

Formalin application is effective for the treatment of Hemorrhagic Proctitis caused by radiation therapy

Feza Ekiz¹, Mustafa Duman², Sukru Tas³,
Muhammed Fatih Aydin⁴, Musa Akoglu⁵

ABSTRACT

Objective: Radiation proctitis is a serious complication due to pelvic radiotherapy after pelvic malignancies. The aim of this study was to evaluate the efficacy of 4% formalin solution enema application in hemorrhagic proctitis caused by radiation therapy.

Methodology: From February 2008 to February 2009, 13 patients with hemorrhagic radiation induced proctitis were treated in our clinic with 4% formaldehyde solution enema application. They were followed up to six months after the treatment.

Results: In all cases, bleeding ceased after the first application. One of the patients experienced re-bleeding three weeks after the formalin application, and repeated formalin enema application controlled the bleeding. Follow up evaluation at sixth month showed no signs of acute proctitis or rebleeding. Two patients suffered from perianal pain during the first two months after the formalin application, however symptoms improved after that.

Conclusion: 4% formaldehyde solution application for treatment of hemorrhagic radiation induced proctitis, can be performed easily and is a well tolerated technique with good long term results.

KEY WORDS: Hemorrhagic radiation proctitis, Formaldehyde, Pelvic radiotherapy.

Pak J Med Sci October - December 2011 Vol. 27 No. 5 1051-1054

How to cite this article:

Ekiz F, Duman M, Tas S, Aydin MF, Akoglu M. Formalin application is effective for the treatment of Hemorrhagic Proctitis caused by radiation therapy. Pak J Med Sci 2011;27(5):1051-1054

INTRODUCTION

Radiation therapy is an effective treatment for pelvic malignancies. Radiation proctitis is a well known complication of pelvic radiotherapy.¹⁻⁵

Ischemia resulting from progressive submucosal fibrosis and endarteritis obliterans gives rise to telangiectatic neovascularity which is prone to bleeding.^{6,7} The initial acute reaction after radiation appears within the first two weeks of treatment and late complications such as bleeding, pain, diarrhea or stenosis may appear in months or years.²

Chronic radiation injury such as fistula, ulceration, and bleeding occur in 5%-20% of the patients. Chronic radiation induced proctitis leads to recurrent or massive hemorrhage, which may necessitate hospitalization and may require repeated blood transfusions.^{2,6,8} Common medical therapy for radiation induced rectal proctitis in clinical practice includes non-steroidal anti-inflammatory agents such as oral or topical sulfasalazine, acetylsalicylic acid and ibuprofen, oral corticosteroids, rectal steroid retention enema, sucralfate enemas and bile-acid sequestering resins, short chain fatty acid enemas.

1. Feza Ekiz, MD,
 2. Mustafa Duman, MD,
 3. Sukru Tas, MD,
 4. Muhammed Fatih Aydin, MD,
 5. Musa Akoglu, MD,
 - 1-3,5: Department of Gastrointestinal Surgery,
 - 1-5: Kartal Kosuyolu Training and Research Hospital, Istanbul - Turkey.
- Correspondence:
Mustafa Duman, MD,
Kartal Kosuyolu Yuksek Ihtisas Egitim ve Arastirma Hastanesi;
Denizer Caddesi, Cevizli Kavsagi; No:2 Cevizli / Kartal,
Istanbul, Turkey.
E-mail: drmustafaduman@hotmail.com

- * Received for Publication: April 9, 2011
- * 1st Revision Received: April 27, 2011
- * 2nd Revision Received: July 22, 2011
- * Final Revision Accepted: July 30, 2011

However these drugs are not sufficiently effective and have only a limited benefit.^{9,10} Surgical excision of the rectum is difficult and may be associated with a significant morbidity and even mortality due to advanced primary disease, adhesions and the poor healing of irradiated tissue. Surgery is only performed in the presence of necrosis, perforation, stricture or life threatening hemorrhage.¹⁰ Endoscopic therapy with a variety of devices (bipolar cautery, YAG laser, argon laser, heater probes, and more recently, argon plasma coagulation) has been reported to be effective in management of radiation induced bleeding.^{6,11-13}

Formalin treatment has also been studied and most of the data suggest that it is an effective method of treating radiation induced hemorrhagic proctitis. No significant local or systemic toxic effects were observed following rectal instillation of 4% formalin. Its mechanism of action is likely to be local chemical cauterization of telangiectatic mucosal vessels.^{6,10} Here we present our experience in 13 patient whose hemorrhagic radiation proctitis were treated with 4% endoluminal formalin application.

METHODOLOGY

Between February 2008 and February 2009, 13 patients who were admitted with rectal bleeding were included in this study. We got written consent from each patient for the diagnostic and therapeutic applications approved by local ethics committee. All of these patients had a history of radiotherapy to pelvic region and multiple blood transfusions because of recurrent rectal bleeding. Endoscopic examinations were performed to all patients; to exclude other causes of bleeding as well as to

determine the extent radiation induced damage (Fig.1). Bowel preparation was performed with a single dose of rectal phosphate enema.

The procedure was performed without anesthesia or sedation. The patient was placed in prone facedown position; the perineum was protected with Vaseline. 50ml 4% formaldehyde solution was instilled into the lumen of the rectum and after 30 seconds rectum was washed out with 50ml of saline solution. This procedure was repeated 7 times during same session.

All patients were discharged the next day. Follow up examinations were scheduled after 7 days, 14 days, and 1, 3 and 6 months. All patients underwent control sigmoidoscopy 1 month after formaldehyde treatment. Patients' medical history and treatments are summarized in Table-I.

RESULTS

Of the 13 patients, 8 were male and 5 were female. The mean age of the patients was 64.8 year (range, 45-79 years). The eight male patients had previously been irradiated for prostatic cancer. Three female patients were irradiated for cancer of the cervix. Two of the female patients underwent irradiation for endometrium cancer. The median time between radiotherapy and onset of bleeding was 6 months (range, 4-10 months). All patients had a history of varying amounts of blood transfusion because of rectal bleeding. Five patients received steroid enemas and sucralfate enemas before admission.

Bleeding ceased after the first application in all patients. The procedure was well tolerated. One of the patients had serious pain during the formaldehyde instillation. Rebleeding occurred in only one

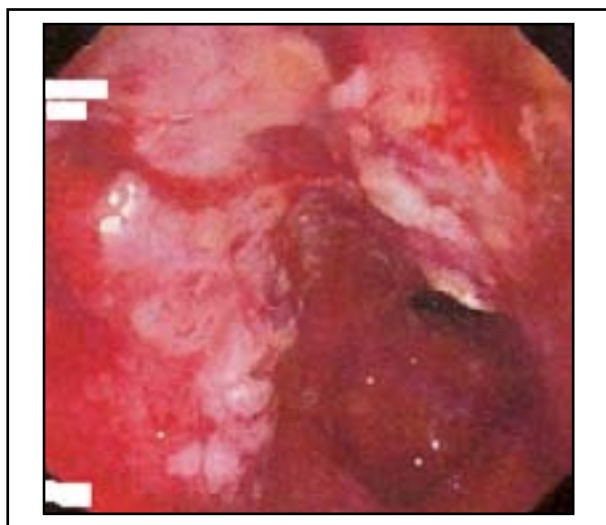


Figure.1: Endoscopic examination of rectum

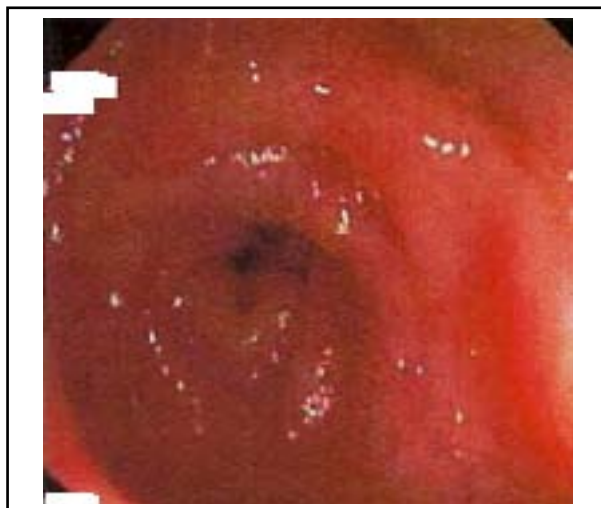


Figure.2: Control sigmoidoscopy.

Table-I: Patients medical history and treatments.

<i>Patient</i>	<i>Sex</i>	<i>Previous neoplasm</i>	<i>Previous treatment</i>	<i>Formaldehyde applications</i>
1	F	Cervix	None	1
2	M	Prostate	Steroid enema	1
3	M	Prostate	Sucralphate	1
4	M	Prostate	Steroid enema	1
5	F	Cervix	None	2
6	F	Endometrium	None	1
7	F	Cervix	Steroid enema	1
8	M	Prostate	Steroid enema	1
9	M	Prostate	None	1
10	M	Prostate	Steroid enema	1
11	M	Prostate	None	1
12	F	Endometrium	None	1
13	M	Prostate	Sucralphate	1

patient three weeks after the formalin application and a repeat formaldehyde enema controlled the bleeding. One of the patients was found to have co-existent asymptomatic diverticular disease. Two patients suffered from mild perianal pain during the first two months after formaldehyde application and these symptoms improved by NSAID drugs.

Control sigmoidoscopy was performed one month after formaldehyde treatment for all patients. No hemorrhage was observed. Hyperemia without fragility was present in all patients. Telangiectatic neovascularities were found to be significantly diminished in all patients (Fig.2). In one of the patients, exuda formations were observed.

There were no signs of hemorrhage in control examinations on the third and sixth months after the treatment. In these control examinations; complete blood count, BUN, creatinine, liver function tests and serum electrolyte levels were normal.

DISCUSSION

Hemorrhagic proctitis caused by radiation therapy affect less than 10% of patients irradiated for pelvic tumors.^{2,14} Other common rectal bleeding causes include colonic and rectal neoplasms, perirectal disease and diverticulosis can manifest with a pattern resembling to that of proctitis caused by radiation.^{14,15} Because of this, all patients with bleeding after radiotherapy should be investigated with at least, flexible sigmoidoscopy.

There are many alternative techniques and agents reported as therapeutic options and also under investigation. There is a lack of clear evidence from prospective randomized studies. Most of our knowledge about treatment of hemorrhagic proctitis caused by radiation therapy is data from these

heterogeneous reports. Currently the best treatment of choice in hemorrhagic proctitis seems to be topical formalin application.¹³ We had performed this prospective study to make a contribution for existing data in literature.

This prospective study shows that formalin application is an effective treatment for hemorrhagic proctitis caused by radiation therapy. A large number of modalities have been proposed for hemorrhagic radiation proctitis.¹⁴ Rectal steroids or salicylate are widely used despite the lack of valid evidence of efficacy.¹⁶ Treatment of hemorrhagic proctitis with monopolar or bipolar electrocoagulation, laser procedures and more recently argon plasma coagulation (APC) has led to higher rates of therapeutic success and longer periods of symptomatic control. However laser procedures and electrocoagulation are associated with severe morbidity derived from the difficulty of assessing the depth of the thermal effect on the rectal wall.¹⁷ Safety of APC is related to the limited depth of coagulation and the low risk of local perforation.^{17,18} Nd:YAG laser option has similar results as APC but is a more expensive treatment of choice with a higher incidence of side effects.¹⁸ These techniques seem to have good results. Nevertheless, they can only be used in selected centers, are time-consuming and expensive as well as necessitate repeated treatment sessions and may result in bowel perforation.^{2,17,18} The formalin application by instillation with low concentration for limited intervals has safe margins about side effects and is easier to perform and cost effective according to alternative techniques.¹⁹

Formaldehyde was first used for treatment of radiation induced hemorrhagic cystitis and a 4% formaldehyde solution has been used effectively for

hemorrhagic radiation induced proctitis worldwide for 20 years.^{1,2,7,11,19} In our study, approximately 90 percent of patients (12 of 13 patients) had complete cessation of bleeding. Only one of the patients re-bled 3 weeks after the formalin application and blood transfusion was not required in this patient. This result was achieved after a single treatment session in 12 of 13 patients. This successful result is similar to those of recent studies conducted with formalin application.^{1,2,6,10,11} Two patients suffered from mild perianal pain during the first two months after formalin application. Furthermore, no systemic side effects were detected at follow up examinations. In addition local morbidity of formalin application was acceptable in our experience. There were no detected anorectal ulceration, anorectal stricture and anal incontinence. Experimental evidence has shown a modest rise in serum formic acid levels following rectal instillation of 4% formaldehyde. On the other hand the raised serum formic acid levels have shown to be non toxic.^{1,10}

Hemorrhagic proctitis caused by radiation therapy in acute or late fashion is an urgent status and treatment choice has to be focused on cessation of bleeding and availability of the technique with safety. We recommend topical application of formalin with a concentration of 4% by instillation – irrigation method for short intervals. This technique has an efficacy of over 90% with complete response. There is a lack of control group in this prospective study and these results has to be accepted as preliminary based on our experience on hemorrhagic proctitis. Our results show that rectal formalin application is an effective, easy and cheap treatment method for bleeding from radiation induced proctitis. A major advantage of this technique is that it does not necessitate a specialized center and sophisticated instruments. Further prospective randomized controlled studies which have criteria as quality of life, severity of proctitis with objective measures and longer follow up periods will be necessary to evaluate the efficacy and rate of recurrent bleeding.

REFERENCES

1. Lee S, Park Y, Sohn S. Formalin application for the treatment of radiation induced hemorrhagic proctitis. *Yonsei Med J* 2007;48(1):97-100.
2. Chautems RC, Delgadillo X, Brandt LB, Deleaval JP, Marti M, Roche B. Formaldehyde application for haemorrhagic radiation-induced proctitis: A clinical and histological study. *Colorectal Disease* 2003;5:24-28.
3. Korkut C, Asoglu O, Aksoy M, Kapran Y, Bilge H, Korkut NK, et al. Histopathological comparison of topical therapy modalities for acute radiation proctitis in an experimental rat model. *World J Gastroenterol* 2006;12(30):4879-4883.
4. Beasley M, Driver D, Dobbs J. Complications of radiotherapy: Improving the therapeutic index. *Cancer Imaging* 2005;5:78-84.
5. Turina M, Mulhall M, Mahid SS, Yashar C, Galandiuk S. Frequency and surgical management of chronic complications related to pelvic radiation. *Arch Surg* 2008;143(1):46-52.
6. Parades V, Etienney I, Bauer P, Bourguignon J, Meary N, Benoit M, et al. Formalin application in the treatment of chronic radiation induced hemorrhagic proctitis- an effective but not risk free procedure: A prospective study of 33 patients. *Dis Colon Rectum* 2005;48:1535-1541.
7. Ifadhlil AA, Alazmi WM, Ponich T, Howard JM, Prokopiw I, Alaqeel A, et al. Efficacy of argon plasma coagulation compared with topical formalin application for chronic radiation proctopathy. *Can J Gastroenterol* 2008;22(2):129-132.
8. Buyukberber M, Savas MC, Gulsen MT, Koruk M, Kadayifci A. Argon plasma coagulation in the treatment of hemorrhagic radiation proctitis. *Turk J Gastroenterol* 2005;16(4):232-235.
9. Kan S, Chun M, Jin YM, Cho MS, Oh YT, Ahn BO, et al. A rat model for radiation induced proctitis. *J Korean Med Sci* 2000;15:682-689.
10. Ismail MA, Qureshi MA. Formalin dab for hemorrhagic radiation proctitis. *Ann R Coll Surg Engl* 2002;84:263-264.
11. Tsujinaka S, Baig MK, Gornev R, Garza C, Hwang JK, Sands D, et al. Formalin instillation for hemorrhagic radiation proctitis. *Surgical Innovation* 2005;12(2):123-128.
12. Cavcic J, Turcic J, Martinac P, Jelincic Z, Zupancic B, Pezerovic RP, et al. Metranidazole in the treatment of chronic radiation proctitis: clinical trial. *Croat Med J* 2000;41:314-318.
13. Denton AS, Andreyev HJN, Forbes A, Maher EJ. Systematic review for non surgical interventions for the management of late radiation proctitis. *Bri J Cancer* 2002;87:134-143.
14. Williams HRT, Vlavianos P, Blake P, Dearnaley DP, Tait D, Andreyev HJN. The significance of rectal bleeding after pelvic radiotherapy. *Aliment Pharmacol Ther* 2005;21:1085-1090.
15. Moore EM, Magrino TJ, Johnstone P. Rectal bleeding after radiation therapy for prostate cancer: endoscopic evaluation. *Radiology* 2000;217:215-218.
16. Canard JM, Vedrenne B, Bors G, Claude P, Bader R, Sondag D. Treatment of radiation proctitis by coagulation: long term results. *Gastroenterol Clin Biol* 2003;27:455-459.
17. Higuera CS, Arribas M, Gomez R, Villoria AP, Moreno MJ, Gonzalez B. Efficacy and safety of argon plasma coagulation for the treatment of hemorrhagic radiation proctitis. *Rev Esp Enferm Dig* 2004;96(119):758-764.
18. Tormo V, Jorgensen W, Castillo GG, Ruiz F, Egea M. Effectiveness of argon plasma coagulation in treatment of chronic actinic proctitis. *Rev Esp Enferm Dig* 2009;101(2):91-96.
19. Cotti G, Seid V, Araujo S, Souza AHS, Kiss D, Gama AH. Conservative therapies for hemorrhagic radiation proctitis: A review. *Rev Hosp Clin* 2003;58(5):1.

Contribution of Authors:

Feza Ekiz, Mustafa Duman, Muhammed Fatih Aydin designed the research;
Feza Ekiz and Muhammed Fatih Aydin performed the research;
Feza Ekiz, Mustafa Duman, Sukru Tas, Musa Akoglu wrote the paper.