Application of 4% formaldehyde under electronic colonoscope as a minimally invasive treatment of chronic hemorrhagic radiation proctitis

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BACKGROUND: To investigate the effectiveness of topical application of 4% formaldehyde as a minimally invasive treatment of rectal bleeding due to chronic radiation proctitis (CRP) under direct vision of electronic colonoscope.

METHODS: The clinical data of 13 CRP patients complicated with ≥ grade II bleeding admitted to our hospital between January 2003 and December 2018 were retrospectively analyzed. Under the guidance of electronic colonoscope, 4% formaldehyde combined with 5-aminosalicylic acid (5-ASA) suppositories was topically applied. Patients were followed up for two months after treatment, and the therapeutic effectiveness was observed and analyzed.

RESULTS: The rectal bleeding due to CRP was markedly reduced after topical application of 4% formaldehyde under colonoscope in all 13 patients. The bleeding stopped after one treatment session in 11 patients and after the second session in 2 patients. 5-ASA was also applied along with the use of 4% formaldehyde. The therapeutic effectiveness was satisfactory during the 1- and 2-month follow-up period.

CONCLUSION: Topical application of 4% formaldehyde under the direct vision of colonoscope as a minimally invasive treatment for CRB-induced bleeding is a simple, effective, affordable, and repeatable technique without obvious complications, which deserves further exploration and promotion.

KEY WORDS: Radiation proctitis; Rectal bleeding; Formaldehyde

INTRODUCTION
Cancer has become one of the major public health issues in China. According to the latest statistics, the mortality of malignant tumors accounts for 23.91% of all-cause deaths, and the case-fatality rates of malignant tumors have continued to rise in the recent decade.¹,² Radiotherapy is an important component of multiple treatment modalities for tumors. About 35%–61% of patients with pelvic malignancies have received pelvic radiotherapy at different doses.³,⁴ Although radiotherapy significantly prolongs the survival of tumor patients, the incidence of radiation enteritis gradually increases, and rectal bleeding caused by radiation proctitis is one of the most intricate complications of pelvic radiotherapy, with an incidence of 5%–10%.⁵ The current treatments for rectal bleeding caused by radiation proctitis include topical injection therapy, hemostatic particle spraying, and argon plasma coagulation. Although these methods can temporarily stop bleeding, their exact effectiveness is unclear. To investigate the effectiveness of topical application of formalin in treating rectal bleeding caused by chronic radiation proctitis (CRP), we retrospectively analyzed the clinical data of 13 CRP patients who were admitted to our hospital between January 2003 and December 2018 and treated with topical application of 4% formaldehyde under the guidance of endoscopy.
METHODS

Patients

Thirteen CRP inpatients admitted to the First Affiliated Hospital of Zhejiang University School of Medicine from January 2003 to December 2018 who were treated with endoscopic topical application of formaldehyde were enrolled in this study. There were 3 males and 10 females (with a ratio of 1:3.3), aged 39–72 years (mean age 58.3 years). Three patients had prostate cancer and ten had cervical cancer. Five patients were severely anemic. All patients met the following inclusion criteria: i) inpatients; ii) a history of pelvic tumors and radiotherapy; iii) colonoscopy showed diffuse intestinal bleeding, blurred vascular pattern, fragile and erosive mucosal membrane, patchy or crater-like ulcers, and mucosal telangiectasia, indicating a radiation toxicity grade of 2 or 3 according to the Toxicity Criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer Radiation Morbidity Scoring Criteria; and iv) different degrees of bloody stools, with or without symptoms such as abdominal pain and diarrhea, for more than 3 months.

Exclusion criteria were: i) with a radiation toxicity grade of 1 or 4; and ii) the possibility that the bleeding was caused by cancer recurrence/metastasis, inflammatory bowel disease, and other diseases cannot be ruled out.

Treatment protocol

After adequate preoperative examinations, the patient first underwent total intestinal lavage for routine electronic colonoscopy to exclude hemorrhagic diseases such as colon polyps and tumors. If the bleeding site was located in the sigmoid colon and the proximal rectum, the bleeding/oozing site was determined under the biopsy hole. The patient’s body position was continuously changed to obtain the best position that allowed the saline to exactly cover the bleeding/oozing site. After the normal saline was aspirated, 4% formaldehyde was injected to cover the bleeding/oozing site. When the intestinal mucosa became whitish or the bleeding/oozing stopped, the formaldehyde solution was aspirated immediately, and then the normal saline was injected to rinse the residual solution. If the bleeding/oozing site was close to the anus, a cotton ball soaked with 4% formaldehyde was applied guided by anoscope to compress the bleeding site at the intestinal mucosa until the bleeding/oozing stopped or the intestinal mucosa became whitish. The duration of application usually lasted dozens of seconds to 3 minutes. The 5-aminosalicylic acid (5-ASA) suppositories were used simultaneously.

Therapeutic evaluation criteria

Follow-up was carried out 1 and 2 months after the treatment, and symptoms including fecal urgency, rectal bleeding, and anal pain were observed and assessed. The severity of radiation proctitis was assessed using the RTOG scoring system: grade II, moderate diarrhea or colic, bowel movement >5 times daily, excessive rectal mucus, or intermittent bleeding; and grade III, obstruction or bleeding requiring surgery. The anal pain was evaluated using a visual analogue scale (VAS), with 0 point being no pain and 10 points being the most unbearable pain.

Statistical analysis

Data were analyzed using the SPSS for Windows 16.0 software package.

RESULTS

General information

Among these 13 patients, there were 3 men and 10 women, aged 29 to 72 years (mean: 63.9 years). The primary tumors included prostate cancer (n=3) and cervical cancer (n=10). Bleeding occurred 4–15 months (mean: 9 months) after radiotherapy. According to the RTOG scoring system, the radiation toxicity grade was 2 in 9 cases and 3 in 4 cases.

In all these 13 patients, the bleeding/oozing at the intestinal mucosa stopped and the mucosa became whitish immediately after treatment under the direct vision of colonoscope. The bleeding stopped after a single session of treatment in 11 patients (11/13, 84.6%). In the remaining two patients (2/13, 15.4%), the bleeding was not thoroughly stopped or recurred after the first treatment session, and a second treatment was given on the second and third postoperative day, respectively, and the bleeding was successfully ceased. No severe complications such as intestinal perforation occurred during the treatment. One patient complained of anal pain (VAS 2–3 points) during the treatment, while no obvious pain was noted among the remaining 12 patients (VAS 0–1 point).

All the patients were followed up for 1–2 months after treatment and no bleeding was observed. No complications such as anal incontinence or anal stenosis occurred during the follow-up period. The subjective evaluation was satisfactory by all 13 patients. In the 5 patients who had severe anemia and received blood-
component transfusion before operation, the anemia improved to varying degrees, and no further blood transfusion was required after the treatment. One patient experienced bearable anal pain (VAS 2–3 points) during the treatment, and the symptom was markedly alleviated (VAS 0–1) based on a second evaluation 2 weeks later.

**DISCUSSION**

Radiation proctitis is a severe complication after radiotherapy for pelvic tumors. Its main clinical manifestation is rectal bleeding, and other symptoms include abdominal pain, diarrhea, intestinal narrowing, anal incontinence, and intestinal fistula. Acute hematochezia often occur during radiotherapy and can be resolved spontaneously when the radiotherapy is terminated. Chronic hemorrhage often occurs 1 year after radiotherapy.

Endoscopic findings include the followings: the mucosal vascular pattern is blurred or invisible; red and congested mucosa shows patchy distribution, with irregular boundaries; oozing is seen frequently, and bleeding sites are obviously visible; the intestines can become narrow and hard, accompanied by erosion, and contact bleeding can easily occur; and blood stains are common in the intestine. The pathological manifestations of chronic hemorrhage include mucosal edema, mild inflammation, neovascularization, and mild fibrosis. Two cases in our series experienced hematochezia during radiotherapy, which was resolved after discontinuation of radiotherapy and symptomatic treatment. The chronic bleeding occurred one year after radiotherapy in the all cases. Bleeding is refractory in all radiation proctitis cases and conservative treatments are often ineffective. In our series, 5 patients had bleeding temporarily stopped after systemic use of hemostatic drugs and retention enema with norepinephrine, but the bleeding recurred within a short period of time. Repeated blood transfusions were thus required to maintain the hemoglobin level due to the persistent bleeding accompanied by severe anemia. The bleeding in radiation proctitis patients is often diffuse, leading to poor electrocoagulation outcome under colonoscope, even with the risk of intestinal perforation. Miles surgery may be required to control the bleeding, but the surgical trauma can be large in patients who have undergone radiotherapy.

Formaldehyde may create thrombi inside the neovessels in the mucosa layer through protein coagulation, thus exerting an effect of hemostasis. It acts superficially and does not extend beyond the mucosal layer. It has been reported that topical application of formalin is performed via transanal instillation or under direct vision, but the effect is limited due to its poor accuracy in targeting sites and it may cause ulcer formation, rectal stenosis/perforation, rectovaginal fistula, anal incontinence, and even death. Therefore, we recommend injection or direct application of 4% formaldehyde under the direct vision of the endoscope because this technique avoids accidentally injuring the intestinal mucosa without bleeding and thus reduces complications and increases safety.

Application of formaldehyde for treating CRP-induced bleeding was first described in 1986; however, the reported concentrations of formaldehyde are controversial. According to the literature, the concentrations of formaldehyde used were 3.6%, 4%, and 10%, and the operating methods included retention enema, use of pre-soaked gauze, and topical perfusion. Haas et al treated 100 patients by applying a gauze soaked with 10% formaldehyde to the rectal wound; after an average of 3.5 sessions of treatment, bleeding stopped in 93 patients, and the complication (anal pain) rate was 1.1%. Denton et al analyzed the clinical data of 202 patients from 16 studies and found that the effectiveness rate ranged from 55% to 100%, and the incidence of severe complications was 7%. In our study, 4% formaldehyde was injected or directly applied under the direct vision of electronic colonoscope, yielding satisfactory results. The effectiveness rate was 84.6% after a single treatment session. Although we modified the treatment, the single-attempt success rate was not as high (100%) as reported in the literature, which may be associated with the factors that the intestinal mucosal lesions in these CRP patients were diffuse and one or more treatment sessions were needed to control the bleeding/oozing sites.

In the present study, no bleeding recurrence was found within 2 months after surgery; no blood transfusion was needed after treatment for 5 severely anemic patients requiring blood transfusion to maintain hemoglobin level before operation; and symptom was alleviated in one patient who experienced anal pain during treatment. Compared with the retention enema and argon plasma coagulation, this new technique has better clinical outcome with fewer side effects.

However, due to its retrospective design, the present study was limited by its small sample size. Therefore, the clinical effectiveness of 4% formaldehyde in treating rectal bleeding due to CRP still requires further clinical observations with more accumulated cases.
CONCLUSION
We conclude that topical application of 4% formaldehyde as a minimally invasive treatment for CRP-induced bleeding under the direct vision of colonoscope is a simple, effective, affordable, and repeatable technique that deserves further promotion in clinical practice.

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