ltd., Germany) (determined at 25°C). In this study, the considered normal pH values of the pelvic draining were consulted by the mean pH values in Group nAL, which ranged from 7.200 to 7.700.

The patient was placed in a modified lithotomy, right side down, Trendelenburg position. For patients undergoing laparoscopic surgery, an initial 12-mm port placement was carried out using the open technique, and pneumoperitoneum was accomplished using carbon dioxide. A standard 10-mm laparoscope was inserted through the 12-mm trocar, and then two 5-mm ports were inserted in the upper right and left abdominal quadrants and two more 12-mm ports were placed in the lower right and left abdominal quadrants under laparoscopic guidance. For patients undergoing open surgery, a median incision in lower abdomen was made to expose surgical field.

Clinical AL was defined as the presence of leakage signs and confirmed by diagnostic work-up; consequently, additional surgical treatment was mandatory. All patients diagnosed with AL in present study were defined as the presence of leakage signs (pelvic abscess, fecal or purulent discharge from a drainage tube or wound, peritonitis) and confirmed by radiographic work-up or by operative findings between the 6^{th} and 12^{th} POD (mean 8^{th} POD). The AL in this study was determined by ICD-9 codes 997.4, 567.22 (abdominopelvic abscess), and 569.81 (fistula of the intestine).

Differences between groups were evaluated based on the chi-square or Fisher's exact test for the dichotomic variables and on the ManneWhitney test for the continuous variables. Significance was calculated at the 95% CI and p value < 0.05. The ROC (receiver operator characteristic) curves of pH value were used to determine the best cut-off values for AL. The ROC curves are a plot of the sensitivity (true positives) of the test against 1-specificity (false positives), for each threshold of the test (each pH value level). Each point on the ROC curve represents a particular pair of sensitivity and (1-) specificity for each determined threshold. Statistical analyses were performed using IBM SPSS statistics 19.0 for Windows (SPSS Inc; IBM, Chicago, IL).

Research experience

We have published medical researches that were conducted in Jiangsu Cancer Center elsewhere (Huang et al., 2011; Li et al., 2011; Li et al., 2011; Li et al., 2011; Xu et al., 2011; Xu et al., 2011; Xu et al., 2011; Yan et al., 2011; Zhang et al., 2011; Gong et al., 2012; Liu et al., 2012; Gu et al., 2013; Li et al., 2012; Shu et al., 2012; Zhan et al., 2012; Zhan et al., 2012; Xu et al., 2012; Xu et al., 2012; Yu et al., 2012; Zhang, et al., 2012; Zhang et al., 2012; Chen et al., 2013; Dai et al., 2013; Deng et al., 2013; Huang et al., 2013; Liu et al., 2013; Liu et al., 2013; Liu et al., 2013; Lu et al., 2013; Sun et al., 2013; Wei et al., 2013; Wu et al., 2013; Yang et al., 2013; Yin et al., 2013; Yin et al., 2013)

Results

The clinical characteristics of the selected sample stratified by goup are detailed in Table 1. The overall AL rate was 7.6% (57/753 patients). A total of 753 patients [452 male patients (60.0%)] with a median age of 65 (50-74) years at the time of surgery were included. The physical

Table 1. Clinical Characteristics of the Selected Sample Stratified by Group

Variable	Group nAL(n=696)	Group AL(n=57)	*p* value
Age mean (IQR) y	61(50-69)	68 (55-74)	
<65	518	15	*p*<0.001
≥65	178	42	
Gender			
Male	406	46	*p*<0.001
Female	290	11	
Physical status (ASA score)			
ASA≤2	607	47	*p*=0.307
ASA≥3	89	10	
Tobacco abuse			
≤4 cigarettes per day	395	16	*p*<0.001
≥5 cigarettes per day	301	41	
Alcohol abuse			
≤2 glasses per day	476	42	*p*=0.407
≥3 glasses per day	220	15	
Tumor site (from the anal verge)			
<4 cm	112	46	*p*<0.001
≥4 cm	584	11	
TNM stage			
I~II	366	33	*p*=0.44
III	330	24	
Preoperative BMI			
<35	669	32	*p*<0.001
≥35	27	25	
Surgical approach			
Laparotomy	616	49	*p*=0.566
Laparoscopy	80	8	
Preventive ileostomy			
No	647	56	*p*=0.123
Yes	49	1	
Neoadjuvant chemoradiotherapy			
No	680	54	*p*=0.170
Yes	16	3	
Diabetes mellitus			
Abesence	664	55	*p*<0.001
Presence	32	9	

status of patients at large were ASA 1 or 2 (86.9%). One hundred and fifty eight (21.0%) patients presented rectal cancer within 4 cm from the anal verge. Among all the patients, 45.4% (342) & 32.2% (235) of whom abused tobacco and alcohol, respectively. Three hundred and fifty four (47.0%) sufferers were diagnosed with phrase III rectal cancer pathologically and postoperatively. The preoperative BMI was equal or greater than 35 (severe obesity) in 52 (6.9%) patients. Nineteen (2.5%) patients received neoadjuvant chemoradiotherapy. A preventive ileostomy was proceeded in 50 (6.6%) sicks, and a laparoscopic surgery was performed in 88 (11.7%) patients. Forty one (5.4%) patients presented diabetes mellitus preoperatively.

The correlations between clinical characteristics and AL are summarized in Table 1. Univariate analysis

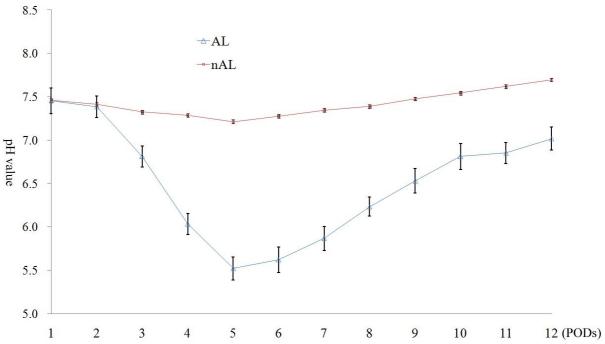

Figure 1. Evolution of PH Values in the Postoperative Period in Patients with and Without AL

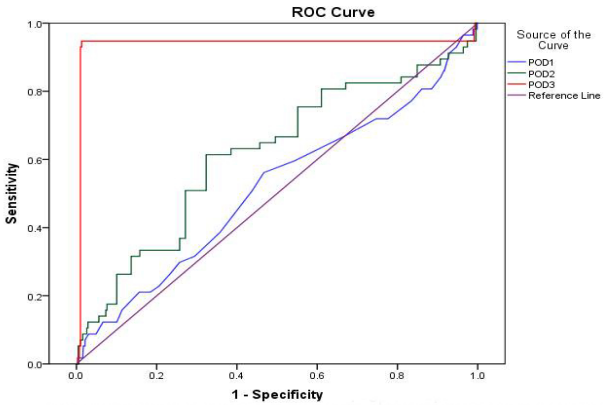

Figure 2. Receiver Operator Characteristic (ROC) Curve for Cut-off Analysis of Pelvic Drainage PH Value on POD1, 2 and 3 in Patients with AL

demonstrated that AL was more common in patients with elder age (*p*<0.001), male gender (*p*<0.001), tobacco abuse (*p*<0.001), lower tumor site (*p*<0.001), high preoperative BMI (*p*<0.001), diabetes mellitus (*p*<0.001). Preventive ileostomy and neoadjuvant therapy tended to be associated with the development of anastomotic leakage, with *p* values less than 0.20. Surgical approach, Alcohol abuse, ASA score and TNM stage were not significant risk factors in univariate analysis.

The diagnosis of AL was performed between the 6th and 12th POD (mean 8th POD). There was no statistically significant difference of pH value of pelvic drainage on POD1&2 between the two groups. In the postoperative period, however, it was clearly observed that from POD3 onwards, the values of pelvic pH were significantly lower in group AL (Table 2). The alterations of mean pH values in group nAL were different from group AL. The mean pelvic pH values of both group nAL and AL reached their bottom on POD6, followed by a rapid rise in Group AL while a slight rise in Group nAL, thereafter (Figure 1).

On POD2, mean pH value was 7.384 in group AL and 7.412 in group nAL (*p*=0.821). On POD3, those values were 6.811 in group AL and 7.325 in group nAL (*p*<0.001)

Table 2. Mean Values of pH in the Postoperative Periods (Group AL; Group nAL)

	pH value											
	POD1	POD2	POD3	POD4	POD5	POD6	POD7	POD8	POD9	POD10	POD11	POD12
Group AL	7.453	7.384	6.811	6.034	5.522	5.621	5.867	6.234	6.529	6.812	6.852	7.017
Group nAL	7.459	7.412	7.325	7.285	7.211	7.277	7.346	7.387	7.476	7.543	7.618	7.697
p	0.968	0.821	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Table 3. Sensitivity and Specificity of pH Value of Pelvic Drainage Used as a Cut-off in the Identification of AL, Calculated on POD 2 and 3 (ROC analysis)

pH value	POD2		POD3	
	sensitivity(%)	specificity(%)	sensitivity(%)	specificity(%)
6.691	99.4	5.3	99	10.5
6.875	99.4	5.3	99	84.2
6.911	99.4	5.3	99	93
6.978	99.4	5.3	98.7	94.7
7.058	99.3	5.3	98	94.7
7.108	99	5.3	95.5	94.7

(Table 2). Based on the evaluation of the ROC curves (Figure 2), a cut-off value of 6.978 on POD3 maximized the sensitivity (98.7%) and specificity (94.7%) of pH value in predicting the risk of leakage (Table 3).

Discussion

The AL rate after colorectal surgery varies between 1% and 40%, rest with the definition of AL and on the type of resection performed, being higher in extraperitoneal anastomosis (Bellows et al., 2009). The rate of 7.6% in this study falls within the range of previously published series. This rate is, however, lower than the average leakage rate of 10% reported in a systematic review (Paun et al., 2010). It is also lower than the leakage rate reported in a similar study from Denmark looking at this complication using a population database (Bertelsen et al., 2009).

It is not different from comparable reports that the low leakage rate in the present study could be explained by the fact that may be a reflection of technically skilled surgery. Success to mobilize the splenic flexure, success to perform high ligation of the inferior mesenteric artery to ensure the collateral blood supply, and success to test the integrity of the anastomosis can contribute to the low leakage rate.

In previous study, this complication is associated with high mortality (4%-15%), result in more than a third of hospital deaths after colorectal surgery (Bokey et al. 1995). Hence, the need for an early diagnosis of AL turns into clear. However, this diagnosis is always difficult in the early postoperative days because of lack of clinical manifestations present at that time, which contributes to increased morbidity and mortality. The develop a fever, presence of infectious or abdominal symptoms, such as pain and tympany do not allow an early diagnosis of leakage, as these symptoms usually occur after POD5. Nevertheless, in accordance with some studies, these may be perceived as complications that precede by several days the diagnosis of AL. Not only the presence of fever and abdominal symptoms, but also the time it takes to recover bowel function, are lacking in specificity in identifying patients with AL (Bellows et al., 2009; Ortega-Deballon et al., 2010).

In the light of the viewpoint that the delayed diagnosis (after POD5) of AL is related to a mortality of 18%, but bottommost morbidity if diagnosed and treated before POD5. Early detection of the complication is imperative for prompt establishment of treatment, making early characteristic markers utile (Alves et al., 2002).

The abbreviation pH can be viewed as power of the concentration of the Hydrogen ion. In technical terms, pH is the negative logarithm of the activity of the solvated hydronium ion, more often expressed as the measure of the hydronium ion concentration. In chemical field, pH is a measure of the acidity or basicity of an aqueous solution. The pH value is stemmed from a set of standard solutions whose pH is established by international agreement (Covington et al., 1985). Measurements of pH are important in medicine, biology and many other scientific applications. In present study, sequential postoperative pelvic drainage determinations of pH value that was determined by the pH meter, pp-15 (Sartorious Ltd., Germany), which was accurate and convincing. Its advantage and convenient, makes pH a valuable marker for detecting disease activity, inflammatory response and the appearance of postoperative complications. Based on the academic and technical applications above, the pH values of both groups in the postoperative periods were determined in this series.

The anastomosis after a low anterior resection, however, usually leads to local acute inflammation at the anastomotic site in pelvic cavity. It has been reported that the decreased pH at the site of an inflammatory reactions is attributed to the local increase in the concentration of lactic acid produced by the glycolytic activity of the polymorphonuclear leukocytes of the exudates, furthermore, although the blood pH remained unchanged, the pH of the inflammatory exudate decreased with time showing a definite fall at 24 hour and reaching the lowest value at 72 hour (Donald et al., 1971).

Numerous studies of the cellular and molecular mechanism about pH and acute inflammation indicated that large numbers of cells, cytokines, ions and inflammatory mediators migrate from the blood into the exudate during acute inflammatory reactions. It has been proven that the inflammatory cells, with the ability to produce free radicals, are working in a surrounding environment of low pH so that the free radical can mediate tissue injury. Moreover, it is showed that production of superoxide and nitric oxide was also pH-dependent. Impaired pH, regulation of exudative cells mediate cellular dysfunction and impaired resolution of infection at inflammatory sites (Dahlén et al., 1981; Hackam et al., 1996; Benz et al., 1997). In recent years, it was reported that the acute inflammatory responses via inducing neutrophil activation as well as delaying spontaneous apoptosis and extending neutrophil functional lifespan, based on a mechanism dependent on activation of phosphatidylinositol 3-Kinase/Akt and ERK pathways, which were intensified by pH-Dependent regulation of leukocyte 5-lipoxygenase activity in inflammatory exudates. In addition, low pH can also increase stabilin-1 expression and stabilin-1 phagocytosis in macrophages. Extracellular acidification (pH 5.5-7.0) up-regulates stabilin-1 expression in macrophages, thereby modulating the phagocytic capacity of macrophages. Furthermore, extracellular acidosis in peripheral tissues contribute to the initiation of adaptive immune responses by DCs, favoring the development of Th1 immunity (Trevani et al., 1999; Carbonell et al., 2002; Martínez et

al., 2006; Martínez et al., 2007; Park et al., 2012).

To sum up, the acidic microenvironments during inflammatory reactions against pathogens are the outcome of local acid production by anaerobic, glycolytic infiltrating neutrophils and macrophages, and low oxygen tensions in inflammatory regions. As is mentioned above, together with clinical signs and other inflammatory markers, pH level can be evaluated as an indicator of an unfavorable postoperative course. Given the potential complications associated with AL in rectal surgery, particular emphasis has also been given to this marker in this area.

For the reason that tissue ischemia at the anastomotic loop by a double stapling technic of a leaking anastomosis, it seems to be responsible for the appearance of an intense and early inflammatory response, with subsequent decreased pelvic pH value. The theory stating that poor tissue perfusion increases the risk of anastomotic complications. In a series of animal and human models, the decrease in anastomotic tissue oxygen tension that causes changes in the healing process could be demonstrated (Shandall et al., 1985; Sheridan et al., 1987; Attard et al., 2005). The decrease in anastomotic intramucosal pH level in the postoperative period is significantly associated with increased risk of dehiscence and supports the theory that poor tissue perfusion of an anastomosis starts early and increases the risk of complications (Millan et al., 2006).

In the present study, we have, for the first time, demonstrated that a rapid decrease (6.811) of the pelvic drainage determinations of pH value is on 3rd POD (72 hours after surgical trauma) and the lowest one (5.522) is on POD5 (120 hours after surgical trauma). Thus, somehow, the results are consistent with the reports above for a acute inflammation of surgical injury combining with the acidic stubborn stool leaked from the fistula of the anastomosis, which brings about a secondary infection so that bottom of the pelvic pH value in patients with AL shifts to POD5. On the other side, the pH level of patients without AL goes slowly down to its bottom of 7.211, then smoothly goes up to its top of 7.697, caused by operative trauma only. The changes observed in postoperative pH value of pelvic drainage in patients who developed leakage demonstrate the presence of an inflammatory process after the surgical procedure (and before the occurrence of clinical manifestations).

In this series, we observed that from the third POD onwards, mean pH value was significantly lower in the group who developed leakage, and the diagnosis of the complication was made on the very day, then this marker remained declining until POD5. These results have never been reported before and seem to suggest that the early and sustained decrease of postoperative pelvic pH value may be used as a predictor of AL in patients underwent rectal surgery. Thus, the pretty marker is superior to the others, such as C-creative protein (CRP), which is a hot marker that has been studied repeatedly in present day (Welsch et al., 2007; Matthiessen et al., 2008; Ortega-Deballon et al., 2010; Woeste et al., 2010). The high level CRP in patients with AL may be caused by other infections including respiratory, urinary tract and surgical wound infections, which should be excluded; however the low pH value of pelvic draining in patients with AL is not necessary to exclude those infectious complications.

Currently procalcitonin has been studied as another earlier marker of inflammatory changes, but squint towards reflect the magnitude of the systemic inflammatory response only on the first half POD, especially after major operation and has to be interpreted with caution (Lagoutte et al., 2012; Garcia-Granero et al., 2013; Ortega-Deballon et al., 2013).

It is possible that some patients in group nAL might have had a subclinical anastomotic leakage. However, these patients usually do not require therapeutic intervention and our primary goal was to achieve an early identification of clinically significant complications, associated with increased morbidity and mortality, and that might benefit from earlier treatment.

Present study is a retrospective analysis of a large sing-center database with limitations. Coding for comorbidities and postoperative complications may result in skewed results due to the vague nature of ICD-9 definitions for these variables. This retrospective review, however, is one of the largest and most comprehensive studies investigating the risk factors for AL after anterior resection.

In summary, according to the results of present study, an early and persistent decline of pH value of pelvic drainage after rectal surgery with anastomosis, is a marker for predicting and diagnosing AL. A cut-off value 6.978 determined at 25°C on POD3 maximizes sensitivity and specificity. Daily postoperative pelvic pH value measurements may therefore be useful in identifying those patients requiring careful clinical reassessment and possibly imaging to confirm or exclude AL.

Acknowledgements

The authors declare that there is no conflict of interest with any one that could bias the work. Dr. Xin-En Huang is supported in part by a grant from Jiangsu Provincial Administration of Chinese Medicine (LZ11091), and in part from a special research fund of Organization Department of Jiangsu Provincial Party Committee, Talent Work Leading Group of Jiangsu Province (333 High-level Talents Training Project).

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