Original Article

Randomized Control Trial Comparing Management of Radiation Proctocolitis with Sucralfate Instillation via Colonoscopy and Argon Plasma Coagulation

Sirikurnpiboon S, MD[1], Wannaprasert J, MD[1], Ratanachu-ek T, MD[1]

[1] Department of Surgery, Rajavithi Hospital, College of Medicine, Rangsit University, Bangkok, Thailand

Background: One frequent sequela after radiotherapy for pelvic cancer is radiation proctocolitis. Bleeding is a common clinical presentation, with a wide range of severity. Radiation causes DNA, protein and lipid damage leading to mucosal friability and neovascular telangiectasias. The present study compared the results of local management of radiation-induced proctocolitis and evaluated factors related to failure under colonoscopy of sucralfate instillation and Argon plasma coagulator (APC).

Objective: To compare results of treatment of radiation proctitis with sucralfate to outcomes with APC.

Materials and Methods: The study was conducted from 2012 to 2016. Inclusion criteria were patients who were: (1) diagnosed with radiation proctocolitis from clinical examination with colonoscopy and pathology; and (2) aged from 18 to 80 years. Exclusion criteria were patients who: (1) Refused to undergo treatment; (2) had severe co-morbidities; or (3) were lost to follow-up. The patients were randomized into 2 groups, and data was collected regarding patient demographics; previous cancer disease; onset of clinical bleeding per rectum after last radiotherapy session, and hematocrit level before and during treatment.

Results: Of the 130 patients, 54 were randomised into the sucralfate group and the other 76 into the APC group. The mean age of the sucralfate group was 62.15±10.00 compared with 62.27±8.07 in the APC group. Time to presentation after last radiotherapy session were 7.16±4.97 and 6.15±4.18 years (p = 0.447), the first hematocrit before treatment were 34.86±4.61 and 32.17±6.52 (p = 0.010), and the failure rate in treatment in the sucralfate and APC groups were 5.6% and 15.8% (p = 0.096) respectively. The factors related to failure in both treatments were age ≥60 years, Hct at presentation ≤30 mg %, need blood transfusion, extension of disease above rectum, high rectal telangiectasia distribution grade, full circumferential involvement, and ulceration.

Conclusion: Sucralfate instillation for treatment of radiation proctocolitis is not inferior to APC. The factors related to failure in management were severity and extension of disease.

Keywords: Radiation proctitis, APC, Sucralfate, Colonoscopy

J Med Assoc Thai 2019;102(Suppl.4):104-10
Website: http://www.jmatonline.com

Radiotherapy is widely used in management of pelvic organ cancers such as those of the cervix, uterus, prostate, and rectum. Complications after radiotherapy are inevitable and there is a 30% incidence of chronic radiation proctopathy. The clinical indications of chronic radiation proctopathy are hematochezia, tenensmus, cramping abdominal pain, constipation and diarrhea[1]. Radiation-induced microvascular damage leads to mucosal friability and neovascular telangiectasias in cases of rectal bleeding[2]. The many kinds of bleeding management techniques can be classified into 4 groups: firstly, endoscopic instruments such as argon plasma coagulators (APC)[2], Nd: YAG[3], and heat probes[4]; second, medication such as 5-ASA, formalin, sucralfate and steroids[5]; third, surgery; and fourth, systemic therapy, such as hyperbaric oxygen. Among endoscopic management techniques, APC is widely used because it can minimize the risk of deep mucosa injury, as it is a non-contact cauterization mechanism. APC does entail some complications, however, in the form of rectal pain, tenesmus, recurrent bleeding and rectal stenosis[6,7]. Sucralfate is a medication which is easy to use: its mechanism involves binding to inflame or denude mucosal cells to stimulate mucus and bicarbonate production, and induce prostaglandin synthesis to improve cell proliferation and mucosal blood flow[8]. This study compared the results of the use of APC and sucralfate instillation in management of bleeding radiation proctopathy.

Correspondence to:

Sirikurnpiboon S.

Department of Surgery, Rajavithi Hospital, 2 Phyathai Road, Ratchathewi, Bangkok 10400, Thailand.

Phone: +66-2-3548108 ext. 3140

E-mail: laizan99@hotmail.com

Materials and Methods

The prospective study was conducted from 2012 to 2016. Inclusion criteria were patients who: (1) were diagnosed with radiation proctocolitis from clinical examination with colonoscopy and pathology; (2) were aged

How to cite this article: Sirikurnpiboon S, Wannaprasert J, Ratanachu-ek T. Randomized Control Trial Comparing Management of Radiation Proctocolitis with Sucralfate Instillation via Colonoscopy and Argon Plasma Coagulation. J Med Assoc Thai 2019;102(Suppl.4):104-10.

from 18 to 80 years; and 3 had clinical presentation ≥3 months. Exclusion criteria were patients who: (1) refused to undergo treatment or colonoscopy; (2) had severe co-morbidities; (3) were lost to follow-up; (4) presented with rectovaginal or rectovesicle fistula; (5) presented with sepsis; (6) presented with bleeding with shock; or (7) were allergic to sulfasalazine, metronidazole or ciprofloxacin. The patients were randomized into 2 groups, and data was collected in relation to demographics, previous cancer disease, onset of clinical bleeding per rectum after last radiotherapy session, and hematocrit level before and during treatment.

Colonoscopy was performed by a colorectal or general surgeon on a random basis. In the APC group, the APC equipment consisted of an APC probe with a diameter of 2.3 mm, an argon delivery unit, and a high-frequency unit (ERBE APC2, ERBE Elektromedizin GmbH, Tubingen, Germany). The APC eradicated as much telangiectasia as possible, as shown in Figure 1. In the sucralfate group, the sucralfate suspension (Siam pharmaceutical, Bangkok, Thailand; 1 gram/5 ml) was instilled with an inflation pressure lithotripsy device (Boston scientific, USA) connected to a metal-tip cannula. Instillation of 240 ml was performed from the rectosigmoid to the low rectum as shown in Figure 2.

Patients were scheduled to undergo colonoscopy every 2 weeks until clinically improved. All patients were prescribed Sulfasalazine (500 mg) 2 tablet, twice a day during treatment, with Metronidazole (400 mg) 1 tab, three times a day and Ciprofloxacin (500 mg) 1 tab, three times a day, for the first week.

Complete blood count (CBC) for all patients was performed at OPD, 1st colonoscopy, 6th week, 12th week, and at 6-month follow-up.

Failure was defined as any one of the following scenarios: (1) unable to stabilize hematocrit (Hct) level after 3 months; (2) patients needed blood transfusion ≥3 times to maintain Hct level; and (3) patients presented with massive bleeding with shock after first treatment.

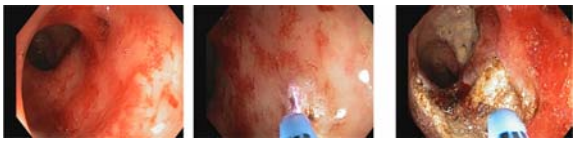

Figure 1. APC eradicated telangiectasia.

Figure 2. Sucralfate instillation instruments and colonoscopic view.

Statistical analysis

The authors used Chi-square analysis and Fisher-exact test to compare factors of recurrence while student t-test and Mann-Whitney U test were employed to compare basic characteristics of the patients such as age and underlying diseases in the two groups (The IBM SPSS statistics version 22). The study was approved by Rajavithi Hospital ethical committee (No. 093/2556).

Results

Six patients were excluded because they were lost to follow-up after treatment or presented with rectovaginal fistula, and the remaining 130 patients were divided into a sucralfate and an APC group consisting of 54 and 76 patients respectively. The mean age of the sucralfate group was 62.15±10.00 compared to 62.27±8.07 m in the APC group. Time to presentation after last radiotherapy session and first hematocrit before treatment were 7.16±4.97 and 6.15±4.18, and 34.86±4.61 and 32.17±6.52 respectively. There was no significant difference in demographic data, as shown in Table 1.

No differences in colonoscopic findings between the two groups were identified, but the APC group had a higher median number of treatments, as shown in Table 2.

At the 6-week follow up, Hct levels were significantly different, but not at the two subsequent follow-up visits, and there were no other significant differences in clinical data, including need for transfusion, as shown in Table 3. There were no serious adverse drug reactions. There were three incidences of failure in the sucralfate group. All of these patients underwent salvage surgery (2 cases underwent abominoperineal resection (APR) and another underwent colostomy), but 2 of them in APR died, succumbing to post-operative pneumonia. There were 12 episodes of failure in the APC group; 10 patients had salvage surgery (Colostomy 6 patients, APR 4 patients) and 8 of them died. 2 patients in APR died from post-operative pneumonia and myocardial infarction. 1 patient in colostomy died from post-operative pneumonia. Other 5 were died after discharged 30 days at community hospital, 4 patients in undefined medical condition and 1 patient from pneumonia. And the author can not gathered information of mortality of 2 case before salvage surgery form community hospital and there family. There were no significant differences in the failure rates of the 2 groups, as shown in Table 4.

Univariate analysis showed that age >60 years was a factor of failure in both treatment groups, Hct before treatment ≤30%, need for blood transfusion, high level of telangiectasia extension, more than half circumferential involvement, rectal telangiectasia density (RTD) grade and ulceration were also significant with *p*-values of less than 0.05. Multivariate analysis showed that Hct before treatment d" 30% (odds ratio (OR) 33.352, 95% CI 1.342 to 829.005), high level of telangiectasia extension (OR 7.096, 95% CI 1.114 to 45.219), and need for blood transfusion (OR 28.759, 95% CI 1.267 to 652.790) were significant.

Table 1. Demographic data (n = 130)

Factors	Sucralfate group (n = 54)	APC group (n = 76)	*p*-value
Sex			
Male: female	9:45	13:63	0.948
Age, n (%)			0.508
≤60 years	23 (42.6)	28 (36.8)	
>60 years	31 (54.7)	48 (63.2)	
ECOG score, mean ± SD			0.509
1	32 (59.3)	40 (52.6)	
2	17 (31.5)	28 (36.8)	
3	5 (9.3)	8 (10.5)	
History of anticoagulant use, n (%)	21 (38.9)	22 (28.9)	0.235
Endoscopist, n (%)			0.465
Colorectal surgeon	34 (63.0)	43 (56.6)	
General surgeon	20 (37.0)	33 (43.4)	
Onset after radiotherapy (mean ± SD) (years)	7.16±4.97	6.55±4.18	0.447
Onset after radiotherapy, n (%)			0.835
≤5 years	26 (40.6)	38 (59.4)	
>5 years	28 (42.4)	38 (57.6)	
Cancer cause of radiotherapy, n (%)			0.788
CA cervix	44 (81.5)	61 (80.3)	
CA corpus	0 (0.0)	1 (1.3)	
CA prostate	9 (16.7)	13 (17.1)	
CA rectum	0 (0.0)	1 (1.3)	
CA anus	1 (1.9)	0 (0.0)	
Hct before colonoscopy (mean ± SD)	34.86±4.61	32.17±6.52	0.010*
Group Hct before colonoscopy, n (%)			0.009
≤30%	7 (13.0)	25 (32.9)	
>30%	47 (87.0)	51 (67.1)	

* = Significant at $p<0.05$

Table 2. First colonoscopic findings (n = 130)

Factors	Sucralfate group (n = 54)	APC group (n = 76)	*p*-value
Number of treatments (median) (min-max)	1 (1 to 6)	2 (1 to 6)	0.029*
Colonoscopic area involvement			
Extension upward, n (%)			0.982
Low rectum	21 (38.9)	29 (38.2)	
Mid rectum	9 (16.7)	11 (14.5)	
Upper rectum	11 (20.4)	17 (22.4)	
Sigmoid	13 (24.1)	19 (25.0)	
Circumferential involvement, n (%)			0.160
One quarter	17 (31.5)	16 (21.1)	
Half	23 (42.6)	26 (34.2)	
Third quarter	6 (11.1)	12 (15.8)	
Full circumferential	8 (14.8)	12 (28.9)	
Colonoscopic finding, n (%)			
Ulceration	5 (9.3)	12 (15.8)	0.276
Stricture	4 (7.4)	6 (7.9)	0.918
Rectal telagiectsia density (RTD) grade scale (median)(min-max)	2 (1 to 3)	3 (1 to 3)	0.126

* = Significant at $p<0.05$

Discussion

Chronic radiation proctopathy entails a number of complex management issues owing to the long-lasting effect of radiation and the wide variety of clinical treatments. One common symptom is bleeding, caused by ischemia from progressive intimal fibrosis and obliterative endarteritis[9]. In

Table 3. Outcome of follow-up data (n =130)

Factors	Sucralfate group (n = 54)	APC group (n = 76)	*p*-value
Clinical bleeding at 6-week follow-up, n (%)	15 (30.0)	28 (38.9)	0.312
Hct at 6 weeks, (mean ± SD)	36.34±3.54	34.09±5.41	0.006*
Clinical bleeding at 3-month follow-up, n (%)	9 (23.1)	14 (21.9)	0.887
Hct at 3 months, (mean ± SD)	37.06±2.88	35.24±5.31	0.128
Clinical bleeding at 6-month follow-up, n (%)	3 (7.7)	7 (11.5)	0.736
Hct at 6 months, (mean ± SD)	38.67±3.02	37.51±4.82	0.151
Clinical urgency before treatment, n (%)	3 (5.6)	8 (10.5)	0.360
Clinical urgency after treatment, n (%)	2 (3.8)	8 (10.7)	0.194
Clinical frequency >3 times/day before treatment, n (%)	14 (26.4)	22 (28.9)	0.752
Clinical frequency >3 times/day after treatment, n (%)	6 (11.3)	8 (10.5)	0.887
Tenesmus before treatment, n (%)	11 (20.4)	9 (12.3)	0.219
Tenesmus after treatment, n (%)	9 (16.7)	9 (12.9)	0.469
Urgency, n (%)			0.242
Improved	3 (60.0)	3 (27.3)	
No change	1 (20.0)	7 (63.1)	
Worsened	1 (20.0)	1 (9.1)	
Frequency, n (%)			0.341
Improved	11 (64.7)	15 (65.2)	
No change	3 (17.6)	7 (30.4)	
Worsened	3 (17.6)	1 (4.3)	
Tenesmus, n (%)			0.778
Improved	8 (47.1)	8 (53.3)	
No change	3 (17.6)	1 (6.7)	
Worsened	6 (35.3)	6 (40.0)	
Transfusion, n (%)	6 (11.8)	9 (14.8)	0.644

* = Significant at $p<0.05$

Table 4. Failure data

Factors	Sucralfate group (n = 54)	APC group (n = 76)	*p*-value
Failure, n (%)	3 (5.6)	12 (15.8)	0.096
Salvage surgery, n (%)	3 (5.6)	10 (13.2)	0.236
Mortality, n (%)	2 (3.7)	4 (5.3)	0.193
Mortality cause			
Pneumonia	2	3	
MI	0	1	

* = Significant at $p<0.05$
MI = myocardial infarction

management of proctitis, there are many kinds of available options, and the diverse range of treatments can be classified into 4 groups. The first option is chemical application, most commonly with formalin, using its mechanism in hydrolysis protein and creating superficial coagulation over inflamed mucosa[10-12]; however, some reported complications of formalin application are tenesmus, anorectal pain, and fecal incontinence[13,14]. The second group consists of medications such as sulfasalazine, corticosteroids and sucralfate[15,16] which have a wide range of possible outcomes. In the present study, sucralfate was selected because it is not absorbed into the GI tract, and it is relatively cheap. Sucralfate is an aluminum salt of sucrose octasulfate. The mechanism of sucralfate involves forming a viscous coagulum and protective barrier for denuded mucosa[17] and stimulating angiogenesis via increased binding with beta-fibroblast and epidermal growth factor to increase mucosa cell regeneration[18,19]. Reports of its use have revealed alleviated clinical abdominal discomfort while undergoing radiotherapy due to its mechanism in upregulating the p53 pathway leading to a decrease in colonic mucosal cell apoptosis and protection of colonic stem cells[17,20]. In treatment, it has shown a 76.9% success at 4 weeks and up to 92.3% at 16 weeks in enema treatment, and 71% of cases had no bleeding events at 45-month follow-up[21]; furthermore, there have been no reports of adverse effects. Another reported cohort study revealed a 90% success rate in enema use[22]. The third group involves endoscopic management, including cryoablation[23], bipolar coagulators, and argon plasma coagulation (APC). APC is widely used as a treatment for radiation proctitis due to its mechanism of non-contact coagulation using the inert gas argon as the conducting medium[24]. Success rates of 81% with one APC treatment have been reported[25], and its overall success rate is 76 to 100%[7,25,26]; however, there have been reports of complications such as rectal pain, tenesmus, recurrent bleeding, rectal stenosis[6,7], recto-vaginal fistula[24] and, most severely, bowel explosion[27]. The fourth option is systemic treatment such as hyperbaric oxygen involving promoting angiogenesis and inhibiting bacterial growth[28], but reported complications include ear pain due to barotrauma in 16% of

Table 5. Univariate failure factors

Factors	Failure	*p*-value
Age, n (%)		0.046*
≤60 years (n = 51)	2 (3.9)	
>60 years (n = 79)	13 (16.5)	
Sex		0.465
Male/Female (n = 22/108)	1 (4.5)/14 (13.0)	
ECOG status, n (%)		0.052
1 (n = 72)	4 (5.6)	
2 (n = 45)	8 (17.8)	
3 (n = 13)	3 (23.1)	
History anticoagulant use, n (%)		0.383
Yes (n = 43)	3 (7.0)	
No (n = 87)	12 (13.8)	
Primary disease, n (%)		0.665
CA Cervix (n = 105)	14 (13.3)	
CA Corpus (n = 1)	0 (0.0)	
CA Prostate (n = 22)	1 (4.5)	
CA Rectum (n = 1)	0 (0.0)	
CA Anus (n = 1)	0 (0.0)	
Onset of symptom after radiotherapy, n (%)		0.447
≤5 years (n = 64)	6 (9.4)	
>5 years (n = 66)	9 (13.6)	
Endoscopist, n (%)		0.292
Colorectal surgeon (n = 77)	7 (9.1)	
General surgeon (n = 53)	8 (15.1)	
Hct before treatment, n (%)		<0.001*
≤30 mg % (n = 32)	14 (43.8)	
>30 mg % (n = 98)	1 (1.0)	
Need blood transfusion (n = 15), n (%)	9 (60.0)	<0.001*
Level of extension		<0.001*
Rectum (n = 98), n (%)	4 (4.1)	
Above rectum (n = 32), n (%)	11 (34.4)	
Circumferential involvement, n (%)		<0.001*
≤50% (n = 82)	2 (2.4)	
>50% (n = 48)	13 (27.1)	
RTD grade, n (%)		0.009*
1 (n = 6)	0 (0.0)	
2 (n = 54)	2 (3.7)	
3 (n = 70)	13 (18.6)	
Stricture (n = 10), n (%)	1 (10.0)	1.000
Ulceration (n = 17), n (%)	10 (58.8)	<0.005*

Value are represented as Mean ± SD, median (min-max), * = Significant at $p<0.05$

Table 6. Multivariate failure factors

Factors	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Hct before treatment ≤30%	75.444 (9.330 to 610.074)	<0.001	20.296 (1.352 to 304.780)	0.029*
Need for transfusion	27.600 (7.013 to 108.624)	<0.001	12.342 (1.211 to 125.734)	0.035*
Ulceration	30.857 (8.261 to 115.266)	<0.001	3.886 (0.345 to 43.697)	0.272
>50% Circumferential involvement	14.857 (3.183 to 69.356)	0.001	1.579 (0.153 to 16.264)	0.701
Extension above rectum	12.310 (3.568 to 42.465)	<0.001	8.533 (0.938 to 77.629)	0.057
Age >60 years	4.826 (1.041 to 22.373)	0.044	0.803 (0.60 to 10.713)	0.868

CI = confidence interval; OR = odds ratio, * = Significant at $p<0.05$

cases, myopia in 3.3%, and confinement anxiety in 2%[29]. In this study, the results from sucralfate instillation were comparable with outcomes from treatment with APC in terms of controlling bleeding, with similar colonoscopic findings

and RTD grade[30] in evaluation of clinical bleeding and Hct level. The authors used colonoscopy instillation to control the level, volume and contact time of sucralfate suspension. The advantage of sucralfate is that it is a common and cheap medication; however, its viscosity during instillation is a negative feature. APC is commonly used in endoscopy units, but the price of APC machines is a prohibiting factor in rural hospitals. A combination of sucralfate and APC has not been found to achieve any significant improvement in bleeding control in comparison with the use of APC alone[31].

Comparing the relative efficacies of each treatment is difficult, primarily because there is no universal classification. For example, the simple classification in evaluation of telangiectasia density is easy to use and capable of predicting re-bleeding[30], however, it is more difficult to predict further complications after radiotherapy by evaluations of telangiectasia, mucosal change, ulceration, and level of involvement[32]. Secondly, the endoscopic findings do not always match clinical signs[23,33].

Some limitation of the present study were that we did not collected a transfusion data and details during treatment in some patient due to different in database collection from community hospital, and that the cleansing effect from bowel preparation may have reduced fecal load and trauma to mucosa[34]. The antibiotic metronidazole is capable of improving healing in additional treatment[35]. For reduce confounding factor and incomplete in follow-up data in next study were no antibiotic prescription, and strict in follow up schedule.

What is already known on this topic?

Chronic radiation proctopathy is difficult to manage due to lack of universal classification to be a guideline. In both arm of treatment, Sucralfate and APC were acceptable treatment in general practice.

What this study adds?

The present study demonstrated comparable result of sucralfate instillation and APC in same extension and degree of circumferential involvement.

Potential conflicts of interest

The authors declare no conflicts of interest.

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