

## Treatment of hemorrhagic radiation-induced proctopathy with a 4% formalin application under perianal anesthetic infiltration

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### Abstract

**AIM:** To evaluate the results of hemorrhagic radiation proctopathy treatment with a 4% formalin application.

**METHODS:** A prospective study was performed. Over a three-year period, 38 patients underwent 4% formalin application under perianal anesthetic infiltration for hemorrhagic radiation proctopathy. All patients included in the study were irradiated for prostate cancer. The patients ranged in age from 56-77 years (average  $70 \pm 5$  years). All of the patients were referred for formalin therapy after noninvasive management had failed. Twenty-four (63.2%) patients underwent a single application, 10 (26.3%) patients underwent 2 applications,

and 4 (10.5%) patients underwent 3 applications.

**RESULTS:** Two to 36 mo (average  $12 \pm 3$  mo) following treatment, 34 patients were interviewed (four were lost to follow-up). Twenty (58.8%) subjects reported complete cure, 8 (23.5%) subjects reported significant improvement, and 6 (17.7%) subjects reported no change. One patient (who underwent a colostomy at a regional hospital with no specialized services available for previous bleeding episodes from radiation proctopathy) was cured, and the colostomy was closed. One patient (2.6%) developed rectal mucosal damage after the second application.

**CONCLUSION:** A 4-min application of 4% formalin for hemorrhagic radiation-induced proctopathy under perianal anesthetic infiltration in patients who have received external radial radiation therapy for prostate cancer is simple, reasonably safe, inexpensive, generally well tolerated, and effective.

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**Key words:** Formalin application; Radiation proctopathy; Rectal bleeding; Prostate cancer

**Core tip:** In a prospective study conducted from 2006 to 2009, 38 patients underwent 4% formalin application under perianal anesthetic infiltration for hemorrhagic radiation proctopathy. Based on the rectal-telangiectasia density classification, eight (21.1%) patients had grade I proctitis, 23 (60.5%) patients had grade II proctitis, and seven (18.4%) patients had grade III proctitis. A piece of gauze soaked with 4% formalin was applied to the entire diseased rectal mucosa and remained for 4 min under perianal anesthetic infiltration. Twenty patients (58.8%) reported complete cure, eight patients (23.5%) reported significant improvement, and

six patients (17.7%) reported no change. Application of 4% formalin under perianal anesthetic infiltration in patients who received external radial radiation therapy for prostate cancer was simple, safe, and effective.

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## INTRODUCTION

Radiotherapy is a common treatment modality for carcinoma of the female genital tract, prostate, and urinary bladder<sup>[1]</sup>. Because of its fixed position in the pelvis and because of its proximity to the treated organs, the anorectal area is the most common site of bowel injury following pelvic radiotherapy. Chronic hemorrhagic radiation proctopathy occurs in 1%-5% of patients following radiotherapy for pelvic malignancy<sup>[2]</sup>.

The gross pathologic changes can be acute, subacute, or chronic. Acute changes occur during and immediately after radiotherapy in the form of hyperemia, edema, and extensive inflammatory cell infiltration of the mucosa. To a variable extent, subacute and chronic changes begin after 2 to 12 mo of regeneration. In the vessels, there may be endothelial swelling leading to fibrosis of the connective tissues (intima) and endarteritis. Damage of the vessels increases the formation of arteriovenous shunts, *i.e.*, telangiectatic neovasculature that is fragile and prone to bleeding. Ulcers, strictures, and fistulae may also develop<sup>[3]</sup>. More often, patients will experience functional symptoms of proctopathy, such as urgency, tenesmus, mucoid rectal discharge, abdominal pain, and sphincter irritability<sup>[4]</sup>.

No standard treatment exists for this condition. The primary treatment of radiation proctopathy is medical (or non-invasive). If non-invasive treatment is ineffective, then invasive treatment is considered. One such treatment is formalin application. Formalin is a solution of formaldehyde mixed with methanol that is commonly used to fix tissue samples for histological examination. Applied topically, formalin acts as a chemical cautery of telangiectatic mucosal vessels, and its main action is the sclerosing and sealing of fragile neovasculature<sup>[4]</sup>. In 1969, Brown *et al.*<sup>[5]</sup> were the first to use formalin to treat radiation-induced hemorrhagic cystitis. Inspired by this experience, in 1986, Rubinstein *et al.*<sup>[6]</sup> were the first to apply formalin to treat hemorrhagic radiation proctopathy. However, this treatment modality did not become popular until 1993, when Seow-Choen *et al.*<sup>[4]</sup> reported their data, which indicated a high success rate. Rectal instillation of various concentrations of formalin solu-

tion has been used by several groups to control severe or refractory bleeding from radiation proctopathy, with encouraging results<sup>[1-16]</sup>. The local application of 4% formalin is safe and highly effective in both radiation cystitis and radiation proctopathy. We evaluated the use of a 4% formalin gauze (surgical swab) in patients with radiation proctopathy as an outpatient procedure under perianal anesthetic infiltration<sup>[17]</sup>.

## MATERIALS AND METHODS

This study was approved by the Lithuania Bioethical Committee in 2006.

We conducted a prospective study from July 2006 to July 2009 (3 years). Thirty-eight patients were included. The following inclusion criteria were applied: male patients older than 18 years who had undergone external beam radiotherapy for prostate cancer and developed rectal bleeding as the main symptom of proctopathy. The rectal bleeding occurred not more than two years post-radiotherapy. Proctopathy (classified using the rectal telangiectasia density score) was diagnosed with colonoscopy. Patients were excluded from the study if they met any of the following criteria: the bleeding occurred more than two years after radiotherapy; other symptoms dominated, such as tenesmus, pain, ulceration, or impaired defecation; the patient had impaired coagulation; or the patient was using anticoagulants. All patients provided written informed consent prior to the formalin application.

All patients were referred for formalin therapy after the failure of noninvasive management (peroral sucralfate and topical cortisone were used). The subjects received radical treatment for prostate cancer, including 3D conformal external radiotherapy to the prostate and the base of the seminal vesicles, up to a total dose of 74 Gy (70-74 Gy) over a 7.5-wk period. The patients ranged in age from 56-77 years, with an average of  $70 \pm 5$  years.

Bleeding occurred for all patients during the first two years following treatment. The mean timepoint for the onset of symptoms was  $9 \pm 4$  mo (range one week to 24 mo). In one case, hemorrhage occurred one week after treatment; in two cases, during treatment; and in the remainder of cases, three to 24 mo after treatment. Nineteen patients reported daily blood in their stools, and 19 patients reported bleeding two or three times per week. Two patients received blood transfusions for severe anemia, and one patient was treated with a colostomy for severe rectal bleeding at a regional hospital before coming to our institution.

A total colonoscopy was performed in all of the patients to exclude other synchronous causes of hemorrhage and to determine the extent of the radiation-induced damage. We used the rectal telangiectasia density score<sup>[18]</sup>, in which the radiation proctopathy was graded into the following four grades: normal mucosa (Grade 0), fewer than 10 discrete telangiectasias within a luminal view (Grade I), a single coalescing patch of telangiectasias and/or greater than or equal to 10 discrete telangiect-

tasias (Grade II), and the presence of two or more coalescing telangiectatic patches (Grade III). Based on this classification, eight (21.1%) patients had grade I proctitis, 23 (60.5%) patients had grade II proctitis, and seven (18.4%) patients had grade III proctitis.

The formalin application was performed on an outpatient basis in an operating theater. All of the procedures were conducted with the patient in the prone, jack-knife position under perianal anesthetic infiltration, which was performed by injecting a mixture of lidocaine and bupivacaine solution. Vaseline (petroleum jelly) was applied to the perineum and upper anal canal up to the level of the dentate line, both to serve as a lubricant and to protect the skin from unnecessary exposure to formalin. A piece of gauze (surgical swab) soaked with 4% formalin was applied to the entire diseased rectal mucosa and left in place for four minutes. A Fansler proctoscope was used to visualize the radiation-induced rectal lesions and to avoid formalin application to the healthy rectum. At the end of the procedure, the anal canal and the rectum were abundantly rinsed with water.

A complete response was recorded if there were no further episodes of bleeding. Significant improvement was recorded if there was less than one bleeding episode per month. No response was recorded if the bleeding continued as prior to treatment. The patients were treated repeatedly if they exhibited no improvement after four weeks. All of the patients were interviewed using a questionnaire administered by mail or by telephone at 1, 2, 3, 6, 9, 12, 18, 24 and 36 mo after the treatment. Colonoscopy was not repeated after the treatment.

All of the statistical analyses were performed using SPSS version 17 was used (SPSS Inc., Chicago, IL, United States) for Windows.

## RESULTS

Two to 36 mo after treatment (average  $12 \pm 3$  mo), 34 patients were interviewed (four were lost to follow-up). Twenty-four (63.2%) patients were treated with only one formalin application, and 10 (26.3%) patients required a second application because of persistent bleeding. Four patients (10.5%) required three applications. The treatment was effective in 28 cases (82.3%); of these cases, 20 (58.8%) patients reported complete cessation of the bleeding, and eight (23.5%) patients reported significant improvement. Six patients (17.7%) reported no change in the bleeding. One patient, who underwent a colostomy for previous episodes of bleeding due to radiation proctopathy at another hospital, was cured, and the colostomy was closed. One patient (2.6%) developed rectal mucosal damage after the second application and underwent prolonged conservative management (*i.e.*, topical sucralfate, sucralfate enemas, cortisone enemas, analgesics, and mesalazine suppositories); in this case, the bleeding was controlled completely. No other complications occurred.

## DISCUSSION

Currently, no “best” treatment exists for hemorrhagic radiation proctopathy. Non-invasive therapy includes a low-residue diet, laxatives and retention enemas with steroids, rebamipide<sup>[19]</sup> or hyperbaric oxygen therapy<sup>[20]</sup>, oral antibiotics with colonic irrigation<sup>[21,22]</sup>, short-chain fatty acids, pentoxifylline<sup>[23]</sup>, hormonal therapy<sup>[24]</sup>, antioxidants<sup>[25]</sup>, and retinol palmitate<sup>[26]</sup>. However, these treatment modalities have not been proven effective in all cases of chronic hemorrhagic radiation proctopathy.

Studies of hyperbaric oxygen therapy suggest a clear benefit of this modality in the control of bleeding. Unfortunately, this procedure is expensive and requires additional prospective randomized studies to determine its efficacy in cases of rectal bleeding<sup>[16,20]</sup>. In a randomized placebo-controlled trial, retinol palmitate was proven effective in significantly reducing rectal functional symptoms<sup>[26]</sup>. One comparative study recently demonstrated that oral antibiotics combined with colonic irrigation was superior to 4% formalin application in reducing rectal functional symptoms but yielded the same results in controlling bleeding<sup>[22]</sup>.

If non-invasive treatment is ineffective, then invasive procedures may be used. Successful results using endoscopic therapy have been reportedly achieved in controlling bleeding and providing symptomatic relief by reducing the frequency of hematochezia and the necessity for transfusion<sup>[16,27-31]</sup>. Initially, endoscopists used cryoablation<sup>[27]</sup> and heater and bipolar probes<sup>[30]</sup>, followed by neodymium/yttrium aluminum garnet and potassium titanyl phosphate lasers<sup>[29,32]</sup>, which were beneficial. Argon plasma coagulation (APC) is an innovative, no-touch electrocoagulation technique that is used to treat hemorrhagic digestive malformations. Studies have demonstrated the superior efficacy and safety of APC in treating hemorrhagic radiation proctopathy<sup>[28,33]</sup>.

The treatment of hemorrhagic radiation proctopathy with formalin was first reported by Rubinstein *et al.*<sup>[6]</sup> in 1986. The concentration of the formalin solution used, the treatment method (application *vs* instillation<sup>[12]</sup>), and the mucosal contact time vary largely, as reported by different authors. Diverse techniques have been used by different investigators with varying success rates; examples include irrigation of the rectum with a large volume of formalin for 15 min<sup>[33]</sup>, insertion of a formalin-soaked gauze for 2 to 3 min<sup>[4]</sup> or up to cessation of the symptoms<sup>[7,14]</sup>, and repeated instillation of 50 mL of formalin for 30 s<sup>[8]</sup>. Cullen *et al.*<sup>[2]</sup> used 20 mL of a 5% formalin instillation for two or three minutes, with success rates of up to 85%. We used a piece of gauze (surgical swab) soaked with 4% formalin solution, which was applied to the entire diseased rectal mucosa for 4 min.

Several studies have indicated that systemic toxicity arises after more prolonged contact with formalin<sup>[31]</sup>. Systemic toxicity also increases when formalin instillation is used. The optimal concentration of formalin for the

procedure is unknown. Varying concentrations of formalin solution, ranging from 2% to 10%, have been used<sup>[1-4]</sup>. However, a 4% formalin solution has been used most widely. A lower concentration may be safer but is associated with a lower response rate<sup>[1]</sup>. In a study in which 2% formalin was used, the overall response rate was 78.2%, while the complete success rate was only 47.5%<sup>[1]</sup>. The use of 10% formalin has resulted in an overall success rate of 93%<sup>[3]</sup>, which is comparable to 4% formalin, for which the success rates ranges from 70% to 100%. A higher concentration of formalin may result in a higher incidence of complications<sup>[4]</sup>.

Formalin usually causes cessation of bleeding within a short period by acting as a local chemical cautery. It stops the bleeding by sealing the sites of leakage from the neovascularized telangiectatic spots and ulcers. Multiple sessions of formalin application were required in some of the nonresponsive or relapsed patients. In the study by Seow-Choen *et al.*<sup>[4]</sup>, 17 of 29 patients experienced the complete cessation of bleeding one month after a single application; 11 patients experienced only minor bleeding, and one patient continued to experience major rectal bleeding.

Repeated formalin applications resulted in further success in this study. In the investigation by Parikh *et al.*<sup>[14]</sup>, the number of formalin treatments ranged from 1 to 13, with a mean of 3.4. The response rates in other studies have been similar, ranging from 81% to 100%<sup>[1-4]</sup>. We used 4% formalin with a success rate of 82.3%. This response rate is comparable to that of previous studies. Twenty-four of 38 patients in our study were treated with only one formalin application, and 10 patients required a second application because of persistent bleeding. Four patients needed three applications. Decreased cost is a major advantage of formalin over APC and the other treatment modalities. However, APC poses the advantage of reaching lesions beyond the rectum<sup>[33]</sup>.

One patient, who underwent a colostomy at another institution for previous episodes of bleeding from radiation proctopathy, was cured, and the colostomy was closed. One patient (2.6%) developed rectal mucosal damage after the second application. No other complications were observed. Several published reports have also shown no serious complications of local formalin therapy<sup>[7,8,13,14]</sup>. However, a higher incidence of local complications (e.g., anorectal strictures, incontinence, anal ulcers and/or stenosis) has been reported<sup>[10]</sup>. These events may not be entirely caused by formalin, as a higher proportion (36%) of patients in the latter case series had anorectal malignancies. Other complications that have been reported in certain studies include the proximal migration of formalin, which is caused when a rigid sigmoidoscope is used for instillation. Overdistension of the distal rectum with subsequent proximal migration of the formalin should be avoided. In the present study, we used a Fansler proctoscope to visualize the damaged rectal mucosa.

One recently published randomized trial has compared formalin dab treatment with a sucralfate-steroid

retention enema; in that investigation, Nelamangala Ramakrishnaiah *et al.*<sup>[15]</sup> concluded that a 4% formalin dab was superior to a sucralfate-steroid retention enema for treating hemorrhagic proctopathy caused by radiotherapy. Surgery should be reserved for patients who have intractable symptoms, such as strictures and/or fistulas. However, surgery may be technically demanding because of adhesions and other radiation damage in the pelvis. Another surgical concern is that anastomoses involving radiated tissue may break down. Abdominoperineal resection may be the only reliable option in some patients.

The present study had the following limitations: colonoscopy was not repeated after the treatment, we could not relate our results to possible endoscopic changes in the rectum, and the follow-up time was markedly different for our patients in our study.

In conclusion, radiation-induced hemorrhagic proctopathy is a frequent complication following pelvic radiation. In our experience, formalin application therapy was an inexpensive, simple and highly effective therapy for radiation-induced hemorrhagic proctopathy and yielded few complications. We reported a clinical response rate of 82.3%. Therefore, we recommend 4% formalin application as a low-cost treatment for chronic hemorrhagic radiation proctopathy.

## COMMENTS

### Background

Radiation-induced hemorrhagic proctopathy is a common late complication that manifests after irradiation treatment for pelvic malignancies. The condition may present with signs and symptoms ranging from clinically insignificant bleeding during defecation to a debilitating disorder requiring blood transfusions, repeated admissions to the hospital and even surgery, thereby reducing the patient's quality of life. Preventing radiation-induced hemorrhagic proctopathy via different agents during the radiotherapy course has not been successful, and newer external radiation techniques or brachytherapy have not precluded this complication in all cases. Other types of radiotherapy-related damage to the rectum, such as ulcers, strictures or fistulas, are reported much more rarely. This article focuses on formalin applications for hemorrhagic radiation-induced proctopathy in patients undergoing radical external radiotherapy for prostate cancer.

### Research frontiers

Conservative treatment (peroral drugs, suppositories or enemas) may be useful in certain patients suffering from radiation-induced hemorrhagic proctopathy. However, non-responders require other options to treat this condition. Formalin application, argon plasma coagulation, and hyperbaric oxygen therapy appear to be the most effective modalities after failed conservative treatment. Argon plasma coagulation requires specific equipment, hyperbaric oxygen (which is not accessible everywhere), multiple sessions, and a long treatment period, whereas formalin application is a simple and low-cost method that is available in most hospitals.

### Innovations and breakthroughs

Despite the many published articles on formalin therapy for radiation-induced hemorrhagic proctopathy, several questions remain unanswered. What percentage of formalin solution should be used? Which method (application or instillation) is safer and more effective? How long should the mucosal contact period last? How should the application be performed? What type of anesthesia should be used? In this article, the authors attempt to standardize formalin application to address the above-mentioned considerations.

### Applications

The perspectives regarding the future use of the method described in this article are as follows. After failed conservative treatment, other treatment modalities are not universally available. Because of the simplicity of this method, formalin



application for radiation-induced hemorrhagic proctopathy under perianal anesthetic infiltration may be performed in most hospitals by general surgeons who do not necessarily have extensive colorectal experience. Therefore, the standard technique described by their group may be useful for achieving the best possible results with an existing approach.

### Terminology

The authors used the term "radiation proctopathy" rather than "radiation proctitis," both of which describe the same condition. "Perianal anesthetic infiltration" was a better definition of the anesthesia method employed by their group, although it exhibits certain similarities with the "pudendal block" technique described a few decades ago.

### Peer review

There is not much new things, but it is ok to report these clinic data.

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