

Application of 10 Percent Formalin for the Treatment of Radiation-Induced Hemorrhagic Proctitis

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PURPOSE: Rectal instillation of 4 percent formalin solution has been described as a successful treatment for hemorrhagic radiation proctitis recalcitrant to medical treatment. We present our experience with a new method of treatment involving the topical application of 10 percent buffered formalin, which is well tolerated and suitable for office use. **METHODS:** Patients with marked or refractory rectal bleeding and clinical features consistent with radiation proctitis were reviewed. Treatment involved direct application of a 10 percent buffered formalin solution to the affected mucosa using a 16-inch cotton tip applicator applied through a proctoscope in the office setting. **RESULTS:** A total of 100 patients with a mean age of 75 (range, 49-91) years were followed for 18 (range, 1-79) months. The interval from radiation exposure to formalin treatment was 21 months. Overall, 93 percent of patients had cessation of bleeding after an average of 3.5 formalin applications at two-week to four-week intervals. Patients with severe (Grade 3) proctitis and those taking aspirin required an average of 1.5 additional treatments. A total of eight patients rebelled at a mean of 24 months from treatment; however, all responded to further applications of formalin. Three patients complained of anal pain and one experienced dizziness postprocedure for a complication rate of 1.1 percent. **CONCLUSIONS:** We present a simple, cost-effective, and well-tolerated method of controlling hemorrhagic radiation proctitis. It is performed by using materials readily available in the office of a colon and

rectal surgeon, eliminating the need for bowel preparation, anesthesia, or a surgical suite. [Key words: Radiation proctitis; Formalin; Chemical cauterization; Hemorrhagic proctitis]

Radiation therapy is an important treatment modality for pelvic malignancies. The fixed location of the rectum and its proximity to the prostate, cervix, and uterus make it especially vulnerable to secondary radiation injury with resulting proctitis. Although acute radiation proctitis is relatively common and self-limiting, chronic radiation proctitis ranges from 1 to 20 percent and is associated with refractory and morbid rectal bleeding.¹

Several reports have described the rectal instillation of 4 percent buffered formalin solution to control severe or refractory bleeding from radiation proctitis. The instillation is characteristically performed in the operating room with the patient under general or spinal anesthesia.²⁻⁶

In 1997, we described an alternative technique consisting of direct topical application of 10 percent formalin solution performed in the office, without anesthesia or bowel preparation in seven patients.⁷ It has since been our practice to treat hemorrhagic radiation proctitis with 10 percent solution as a first-line therapy. The purpose of this report was to review and update our experience with the topical application of 10 percent formalin for the treatment of marked or recalcitrant rectal bleeding from radiation-induced proctitis.

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Table 1.
Grade of Radiation Proctitis

Grade	Symptoms	Proctoscopic Findings
I	Intermittent rectal bleeding	Telangiectasias
II	Persistent rectal bleeding	Contact bleeding, with or without ulceration
III	Profuse bleeding with falling hemoglobin	Fresh intraluminal blood, often with superficial ulceration

PATIENTS AND METHODS

We reviewed the records of all patients with rectal bleeding from radiation proctitis who had been treated with 10 percent formalin presenting to our clinic from 1995 to 2003. A total of 100 patients were identified, and a retrospective analysis was performed. All patients had clinical evidence of radiation-induced proctitis, which was graded according to frequency of bleeding and proctoscopic findings (Table 1).

All patients were treated in the office without bowel preparation or use of anesthesia. Patient

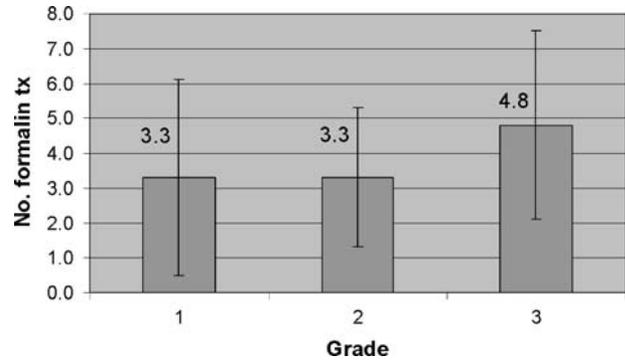


Figure 1. Average number of formalin treatments as a function of severity of proctitis.

Table 2.
Patient Demographics and Characteristics

Male/female ratio	96/4
Mean age (yr)	74 (49–91)
Mean ASA	3 (1–4)
Primary cancer	
Prostate	94
Cervix	3
Bladder	2
Anus	1
Type of therapy	
External beam	79
Brachytherapy	21
Grade	
I	31
II	54
III	15
Previous therapy	
Suppositories	49
Argon beam	12
Heater probe	4
Antiplatelet or anticoagulant use	
Aspirin	22
Coumadin	12
Plavix	7

ASA = American Society of Anesthesiologists' physical status classification.

Data are percentages or numbers with ranges in parentheses.

positioning was identical to our usual examination preference: positioned prone on a Ritter table tilted head down. A rigid proctosigmoidoscope was positioned just proximal to the proctitis and chemical cauterization was performed by applying a 16-inch cotton applicator soaked in 10 percent buffered formalin (Baxter) directly on the mucosa for up to 60 seconds. Care was taken to avoid mucosal contact below the dentate line. Subsequent treatments occurred at mean interval of two to four weeks.

Demographic data were tabulated, and the clinical response to therapy, patient tolerance, and complication rate was evaluated. A complete response was defined as no further episodes of bleeding. A significant response was recorded if the majority of bleeding had ceased, and a failed response was recorded if troublesome bleeding continued after treatment. A rebleed event was defined as rectal bleed requiring one or more additional formalin applications at an interval greater than six months after previous treatment.

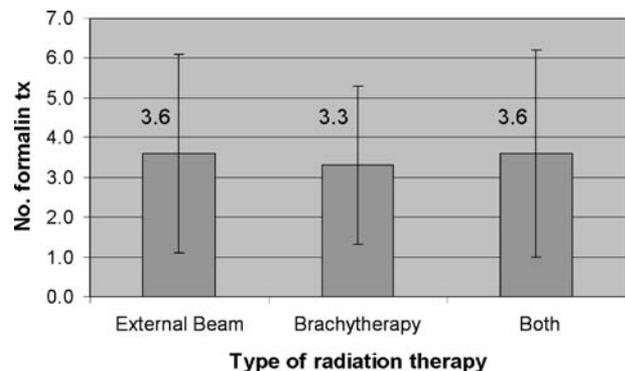


Figure 2. Average number of formalin treatments as a function of type of radiation.

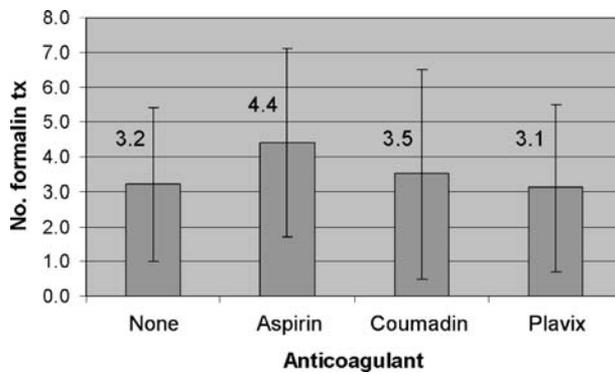


Figure 3. Average number of formalin treatments as a function of aspirin and anticoagulant use.

RESULTS

Ninety-six percent of patients were male with a mean age of 75 (range, 49–91) years and a mean ASA Class 3.^{1–4} Patients presented at a mean interval of 21 (range, 6–111) months after radiation therapy. The majority of patients (94 percent) received radiation for prostate cancer with the remaining having cervical (n=3), bladder (n=2), or anal (n=1) carcinoma. Sixty-five percent were referred after having failed other forms of treatment, including steroid and 5-aminosalicylic acid enemas and argon laser therapy. A summary of patient demographics and characteristics is presented in Table 2.

Topical application of 10 percent formalin resulted in an overall success rate of 93 percent at a mean follow-up of 18 (range, 1–79) months. Patients required an average of 2 (range, 1–7) treatments to achieve a clinically significant response and 3.5 treatments (range, 1–11) to achieve complete cessation of bleeding. More than one-half of the patients had no further episodes of bleeding after three or fewer treatments.

Eight patients experienced at least one episode of rebleeding at a mean interval of 24 (range, 6–60) months after initial successful treatment. All were

successfully treated with an average of 2.25 (range, 1–6) additional formalin treatments.

A total of seven patients (7 percent) failed to respond to 10 percent formalin treatment after receiving a mean of 2.9 (range, 1–5) treatments. They were all subsequently treated with argon beam therapy, with all but one having a significant response.

A total of 4 adverse events were reported during the 350 office procedures for a complication rate of 1.1 percent. Three patients complained of anal pain and spasm, which resolved with conservative measures, including sitz bath and nonnarcotic pain relief during 48 to 72 hours. One patient experienced a transient episode of dizziness on dismount from the Ritter table.

Prognostic factors, including grade of proctitis, type of radiation, antiplatelet and coumadin use, and previous therapy, were not associated with treatment failures. However, those with Grade 3 proctitis and those taking aspirin required up to 1.5 additional treatments (Figs. 1–3).

DISCUSSION

The reported incidence of hemorrhagic chronic radiation proctitis ranges from 1 to 20 percent.¹ Patients typically present 12 to 24 months after radiotherapy, most commonly for prostate or cervical cancer. The most frequent complaint is recurrent bright red blood *per rectum*, which may progress to severe anemia requiring hospitalization and transfusion. On endoscopic evaluation, proctitis is characterized by telangiectasia and friable mucosa with blood in the rectal vault and bleeding on mucosal contact. Surgical options are a last resort with colostomy often surrendering to proctectomy.

Numerous medical treatment modalities have been used to help control the rectal bleeding in patients with radiation proctitis. Hydrocortisone, 5-aminosalicylic acid, sucralfate, and fatty acid enemas have been

Table 3.
Published Reports on the Use of Formalin for the Treatment of Radiation Proctitis

Study	No. of Patients	Method (% formalin)	Mean No. of Treatments	Response Rate (%)	Morbidity (%)
Yegappan <i>et al.</i> ⁵ 1998	55	4% in OR	1.4	89	n/a
Biswal <i>et al.</i> ³ 1995	16	4% in OR	1.1	81	0
Saclarides <i>et al.</i> ⁴ 1996	16	4% in OR	1	75	25
Parikh <i>et al.</i> ¹⁶ 2003	33	4% in office	3.4	88	0

OR = operating room; n/a = not available.

reported with inconsistent and variable results.^{1,8-10} Invasive modalities, such as the Nd:Yag laser, were reported with initial success, but because of the associated higher cost, inconsistent depth of burn, and high complication rate (5-15 percent),^{1,11} it has fallen out of favor. The argon plasma coagulator continues to be a popular option; however, caution is urged because treatment can result in morbid outcomes, including chronic rectal ulceration, stricture, rectovaginal fistulas, and bowel perforation.¹⁰⁻¹³ In our clinic, we have seen several patients with deep rectal ulcers and rectourinary fistulas after argon plasma coagulator therapy.

The use of formalin for the treatment of radiation proctitis was first reported by Rubinstein *et al.* in 1986,⁶ who successfully treated a 71-year-old male with severe rectal bleeding from radiation proctitis *via* instillation of a 4 percent formalin solution. The technique was adopted from reports of intravesical instillation of 4 percent formalin for the treatment of radiation cystitis in the urology literature.^{14,15} In 1993, Seow-Choen *et al.*² published the first case series involving eight patients treated for intractable rectal bleeding from radiation proctitis with instillation of 4 percent formalin under general anesthesia. The bleeding ceased in all patients; however, one developed a worsening stricture requiring Hegar's dilation. In 1996, Yegappan *et al.*⁵ presented 55 patients treated in a similar fashion. He reported a success rate of 89 percent at 12-month follow-up with 35 percent requiring repeated applications. In 1996, Saclarides *et al.*⁴ reported a success rate of 75 percent in 16 patients. Four patients experienced painful anal ulceration and fissuring with persistent symptoms in two.

In 2003, Parikh *et al.*¹⁶ described the application of cotton pledget soaked in 4 percent formalin applied to the proctitis through a rigid sigmoidoscope or operating anoscope. Of 33 patients, 29 (88 percent) had improved or complete resolution of bleeding after a mean of 3.4 treatments and at a follow-up of 18 months.

We report an update to a new method for the treatment of hemorrhagic radiation proctitis, which involves a 16-inch cotton tip applicator dipped in 10 percent buffered formalin solution and applied directly to the proctitis through a rigid proctoscope with the patient positioned on a Ritter table tilted head down. We report a success rate of 93 percent in our retrospective analysis of 100 patients treated in such fashion. These results compare favorably

with published reports describing the use of 4 percent formalin solution (Table 3).

Formalin has a desiccating effect that hydrolyzes protein and coagulates the tissue on a superficial level.¹⁵ When applied directly to mucosa of the rectum, it is this effect that seems to control the bleeding from the telangiectatic capillaries.

We initially applied 4 percent formalin solution, but the clinical response was suboptimal. We altered our treatment by applying 10 percent solution, because this was the initial concentration used for the control hemorrhagic radiation cystitis. Although the 10 percent solution has been since abandoned by the urologist because of a higher reported complication rate involving the bladder and ureter,¹⁵ we have not experienced adverse effects when applied to the rectal mucosa. The paucity of complications can be accounted for by the precise technique with application only to the affected areas under direct visualization for a relatively short period of time compared with reports of rectal instillation of 4 percent solution. The characteristic anterior location of the proctitis facilitates direct visualization when the patient is positioned on a Ritter table, tilted head down. Furthermore, 10 percent solution is readily available at little or no expense in any office in which biopsies are performed, because it is the standard fixative for pathology specimens. This office technique also offers the benefit of requiring no anesthesia or bowel preparation.

CONCLUSIONS

The treatment of hemorrhagic radiation-induced proctitis with topical application of 10 percent formalin is a well-tolerated, safe, and effective therapy. It is an office-based procedure that does not require anesthesia or bowel preparation, thus making it easier and more cost effective than previously described techniques performed in the operating room or endoscopy suite. We report a clinical response rate of 93 percent with a negligible complication rate. Ten percent formalin therapy should be offered as a first-line treatment option for patients with hemorrhagic radiation proctitis.

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