RESEARCH ARTICLE

# Novel and Effective Almagate Enema for Hemorrhagic Chronic Radiation Proctitis and Risk Factors for Fistula Development

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## Abstract

**Radiation proctitis is a common complication after radiotherapy for pelvic malignant tumors. This study was conducted to assess the efficacy of novel almagate enemas in hemorrhagic chronic radiation proctitis (CRP) and evaluate risk factors related to rectal deep ulcer or fistula secondary to CRP. All patients underwent a colonoscopy to confirm the diagnosis of CRP and symptoms were graded. Typical endoscopic and pathological images, risk factors, and quality of life were also recorded. A total of 59 patients were enrolled. Gynecological cancers composed 93.1% of the primary malignancies. Complete or obvious reduction of bleeding was observed in 90% (53/59) patients after almagate enema. The mean score of bleeding improved from 2.17 to 0.83 ($P$<0.001) after the enemas. The mean response time was 12 days. No adverse effects were found. Moreover, long-term successful rate in controlling bleeding was 69% and the quality of life was dramatically improved ($P$=0.001). The efficacy was equivalent to rectal sucralfate, but the almagate with its antacid properties acted more rapidly than sucralfate. Furthermore, we firstly found that moderate to severe anemia was the risk factor of CRP patients who developed rectal deep ulcer or fistulas ($P$= 0.015). We also found abnormal hyaline-like thick wall vessels, which revealed endarteritis obliterans and the fibrosis underlying this disease. These findings indicate that almagate enema is a novel effective, rapid and well-tolerated method for hemorrhagic CRP. Moderate to severe anemia is a risk factor for deep ulceration or fistula.**

**Keywords:** Chronic radiation proctitis - hemorrhage - almagate - risk factor - rectal fistula - enema.

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## Introduction

Radiation proctitis is a common complication after radiotherapy for pelvic malignant tumors, for the fixed location of the rectum and anatomic relationship with other organs (Wang et al., 1998). Acute radiation-induced injury that occurred during radiotherapy is often self-limiting and easy-cured. The chronic modality that can be delayed from months to years after radiation treatment, accounted for 5% to 20% of the cases (Pesee et al., 2010). Chronic radiation proctitis (CRP) is difficult to manage for recurrent rectal bleeding and required blood transfusion in severe cases (Haas et al., 2007; Leiper and Morris, 2007; Patel et al., 2009). There are no well-defined guidelines for the management of CRP. Various medical agents for CRP have been reported , including sucralfate (Kochhar et al., 1988; R et al., 1991), 5-aminosalicylic acid analogue sulfasalazine (R et al., 1991), corticosteroids (R et al., 1991), metronidazole (Eaveiæ, 2000), rebampide (Kim et al., 2008), short-chain fatty acid (Talley et al., 1997), vitamin A (Patel et al., 2009) and pentoxifylline (Hille et al., 2005). Other treatment modalities included endoscopic argon plasma coagulation (APC) (Postgate et al., 2007), hyperbaric oxygen (Charneau et al., 1991), topical formalin application (Patel et al., 2009). Surgical intervention is often reserved for refractory bleeding or complications like fistula and stricture. And the reported procedures included diversion colostomy and proctectomy (Anseline et al., 1981; Khubchandani et al., 1987; Lucarotti et al., 1991; Nowacki, 1991). The results of these methods are variable and the overall efficacy has been unsatisfactory (Kim et al., 2008).

This study was to introduce a novel agent of rectal almagate (aluminium-magnesium hydroxycarbonate hydrate, an antacid agent) enema and evaluate its short- and long-term efficacies for hemorrhagic CRP in our center. Furthermore, we performed analysis of potential risk factors for rectal fistula in CRP patients.

## Materials and Methods

*Patients*

Patients with hemorrhagic CRP treated by hospitalization at the Sixth Affiliated Hospital of Sun

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Yat-Sen University were evaluated from 2007 to 2015. All patients underwent flexible colonoscopy before enema to confirm the diagnosis of CRP. This study was approved by the ethics committee of the Sixth Affiliated Hospital of Sun Yat-Sen University and was in accordance with the provisions of the World Medical Association's Declaration of Helsinki in 1995 (as revised in Tokyo 2004). Due to the retrospective nature of the study, the informed consent was waived.

*Inclusion and exclusion criteria*

CRP patients initially treated with rectal almagate enema were enrolled. Patients with recurrent primary malignancies and had CRP less than 3 months after end of pelvic radiation were excluded. These patients who were treated with almagate enema for less than one week were also excluded.

*Grades and scores*

Symptoms related to CRP, including rectal bleeding and other common concomitant symptoms such as anorectal pain, tenesmus, stool frequencies, were graded before and after enema according to Common Terminology Criteria for Adverse Events (CTCAE) (CTCAE 4.0 – June 14, 2010, National Institutes of Health). Typical endoscopic photos and pathological representative images were collected to present the classical features of CRP. The severity of endoscopic bleeding was scored according to the endoscopic Vienna Rectoscopy Score (VRS) systems (Wachter et al., 2000). Briefly, VRS contains five common endoscopic findings of CRP, i.e., telangiectasia, congested mucosa, ulceration, stricture, and necrosis.

*Almagate retention enema*

Enemas were prepared by diluting 15 ml of almagate suspension (1.5 g) in 30-50ml normal saline. Almagate enemas were administrated through the anal via a soft suction tube inserted 5-8cm into the anal verge twice daily at wards. Enemas were tried to retain in the rectum for about 60 min with intermittent position change from left lateral to supine and to right lateral every 20 minutes. Since no previous experience of almagate enema existed, patients were usually discharged upon the cessation or obvious reduction of rectal bleeding when it was possible and safe to continue enemas by self-administration at home. Response was defined as a 0 or 1 grade of bleeding after enema. In those patients with poor response at 2 weeks, or requiring blood transfusion again were considered to be failed.

*Follow-up*

A long-term follow-up was done by a telephonic questionnaire or by searching medical records of repeated hospitalization for these patients unable to contact. CTCAE grades of bleeding at follow-up were recorded. The qualities of life before enema and at follow-up were also investigated according to the European Organization for Research and Treatment of Cancer (EORTC QLQ C30) (Aaronson et al., 1993). The QLQ-C30 questionnaire was comprised of nine-multi-item scales: five scales of functions (physical, role, emotional, cognitive, and social); three scales of symptoms (pain, fatigue, and nausea/vomiting); and one global health and quality of life scale. Six single-item symptom measures (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) were also included.

*Risk factors*

Referring to the studies conducted by Li et al (Yang and Lv, 2012; Li et al., 2013), demographic and clinical variables which may affect the progression of CRP and thus be possibly related to rectal deep ulcer or fistula (ulcer: ≥3 grades in VRS ) were evaluated: age; cumulative radiation dosage; presence of acute radiation-induced enteritis; concomitant chemotherapy; latency of CRP; duration of symptom; hypertension, diabetes mellitus and previous transfusion requirement; gynecological malignancy; CTCAE grades of bleeding; operations for primary tumors; body mass index (BMI); preoperative anemia; preoperative albumin and total protein in blood; APTT (activated partial thromboplastin time); and SCC (squamous cell carcinoma antigen) were also included in the analysis of risk factors.

*Statistical analysis*

Statistical analysis was performed with SPSS version 13.0 software (IBM, USA). Continuous variables were analyzed by Student's t test, and categorical variables were compared by the Pearson Chi-square test. Parametric test - Wilcoxon rank sum test was performed to compare ranked data such as CTC grades of symptoms, VRS grades of endoscopic findings, and the quality of life. Potential risk factors related to rectal fistula were evaluated by univariate analysis. Multivariate logistic regression analysis was not conducted because only one variable of moderate to severe anemia with a $P$ value less than 0.1. All $P$ values were two-sided and less than 0.05 were considered statistically significant.

## Results

*Patients' democraphics*

A total of fifty-nine patients treated for hemorrhagic CRP at a single center were analyzed. Demographic and clinical data were collected (Table 1). Gynecological cancers composed 93.1% (55/59) of primary malignancies. The mean radiation dosage was 82.5 Gy (range: 40-120 Gy, defined as the cumulative dosage of external and endocavitary radiation, and included the radiation for both the site of primary malignancy and metastatic lymph nodes). The onset of symptoms occurred at a mean 9.3 (range: 0-36) months after radiotherapy. Mean VRS was 3.9 points.

*Typical endoscopic and histo-pathological features of CRP*

There are many symptoms that occurred during the progressive fibrosis course of CRP. We collected typical endoscopic images of CRP presentations after radiotherapy, which will provide guidance for endoscopic physicians to better diagnosis of CRP. Typical endoscopic features of CRP including congested mucosa, telangiectasis, errhysis,

ulceration and erosion were presented (Figure 1). The representative histological features of CRP from resected rectal specimens were also presented in seven patients. These classical features included telangiectasia, damaged integrity and lymphocyte infiltration and reduced mucosa crypts in the mucosa layer; abnormal hyaline-like wall vessels, sporadic radiation fibrocytes and diffused dilated blood vessels in the submucosa layer (Figure 2).

*Symptom scores and short-term efficacies*

All of 59 patients had VRS Grade 2 (50 patients) or Grade 3 (9 patients) of rectal bleeding before enema. After almagate treatment, Grade 0 (16 patients) and Grade 1 (37 patients) of bleeding were observed, which revealed an obvious improvement of bleeding. The mean score of rectal bleeding was improved from 2.17 (before enema) to 0.83 (after enema) ($P$<0.001) The accompanying symptoms of anorectal pain, tenesmus and stool frequency were also significantly improved after the enemas (Figure 3). The overall response rate in controlling bleeding was 90% (53/59). Six patients didn't respond to almagate enema. Of them, four patients were treated with topical 4% formalin and obtained bleeding resolution. The remaining two patients who had refractory anorectal pain and bleeding were managed with a Park's procedure when topical 4% formalin failed (Park's procedure: a sphincter-saving operation which involved resection of the rectum and the perianal anastomosis of the healthy colon to the anal canal, details were described previously) (Parks et al., 1978; Nowacki, 1991). Anorectal pain and bleeding were alleviated after the procedure.

**Table 1. Demographics and Characteristics of 59 Patients with Hemorrhagic Chronic Radiation Proctitis**

| Patient demographics and characteristics | |
|---|---|
| Gender (female/male) | 56/3 |
| Mean age (years, range) | 55 (40-75) |
| Primary malignancy, n (%) | |
| Cervical cancer | 45 (75.9) |
| Endometrial cancer | 7 (12.1) |
| Vaginal cancer | 1 (1.7) |
| Ovary cancer | 1 (1.7) |
| Prostate cancer | 3 (5.2) |
| Cervical and rectal cancer | 1 (1.7) |
| Vulvar melanoma | 1 (1.7) |
| Radiation Therapy, n (%) | |
| Radical irradiation | 37 (62.1) |
| Preoperative | 1 (1.7) |
| Postoperative | 18 (31) |
| Palliative | 3 (5.2) |
| Radiation dosage (Gy, mean, range) | 82.5 (40-120) |
| Presence of acute radiation enteritis, n (%) | 29 (48.3) |
| Onset of symptom (month) | 9.3 (0-36) |
| Duration of symptom (month) | 4.5 (0-24) |
| Previous blood transfusion requirement, n (%) | 8 (13.6) |
| Previous therapy, n (%) | 29 (48.3) |
| Mean Hemoglobin (g/dl, range) | 10.3 (4.2-12.9) |
| Radiation proctitis, n (%) | 47 (79.3) |
| Radiation proctosigmoiditis, n (%) | 12 (20.7) |
| BMI* (kg/m2) | 22.1 (14.6-29.7) |
| Mean VRS#, point (range) | 3.9 (1-5) |
| Hypertension, n (%) | 9 (15.5) |
| Diabetes mellitus, n (%) | 5 (8.6) |
| Previous abdominal/pelvic surgery, n (%) | 25 (43.1) |

*body mass index; # Vienna Rectoscopy Score

*Follow-up*

Over a mean 19.2 (rang: 2-72) months of follow-up, 5 patients were lost to follow up, 54 patients were followed.

**Table 2. CTC Grades of Bleeding before Enemas, After Enemas and at follow-up in 32 Patients Receiving Almagate-Based Retention Enemas Only**

| Grade | Before enemas,n | After enemas,n | At follow-up, n |
|---|---|---|---|
| 0 | 0 | 9 | 6 |
| 1 | 0 | 23 | 16 |
| 2 | 26 | 0 | 8 |
| 3 | 6 | 0 | 2 |

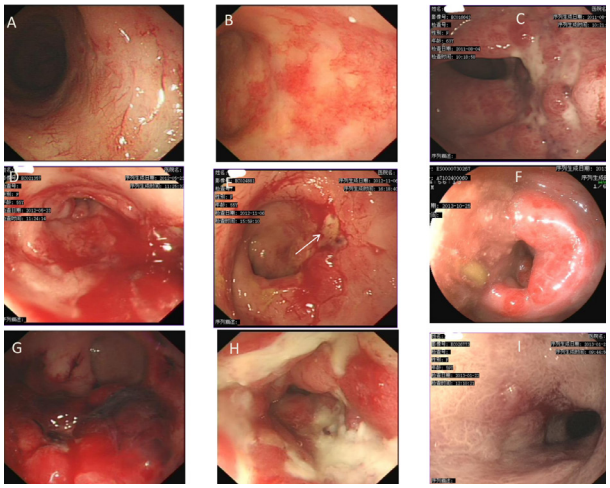

**Figure 1. Typical endoscopic presentations of chronic radiation proctitis (CRP).** (A) mild telangiectasia; (B) multiple confluent telangiectasis; (C) diffuse congested mucosa with confluent telangiectasis; (D) active bleeding; (E) ulceration (arrow); (F-G) severe congested mucosa; (H) erosion; (I) stricture

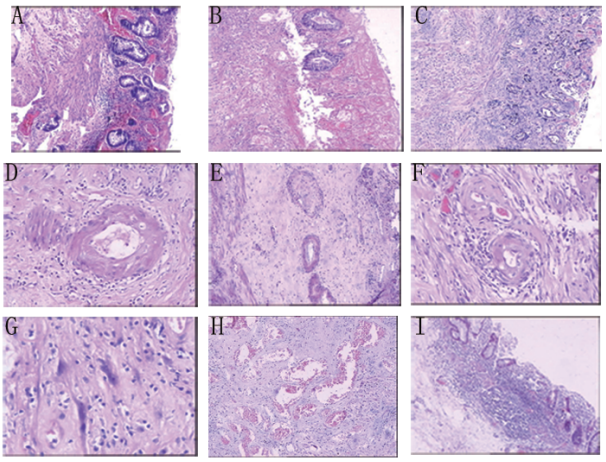

**Figure 2. Representative histo-pathological appearances of chronic radiation proctitis from resected rectal specimens in seven patients.** (A-C) Telangiectasia and damaged integrity in the mucosa layer by H&E staining (magnifications ×100). (D-F) Abnormal hyaline-like wall vessels in the sub-mucosa layer. (G)Sporadic radiation fibrocytes in the submucosa layer. (H)Diffused dilated blood vessels in the submucosa layer. (I) lymphocyte infiltration and reduced mucosa crypts in the mucosa

**Table 3. The quality of life of Pre-enema and at follow-up in Hemorrhagic CRP Patients Assessed by EORTC QLQ-C30 Scale**

| QLQ-C30 Scale | Reference (Normal German population) | Total patients at follow-up (n = 43), mean (SD◆) | | | | Enema only (n = 29),mean (SD) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Pre-enema | Follow-up | Δ (FU)-Pre | Significance | Pre-enemas | Follow-up | Δ (FU)-Pre | Significance |
| Global health | 63.2 | 44.1 (22.0) | 66.0 (20.3) | 21.9 | <0.001 | 48.8 (22.8) | 69.4 (15.4) | 20.6 | 0.001 |
| Physical function | 82.6 | 80.0 (18.3) | 83.3 (21.3) | 3.3 | 0.273 | 84.2 (13.9) | 83.6 (22.3) | -0.6 | 0.905 |
| Role function | 75 | 74.8 (26.8) | 83.7 (28.3) | 8.9 | 0.095 | 81.1 (24.3) | 84.4 (28.3) | 3.3 | 0.62 |
| Emotional function | 62.2 | 77.1 (23.6) | 85.5 (20.0) | 8.4 | 0.008 | 84.4 (15.4) | 89.7 (18) | 5.3 | 0.088 |
| Cognition function | 81.3 | 93.0 (14.7) | 90.3 (11.1) | -2.7 | 0.066 | 95.6 (11.5) | 90 (11.2) | -4.4 | 0.004 |
| Social function | 78.4 | 86.8 (25.6) | 91.9 (16.4) | 5.1 | 0.043 | 97.8 (7.2) | 98.3 (6.7) | 0.5 | 0.785 |
| Fatigue | 34.1 | 29.2 (27.2) | 19.9 (25.5) | -9.3 | 0.049 | 22.2 (20.2) | 15.6 (23.1) | -6.6 | 0.274 |
| Nausea/ vomiting | 5.7 | 2.7 (8.1) | 2.3 (7.8) | -0.4 | 0.783 | 2.8 (7.7) | 3.3 (9.2) | 0.5 | 0.705 |
| Pain | 33.1 | 23.6 (31.9) | 9.7 (19.7) | -13.9 | 0.002 | 12.8 (19.9) | 7.2 (12.9) | -5.6 | 0.04 |
| Dyspnea | 18.8 | 20.9 (29.1) | 13.2 (22.0) | -7.7 | 0.047 | 16.7 (24.4) | 13.3 (20.7) | -3.4 | 0.13 |
| Insomnia | 38.5 | 30.2 (32.4) | 18.6 (27.5) | -11.6 | 0.035 | 25.6 (27.2) | 15.6 (24.3) | -10 | 0.167 |
| Appetite loss | 9.4 | 8.5 (19.4) | 4.7 (13.8) | -3.8 | 0.26 | 2.2 (8.5) | 2.2 (8.5) | 0 | 1 |
| Constipation | 9.1 | 15.5 (27.6) | 6.2 (15.0) | -9.3 | 0.007 | 8.9 (21.3) | 4.4 (11.5) | -4.5 | 0.068 |
| Diarrhea | 9.2 | 21.7 (29.0) | 10.1 (18.6) | -11.6 | 0.009 | 23.3 (29.2) | 10 (17.8) | -13.3 | 0.039 |
| Financial difficulties | 17.1 | 52.7 (24.4) | 48.8 (27.6) | -3.9 | 0.461 | 57.7 (23) | 52.2 (27) | -5.5 | 0.273 |

*, point ( Follow-up) – point (pre-enemas); #, Wilcoxon rank sum test; ◆, Standard variation.

Among them, five patients died of tumor relapse. Ten patients experienced recurrent rectal bleeding. Of these 10 patients, 6 patients responded to re-establishment of almagate enema; 2 patients were managed with topical formalin, which brought a remission of bleeding; the remaining 2 patients were treated with diverting colostomy and bleeding was successfully controlled. During follow-up, 22 patients progressed to rectal deep ulcer (n=8) or rectal-vaginal fistulas (n=14). And these patients with fistulas received diverting colostomy or surgical proctectomy for handling with this embarrassing complication.

*Long-term efficacies*

To exclude the effects of other medical treatments on bleeding, long-term efficacy of almagate enema were evaluated in 32 patients who were administered with only retention enema both at first hospitalization and during follow-up. All of the patients had a Grade 2 (26 patients) or Grade 3 (six patients) severity of bleeding before enema. There were obvious improvements of bleeding in all 32 patients (Grade 0: nine patients; Grade 1: 23 patients) after the treatment. During the follow-up, 22 patients (69%) had complete resolution or obvious improvements of bleeding (Grade 0 in six patients and Grade 1 in 16 patients). 10 patients who failed to enema didn't achieve any improvement of bleeding after enema (Grade 2 in eight patients and Grade 3 in two patients) (Table 2).

*Quality of life*

The quality of life was also evaluated by the EORTC QLQ-C30 scale successfully in 43 of all 59 patients. The results of questionnaire values before enema and at follow-up and their referential values to normal German population (because no similar files of Chinese population were reported previously) were recorded. Osoba and colleagues (Osoba et al., 1998) suggested that differences of 20 points or more could be considered clinically

**Table 4. Univariate analysis of Potential Risk Factors Related to Rectal Deep Ulcer or Fistula in Hemorrhagic CRP Patients**

| Variables | No deep ulcer or fistula (n=37) | Deep ulcer or fistula (n=22) | *P* value |
|---|---|---|---|
| Age, <50/≥50 years | 13/24 | 8/14 | 0.924 |
| Cumulative radiation dosage (Gy), mean (SD) | 80.8 (21.9) | 82.0 (13.0) | 0.92 |
| Acute radiation-induced enteritis, yes/no | 10/22 | 5/13 | 0.797 |
| Concomitant chemotherapy, yes/no | 24/13 | 15/7 | 0.795 |
| CTC grade of hemorrhage before enemas, mean (SD) | 2.1 (0.3) | 2.2 (0.4) | 0.366 |
| Latency of CRP (month), mean (SD) | 9.6 (7.7) | 8.8 (6.8) | 0.678 |
| Duration of symptom (month), mean (SD) | 4.5 (5.0) | 4.4 (4.4) | 0.658 |
| Diabetes mellitus, yes/no | 2/35 | 2/20 | 0.993* |
| Hypertension, yes/no | 6/31 | 3/19 | 0.79 |
| Gynecological malignancy, yes/no | 35/2 | 22/0 | 0.715* |
| Operation for primary cancers, yes/no | 16/21 | 6/16 | 0.22 |
| Anemia, yes/no | 18/19 | 15/7 | 0.144 |
| Moderate or Severe anemia (<90g/l), yes/no | 6/31 | 10/12 | 0.015 |
| Transfusions history, yes/no | 5/32 | 4/18 | 0.63 |
| Total protein (TP), mean (SD) | 67.2 (8.1) | 66.4 (6.8) | 0.611 |
| Albumin (Alb<35g/L), yes/no | 2/35 | 3/19 | 0.539* |
| APTT, mean (SD) | 28.7 (4.6) | 28.5 (3.8) | 0.655 |
| BMI (<17.5kg/m$^2$), yes/no | 1/30 | 2/17 | 0.659* |
| SCC, mean (SD) | 1.1 (0.4) | 0.7 (0.3) | 0.418 |

BMI, body mass index; SD, standard deviation; APTT, activated partial thromboplastin time; SCC, squamous cell carcinoma antigen;* Chi square test with corrections for continuity

**Table Supplement 1. Common Terminology Criteria for Adverse Events (CTCAE) scale for Rectal Toxicity**

| Grade | Bleeding | Pain | Tenesmus | Stool Frequency | Points |
|---|---|---|---|---|---|
| 1 | Mild, intervention not indicated | Mild pain | Mild urgency | 2-4 stools per day | 1 |
| 2 | Moderate, medical intervention | Moderate pain | Moderate urgency | 4-6 stools per day | 2 |
| 3 | Transfusion, special intervention | Severe pain | Severe urgency | ≥7 stools per day | 3 |
| 4 | Life-threatening | - | - | Life-threatening | 4 |

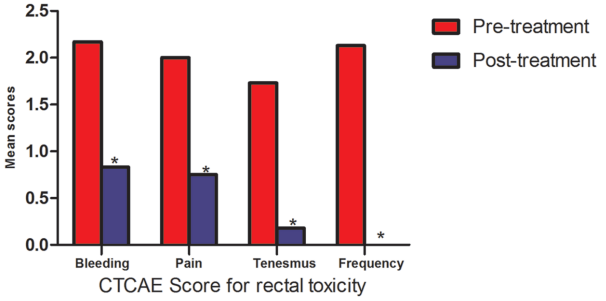


**Figure 3. CTCAE Scores of Different Symptoms Pre- and Post-compound Retention Enemas**

relevant. Global health ($P$<0.001), emotional function ($P$=0.008), social function ($P$=0.043), pain ($P$=0.002), insomnia ($P$=0.035), constipation ($P$=0.007), diarrhea ($P$=0.0009) were improved significantly during follow-up, when comparing to that before enema. Only global health (difference large than 20points) could be considered clinically relevant.

To exclude the potential effects of other medical treatments, we evaluated the quality of life in 29 patients who only received almagate enema for the effects on quality of life. Global health ($P$=0.001), pain ($P$=0.04), diarrhea ($P$=0.039) were improved, and cognition function ($P$=0.004) got worse because of the aging at follow-up. But only global health (difference >20 points) could be considered clinically relevant (Table 3). Therefore, rectal

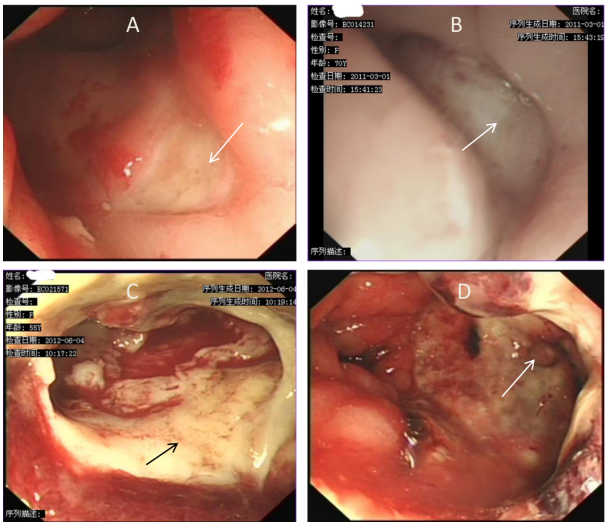


**Figure 4. Typical endoscopic features of rectal deep ulceration, necrosis, and rectal fistula.** (A) large ulceration; (B) deep ulceration; (C) necrosis; (D) rectal-vaginal fistula. (lesions were marked by arrows)

almagate enema can raise the quality of life mainly by improving the global health of patients.

*Potential risk factors for rectal deep ulcer or fistula*

The results of potential risk factors related to rectal deep or fistula were analyzed in all 59 patients. Through

**Table Supplement 2. Vienna Rectoscopy Score (VRS) of endoscopic findings for radiation-induced proctitis (a)**

| | Congested mucosa | Telangiectasis | Ulceration |
|---|---|---|---|
| Score 0 | Focal reddening | None | None |
| Score 1 | Diffuse nonconfluent | Single telangiectasia | None |
| Score 2 | Diffuse confluent | Multiple nonconfluent | None |
| Score 3 | Any | Multiple confluent | Micro ulceration, superficial,<1cm$^2$ |
| Score 4 | Any[b] | Any[b] | Superficial,>1cm$^2$, |
| Score 5 | Any[b] | Any[b] | Deep ulceration, fistula, perforation |

[a]the highest grade of any one parameter qualifies for the attribution to one of the given score levels regardless of the grade achieved in any other parameter, [b] indicates an assumption how to complete the score

univariate analysis, moderate to severe anemia was found to be a risk factor of CRP patients who developed rectal deep ulcer or fistulas ($P$= 0.015), which provided evidence of early surgical intervention for deep ulcer lesions in CRP patients before progressing to embarrassing rectal fistula (Table 4). Because only one variable had a $p$ value less than 0.1, multivariable analysis was not performed. The typical endoscopic images of rectal necrosis, deep ulceration and rectal fistula were also at presentation (Figure 4). Combination of these endoscopic features, radiotherapy history and risk factors of rectal fistula, clinicians can select a more appropriate option for treating CRP patients with deep ulceration, such as early surgical intervention for deep ulcer lesions before they progressed to embarrassing and refractory rectal fistula.

## Discussion

The natural course of radiation enteritis is often characterized by vascular endarteritis and progressive fibrosis of infected intestinal wall (Hasleton et al., 1985). As for CRP, rectal bleeding is the most common symptom and difficult to manage because of recurrence. Sucralfate is a mucosa protector that is widely used for CRP in western countries. Sucralfate can dissolve and form an adherent membrane that can bind to the damaged rectal mucosa, rending it to be a local cytoprotective agent (Gul et al., 2002). Kochhar, et al (Kochhar et al., 1991; Kochhar et al., 1999) conducted two prospective trials in CRP, and found that the short- and long-term responses of rectal sucralfate was 94% and 70%, respectively. But sucralfate enema required a few weeks (4-8 weeks from Kochhar's experience) to obtain improvements of CRP, there is low compliance for patients to experience such a long period of enema in China. So we tried to find out a novel equivalent agent that acts faster. Other reported medical agents for CRP included 5-aminosalicylic acid and its analogue sulfasalazine, steroids like corticosteroids, antibiotics like metronidazole, immune inhibitor rebampide, short-chain fatty acid, and antioxidant pentoxifylline (Kim et al., 2008). Most of these medical agents are helpful for improving only mild to moderate bleeding, and the overall results are not satisfactory. Few studies assessed the long-term effects.

Almagate is a hydrated aluminium-magnesium hydroxycarbonate and is widely used as antacid agent in the management of peptic ulceration in Spain (Rey et al., 2004). Although almagate is one of aluminium-containing antacid compound, it presents more acid neutralizing properties than mucosa protecting. Almagate obtains more potent than other aluminium hydroxide in increasing the pH value in a rapid manner and reducing total acidity of gastric juice produced in rats. (Beckett et al., 1984; Beneyto and Fabregas, 1984) Previous study found that the efficacy in preventing upper gastrointestinal hemorrhage between sucralfate and almagate was equivalent (Lopez-Herce et al., 1992), and the effects of almagate were maybe attributed to excellent antacid property with acid-neutralizing capacity and the possible property of a Ca-antagonist (Mg activity contained in the compound) like Tisacid (Nagy et al., 1990). Based on these reported advantages, almagate shows potential for hemorrhagic CRP.

We reported almagate enema in a relative large-scale of CRP patients, comparing to previous studies. Actually, more than 200 CRP patients have visited our center and about one half of them received initial almagate enema regimens since 2007. In this study, we retrospectively analyzed the efficacy of almagate in controlling hemorrhagic CRP. Equivalent to sulcrafate, 90% of CRP patients responded to rectal almagate enema in the short-term and 69% of patients improved obviously in the long-term follow-up. As expected, the mean duration of responses to alamagate was 12 days and many patients obtained an obvious decrease of rectal bleeding after one week of enema. Almagate acts more rapidly for antacid property than sulcrafate and thus obtain more compliance and satisfaction of patients.

As previous report and our observation, the course of rectal bleeding may last for several years after radiotherapy. Mild or transient bleeding can experience a spontaneous remission requiring non-specific treatment. Moderate to severe bleeding can progress to severe anemia and threaten lives (Cho et al., 1995; Mallick et al., 2015). Therefore, controlling bleeding by medical agents like almagate and sulcrafate, or other aggressive treatments like endoscopic APC and topical formalin, are very essential for patients to help to safely get through this tough period of bleeding. In our study, abnormal hyaline-like wall vessels in the sub-mucosa layer revealed endarteritis obliterans and the fibrosis process of this disease. We also found the quality of life was greatly improved when the bleeding cessation was obtained after enema.

Rectal deep ulcerations after radiotherapy are usually accompanied with refractory anorectal pain. Rectal fistulas, especially rectal-vaginal fistula, usually develop following radiation injury to the front of rectal wall that was adjacent to cervix after radiotherapy of cervical

cancer. Rectal fistulas are refractory for clinicians and are very embarrassing for women because of stool excretion through the vaginal. The quality of life, especially social functions, is greatly affected. In this study, we found moderate to severe anemia was a risk factor of deep ulceration or fistula. We explain that lack of enough blood supply to rectal wall due to severe anemia, can lead to poor healing rate of rectal injury after radiation toxicity injury to the rectum. Thus deep ulcerations can progress to rectal fistula or perforation quickly, and it usually takes 1-2 years after radiotherapy as we observed. However, the efficacies of surgical interventions for rectal-vaginal fistulas are not as well as we can expect. Therefore, it is essential to start early surgical intervention for deep ulcerations with moderate to severe anemia before progressing to fistulas. Surgical interventions such as a simple colostomy for transient fecal diversion, which can rest and accelerate the healing of injured rectum, or a proctectomy for patients with refractory anorectal pain, may be more appropriate treatment options for patients with deep ulcerations.

This study introduces our experience with novel usage of almagate enema for hemorrhagic CRP. Several limitations still existed. Firstly, this study was retrospective and potential recall bias by a telephone questionnaire existed. Secondly, no control group was included and thus we could only make indirect comparisons to other reported treatment like sulcrafate. Thirdly, some patients with other accompanied symptoms received other agents into the enema, such as metronidazole for diarrhea, dexamethasone for rectal irrigated symptoms and human epidermal growth factor for rectal ulcers. But the effects of these agents on bleeding control were not statistical significant (data was not listed). Finally, calculation for cumulative dosage of radiation may be not accurate for different schemes of pelvic radiotherapy, and thus lead to no links between radiation dosage and risk factor of rectal deep ulcer or fistula. Additional prospective randomized-controlled trials incorporating these limitations are required to confirm the efficacy of almagate enema in current treatment options for hemorrhagic CRP.

In conclusion, rectal almagate enema is a novel effective, rapid acting and well-tolerated method for hemorrhagic CRP. Moderate to severe anemia is a risk factor of deep ulceration or fistula.

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## References

Aaronson NK, Ahmedzai S, Bergman B, et al (1993). The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*, **85**, 365-76.

Anseline PF, Lavery IC, Fazio VW, et al (1981). Radiation injury of the rectum: evaluation of surgical treatment. ann surg.

Beckett PR, Llupia J, Lumachi B, et al (1984). Pharmacological studies with almagate, a potent new antacid compound. *Arzneimittelforschung*, **34**, 1367-70.

Beneyto JE, Fabregas JL (1984). Effect of proteolytic enzymes and polypeptides on the antacid activity of almagate and other antacids. *Arzneimittelforschung*, **34**, 1357-60.

Charneau J, Bouachour G, Person B, et al (1991). Severe hemorrhagic radiation proctitis advancing to gradual cessation with hyperbaric oxygen. *Dig Dis Sci*, **36**, 373-5.

Cho KH, Lee CK, Levitt SH (1995). Proctitis after conventional external radiation therapy for prostate cancer: importance of minimizing posterior rectal dose. *Radiol*, **195**, 699-703.

Eaveiæ J (2000). Metronidazole in the Treatment of Chronic Radiation Proctitis: Clinical Trial.

Gul YA, Prasannan S, Jabar FM, et al (2002). Pharmacotherapy for chronic hemorrhagic radiation proctitis. *World J Surg*, **26**, 1499-502.

Haas EM, Bailey HR, Farragher I (2007). Application of 10 percent formalin for the treatment of radiation-induced hemorrhagic proctitis. *Dis Colon Rectum*, **50**, 213-7.

Hasleton PS, Carr N, Schofield PF (1985). Vascular changes in radiation bowel disease. *Histopathol*, **9**, 517-34.

Hille A, Christiansen H, Pradier O, et al (2005). Effect of pentoxifylline and tocopherol on radiation proctitis/enteritis. *Strahlenther Onkol*, **181**, 606-14.

Khubchandani IT, Karamchandani MC, Sheets JA, et al (1987). The Bacon pull-through procedure. *Dis Colon Rectum*, **30**, 540-4.

Kim TO, Song GA, Lee SM, et al (2008). Rebampide enema therapy as a treatment for patients with chronic radiation proctitis: initial treatment or when other methods of conservative management have failed. *Int J Colorectal Dis*, **23**, 629-33.

Kochhar R, Patel F, Dhar A, et al (1991). Radiation-induced proctosigmoiditis. Prospective, randomized, double-blind controlled trial of oral sulfasalazine plus rectal steroids versus rectal sucralfate. *Dig Dis Sci*, **36**, 103-7.

Kochhar R, Sharma SC, Gupta BB, et al (1988). Rectal sucralfate in radiation proctitis. *Lancet*, **2**, 400.

Kochhar R, Sriram PV, Sharma SC, et al (1999). Natural history of late radiation proctosigmoiditis treated with topical sucralfate suspension. *Dig Dis Sci*, **44**, 973-8.

Leiper K, Morris AI (2007). Treatment of radiation proctitis. *Clin Oncol*, **19**, 724-9.

Li N, Zhu W, Gong J, et al (2013). Ileal or ileocecal resection for chronic radiation enteritis with small bowel obstruction: outcome and risk factors. *Am J Surg*, **206**, 739-47.

Lopez-Herce J, Dorao P, Elola P, et al (1992). Frequency and prophylaxis of upper gastrointestinal hemorrhage in critically ill children: a prospective study comparing the efficacy of almagate, ranitidine, and sucralfate. The Gastrointestinal Hemorrhage Study Group. *Crit Care Med*, **20**, 1082-9.

Lucarotti ME, Mountford RA, Bartolo DC (1991). Surgical management of intestinal radiation injury. *Dis Colon Rectum*, **34**, 865-9.

Mallick S, Madan R, Julka PK, et al (2015). Radiation Induced Cystitis and Proctitis - Prediction, Assessment and Management. *Asian Pac J Cancer Prev*, **16**, 5589-94.

Nagy L, Mozsik G, Vincze A, et al (1990). Effects of a novel Hungarian antacid containing Al and Mg (Tisacid) on mucosal prostaglandin generation and oxygen free radicals

in normal rats. *Drugs Exp Clin Res*, **16**, 197-203.
Nowacki MP (1991). Ten years of experience with Parks' coloanal sleeve anastomosis for the treatment of post-irradiation rectovaginal fistula. *Eur J Surg Oncol*, **17**, 563-6.
Osoba D, Rodrigues G, Myles J, et al (1998). Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol*, **16**, 139-44.
Parks AG, Allen CL, Frank JD, et al (1978). A method of treating post-irradiation rectovaginal fistulas. *Br J Surg*, **65**, 417-21.
Patel *P*, Subhas G, Gupta A, et al (2009). Oral vitamin A enhances the effectiveness of formalin 8% in treating chronic hemorrhagic radiation proctopathy. *Dis Colon Rectum*, **52**, 1605-9.
Pesee M, Krusun S, Padoongcharoen P (2010). High dose rate cobalt-60 afterloading intracavitary therapy of uterine cervical carcinomas in Srinagarind hospital - analysis of complications. *Asian Pac J Cancer Prev*, **11**, 491-4.
Postgate A, Saunders B, Tjandra J, et al (2007). Argon plasma coagulation in chronic radiation proctitis. *Endoscopy*, **39**, 361-5.
R K, Patel F, Dhar A, et al (1991). Radiation-induced proctosigmoiditis. Prospective, randomized, double-blind controlled trial of oral sulfasalazine plus rectal steroids versus rectal sucralfate.
Rey E, Poves-Frances C, Sanchez G, et al (2004). Effects of effervescent ranitidine on gastric pH: comparison with almagate and placebo in fasting and postprandial conditions. *Aliment Pharmacol Ther*, **20**, 683-8.
Talley NA, Chen F, King D, et al (1997). Short-chain fatty acids in the treatment of radiation proctitis: a randomized, double-blind, placebo-controlled, cross-over pilot trial. *Dis Colon Rectum*, **40**, 1046-50.
Wachter S, Gerstner N, Goldner G, et al (2000). Endoscopic scoring of late rectal mucosal damage after conformal radiotherapy for prostatic carcinoma. *Radiother Oncol*, **54**, 11-9.
Wang CJ, Leung SW, Chen HC, et al (1998). The correlation of acute toxicity and late rectal injury in radiotherapy for cervical carcinoma: evidence suggestive of consequential late effect (CQLE). *Int J Radiat Oncol Biol Phys*, **40**, 85-91.
Yang L, Lv Y (2012). Possible risk factors associated with radiation proctitis or radiation cystitis in patients with cervical carcinoma after radiotherapy. *Asian Pac J Cancer Prev*, **13**, 6251-5.