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***Retrospective Study***

**Formalin irrigation for hemorrhagic chronic radiation proctitis**

Ma Th *et al*. formalin irrigation and chronic radiation proctitis

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**Abstract**

**Aim:** To assess the efficacy and safety of a modified topical formalin irrigation method in refractory hemorrhagic chronic radiation proctitis (CRP).

**Methods:** Patients with CRP who did not respond to previous medical treatments and presented with grade II–III rectal bleeding according to the Common Terminology Criteria for Adverse Events criteria were enrolled in this study. Patients with anorectal strictures, deep ulcerations, and fistulas were excluded. All patients underwent flexible endoscopic evaluation before the treatment. Patient demographics and clinical data, including primary tumor, radiotherapy and previous treatment options, were collected. Patients received topical 4% formalin irrigation in a clasp-knife position under spinal epidural anesthesia in the operating room. Remission of rectal bleeding and related complications were recorded. Defecation function, remission of bleeding, and other symptoms were investigated at follow-up. Endoscopic findings in patients with rectovaginal fistulas were analyzed.

**Results:**Twenty-four patients (19 female, 5 male) with a mean age of 61.5 ± 9.5 years were enrolled in the study. The mean time from the end of radiotherapy to the onset of bleeding was 11.1 ± 9.0 (range: 2–24) mo. Six patients (6/24; 25.0%) were blood transfusion dependent. The median preoperative Vienna Rectoscopy Score (VRS) was 3 points. Nineteen patients (19/24; 79.2%) received only one course of topical formalin irrigation, and 5/24 (20.8%) patients required a second course. No side effects were observed. One month after the treatment, bleeding cessation was complete in five patients and obvious in 14; the effective rate was 79.1% (19/24). For the long-term efficacy, 5/16, 1/9 and 0/6 patients complained of persistent bleeding at one, two and five years after the treatment, respectively. Three rectovaginal fistulas were found at one month, three months and two years after the treatment. Univariate analysis showed associations of higher endoscopic VRS and ulceration score with risk of developing rectovaginal fistula.

**Conclusion:**Modified formalin irrigation is an effective and safe method for hemorrhagic CRP, but should be performed cautiously in patients with a high endoscopic VRS.

**Key words:**Chronic radiation proctitis; Efficacy; Rectal bleeding; Safety; Topical formalin irrigation

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**Core tip:** The study describes a modified topical formalin irrigation that is well tolerated with long-term effectiveness for refractory hemorrhagic chronic radiation proctitis. The method focuses on improving the safety and reducing complications. The advantages of the procedure are as follows: protection of internal sphincter (spinal epidural anesthesia and the clasp-knife position provide a full anal dilatation instead of dilatation by an anal retractor); protection of proximal normal colonic mucosa (a Foley catheter is inserted into the proximal sigmoid cavity to prevent damage from formalin backflow); targeting of the lesion area; and well-controlled volume and irrigation time.

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**INTRODUCTION**

Radiotherapy is an essential treatment modality for pelvic malignancies such as gynecologic, rectal, and prostate cancer. However, chronic radiation proctitis (CRP) is a common and severe complication in these patients, with 29%–51% suffering from rectal hemorrhage following pelvic radiotherapy[[1](#_ENREF_1),[2](#_ENREF_2)]. The underlying causes for this type of complication include endarteritis obliterans and progressive submucosal fibrosis[[3](#_ENREF_3),[4](#_ENREF_4)].

Refractory hemorrhagic CRP is difficult to manage[[2](#_ENREF_2),[5](#_ENREF_5)-[9](#_ENREF_9)], but previous successful experience in treating cystitis has led to the use of formalin as a treatment option[[10](#_ENREF_10)]. Topical formalin application had been extensively studied, and most results show that it is a simple, safe and effective way to treat hemorrhagic CRP. Formalin can be applied by direct instillation or by endoscopy-guided placement of formalin-soaked gauze[[10](#_ENREF_10)-[14](#_ENREF_14)]. Formalin acts only on the superficial mucosa, which results in rapid deterioration of mucosal blood flow and superficial coagulation necrosis[[3](#_ENREF_3),[15](#_ENREF_15),[16](#_ENREF_16)].

Despite the efficacy, high complication rates after formalin application have been reported, such as anal pain, rectal stricture, and incontinence[[17](#_ENREF_17)]. De Parades *et al*[[18](#_ENREF_18)] conducted a prospective study and suggested that formalin should be used carefully in cases of radiation-induced anorectal stricture, previous anal incontinence, and anal cancer. Is it not clear if topical formalin application causes local ischemia of the rectal wall that results in complications such as stricture and fistulas. Moreover, there are no studies evaluating the safety of application methods, or identifying which patients may not be suitable for this treatment. Therefore, we conducted a retrospective study of patients treated for refractory hemorrhagic CRP, with a focus on improving the safety and reducing the complications of formalin irrigation.

**MATERIALS AND METHODS**

***Patient selection and data collection***

Patients receiving a modified method of topical formalin irrigation for refractory hemorrhagic CRP between August 2007 and November 2013 at the Sixth Affiliated Hospital of Sun Yat-Sen University were enrolled in the study. Criteria for exclusion were: (1) patients with large ulcers, necrosis of mucosa, or stricture [Vienna Rectoscopy Score (VRS): 4–5 points] due to increased risk of perforation; (2) patients with life-threatening bleeds or mild bleeding that could be controlled by medical treatments; (3) patients allergic to formalin; and (4) patients with relapse of a primary tumor. All patients enrolled had grade II–III rectal bleeding according to the Common Terminology Criteria for Adverse Events criteria (CTCAE 4.0; June 14, 2010, National Institutes of Health)[[19](#_ENREF_19)], and had not responded to previous medical treatments such as topical corticosteroids, sucralfate, and 5-aminosalicylic acid. Data encompassing general characteristics, treatment details of the primary malignancy, clinical and endoscopic evaluations, details of topical formalin irrigation, change of rectal bleeding, and potential complications of patients were collected. The study was approved by the ethical committee of the Sixth Affiliated Hospital of Sun Yat-Sen University and met the guidelines of the local responsible governmental agency. Due to the retrospective nature of the study, informed consent was waived.

***Procedures***

All patients received flexible endoscopic evaluations before formalin irrigation and were scored according to VRS criteria[[20](#_ENREF_20)] (Table 1). A 30-min water enema was performed, and patients then received topic formalin irrigation in a clasp-knife position under spinal epidural anesthesia in the operating room. First, a Foley catheter was inserted into the proximal sigmoid cavity in order to prevent formalin backflow. Then, 10–20 ml of 4% formalin was topically irrigated towards the rectal hemorrhagic surface of the mucosa under direct observation for 0.5–3.0 min until bleeding ceased. Meanwhile, a semicircle anal speculum was used to protect the normal mucosa, superficial ulceration, and the anal canal. Finally, water was injected to wash out the remaining formalin. This procedure could be repeated after one week in the absence of obvious cessation of bleeding.

***Follow-up***

Patients were followed-up by telephone after one, three and six months, and then every year for five years after the treatment. The defecation function was evaluated *via* patients’ descriptions at follow-up regarding stool frequencies, existence of tenesmus, fecal incontinence (or sanitary pad use), constipation, and anal pain. Other data recorded included: remission of bleeding (defined as complete cessation, partial remission, unchanged, or worsened), other symptomatic complaints, and subsequent treatments after formalin application. The efficacy of formalin irrigation was determined one month after the treatment.

***Statistical analysis***

All statistical analyses were performed using SPSS version 20 (IBM Corp., Armonk, NY, United States). The Shapiro–Wilk test was used to evaluate the normality of continuous variables. A student’s *t*-test was used to assess normally distributed data (presented as mean ± sd), and a Wilcoxon rank-sum test was performed to assess non-normal distributions (data presented as median and range). Pearson’s *χ2* test was performed to compare categorical variables. Two-sided *P* < 0.05 was considered as statistically significant.

**RESULTS**

***Demographics***

Thirty-one patients were initially enrolled in the study. Twenty-four patients were followed-up for a median 20 mo (Table 2); seven patients did not complete follow-up evaluations (survival status unknown). Primary tumors included cervical, endometrial, prostatic, rectal and ovarian cancers. Patients with gynecologic cancer received external radiotherapy, intracavity irradiation, or both. Patients with prostate or rectal cancer received external radiotherapy or intensity-modulated radiotherapy.

Ten patients (10/24; 41.7%) had other symptoms such as abdominal pain, anal pain, fecal urgency, tenesmus, or diarrhea. The linear extent of proctitis was 3–15 cm from the anal verge. Thirteen patients (13/24; 54.2%) had proximal proctitis change below 7 cm: 11 patients had distal proctitis and associated sigmoiditis was observed in two patients (20 cm from the anal verge). All patients received medical treatments for bleeding such as topical corticosteroids (*n =* 10), sucralfate (*n =* 15), hemostatics (*n =* 18), and traditional Chinese medicine (*n =* 10). No patients were on anticoagulant treatment. No recurrence or metastasis was found for primary pelvic malignancies during follow-up.

***Modified topical formalin irrigation***

Topical formalin irrigation was performed on 20 patients in a clasp-knife position under spinal epidural anesthesia, and four patients were treated in a lithotomy position under general or regional anesthesia because they could not tolerate a clasp-knife position due to their age. The duration of irrigation was 2 min for the majority (*n* = 19) of procedures, and ranged from 30 s to 5 min. All but one of the procedures were performed with 4% formalin (2% was used in one case). Nineteen patients received only one course of topical formalin irrigation, and five patients required a second course. No adverse effects were reported after the treatment.

***Efficacy of formalin irrigation***

One month after the treatment, five patients showed complete cessation of bleeding, 14 presented only minor bleeding, and five patients still had bleeding, for a 79.1% (19/24) effective rate. Three months after the treatment, 6/22 patients presented with bleeding. One year after the treatment, 5/16 patients complained of persistent bleeding, which was reduced to 1/9 patients and 0/6 patients at two and five years after the treatment, respectively.

***Rectovaginal fistulas and associated endoscopic findings***

A total of three Rectovaginal fistulas (RVFs) were reported at one, three and two years after the treatment (Table 3). Surgical interventions were conducted for these patients, including fecal diversion (*n =* 1) and the Parks’ operation(a sphincter-saving operation involving resection of the rectum and perianal anastomosis of healthy colon to the anal canal)[[21](#_ENREF_21)] (*n =* 2).Univariate analysis of endoscopic findings showed that a higher VRS and ulceration score were significantly related to risk of RVF (*P* < 0.05) (Table 4).

**DISCUSSION**

The incidence of radiation proctitis after radiotherapy for pelvic malignant tumors ranges from 5%–20%[[22](#_ENREF_22)]. Rectal bleeding is the most common symptom, and refractory bleeding is problematic. To help control rectal bleeding in CRP patients, sucralfate, 5-aminosalicylic acid, metronidazole, steroids and fatty acids have been used, albeit with inconsistent and unsatisfactory results[[23](#_ENREF_23)]. Endoscopic treatment with argon plasma coagulator (APC) is an effective and popular option for patients with refractory hemorrhagic CRP; however, it can result in morbid outcomes, such as rectal ulceration, stricture, bowel perforation, and RVF[[10](#_ENREF_10)]. In our clinical center, we used APC for several patients with hemorrhagic CRP. The results were satisfactory for patients with limited lesion surface areas, but for patients with massive areas of telangiectasia, complications such as anal pain, tenesmus and rectal stricture were observed.

Topical application of formalin is considered a safe and effective treatment for hemorrhagic CRP with comparable efficacy and fewer complications than APC[[24](#_ENREF_24)]. In this study, modified formalin irrigation was effective in 79.1% of patients after one month, which is similar to previous studies[[10](#_ENREF_10),[12](#_ENREF_12)-[14](#_ENREF_14),[25](#_ENREF_25),[26](#_ENREF_26)]. In our series, 18/24 (75.0%) patients reported rapid reduction in rectal bleeding the second day after the treatment. Endoscopic findings revealed decreased severity of telangiectasia, reflecting the reduction of mucosal blood flow after formalin irrigation. Furthermore, bleeding only persisted in one patient after two years. However, resolution of rectal bleeding cannot be entirely attributed to formalin irrigation, as it may reduce spontaneously when the fibrosis of the rectal wall progresses[[27](#_ENREF_28)].

With an emphasis on safety, we modified the formalin irrigation procedure, resulting in a low rate of complications compared with previous studies[[17](#_ENREF_17),[18](#_ENREF_18),[28](#_ENREF_27)]. The modified method protects the internal sphincter; spinal epidural anesthesia and the clasp-knife position provided a full anal dilatation rather than violent dilatation by an anal retractor. The proximal normal colon mucosa is also protected from formalin backflow by insertion of a Foley catheter, which can reduce risks of colitis and peritonitis. As a semicircle anal speculum was used for visual formalin irrigation, the lesion can be directly targeted, thus preventing damage to the normal rectal mucosa, superficial ulcerations, anal canal, and perianal skin. Moreover, the volume and time of irrigation are well controlled, further reducing risk of unintended damage. Although three patients developed RVF, these may have been a result of the natural progression of CRP. Our analysis shows that a high endoscopic VRS and a high ulceration score are associated with risk for RVF. Therefore, we suggest that formalin irrigation should be more cautiously performed in these patients. Whether formalin damages the deep rectal wall remains an open question[[18](#_ENREF_18)].

There are several limitations in this study that may produce potential bias, including the retrospective nature of the study, small sample size, and empirical therapy. Additional prospective randomized-controlled trials are therefore needed to confirm the efficacy and safety of this method.

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**COMMENTS**

***Background***

Chronic radiation proctitis (CRP) occurs in 5%–20% of patients receiving radiotherapy for pelvic malignant tumors such as cervical and prostatic cancers. The most common symptom is rectal bleeding, which is difficult to manage. Medical and endoscopic treatments have been tried, with unsatisfactory results. Argon plasma coagulator is a popular and effective option for CRP, but results in complications. Thus, it is critical to introduce new treatment options to reduce potential complications.

***Research frontiers***

Recently, different methods utilizing formalin for hemorrhagic CRP have been reported, including direct instillation and endoscopy-guided insertion of formalin-soaked gauze, with efficacy comparable to argon plasma coagulator treatment. However, these methods still result in complications. In this study, a new method is presented for application of formalin with improved safety and few complications.

***Innovations and breakthroughs***

In this series, a modified method of topical 4% formalin irrigation is introduced and shown to be effective and well tolerated for refractory hemorrhagic CRP. This procedure offers protection of the internal sphincter and proximal normal colon mucosa, and targets the lesion area with well-controlled irrigation volume and time.

***Applications***

By improving the safety of topical formalin irrigation and targeting the CRP lesion, complications such as anal pain, rectal stricture, and incontinence can be reduced. Moreover, the efficacy for controlling rectal bleeding can be enhanced, and thus improve the patient’s quality of life.

***Terminology***

The underlying causes of CRP are endarteritis obliterans and progressive submucosal fibrosis due to radiotherapy. Formalin acts on the superficial mucosa of the rectum and results in the rapid deterioration of mucosal blood flow, which leads to superficial coagulation necrosis to resolve bleeding.

***Peer review***

This is an important experience for what is sometimes a difficult problem. The method of application is repeated 3 times in the text (abstract, methods and in the discussion). Installation or irrigation may be more appropriate then application for the technique. Other treatment options like endoscopic plasma coagulation should be discussed.

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**Table 1 Vienna Rectoscopy Score of endoscopic findings for hemorrhagic chronic radiation proctitis**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Score** | **Congested mucosa** | **Telangiectasia** | **Ulceration** | **Stricture** | **Necrosis** |
| 0 | Focal reddening | None | None | None | None |
| 1 | Diffuse, nonconfluent | Single | None | None | None |
| 2 | Diffuse confluent  | Multiple, nonconfluent  | None | None | None |
| 3 | Any | Multiple, confluent  | Micro-ulceration, superficial, < 1 cm2 | None | None |
| 4 | Any | Any | Superficial, > 1 cm2 | > 2/3 regular diameter | None |
| 5 | Any | Any | Deep ulceration, fistula, perforation | ≤ 2/3 regular diameter | Any |

The highest grade of any one parameter qualifies for the attribution to one of the given score levels regardless of the grade achieved in any other parameter.

**Table 2 Patient demographics, *n* = 24 *n* (%)**

|  |  |
| --- | --- |
| **Characteristic** | **Value** |
| Age, yr | 61.5 ± 9.5 |
| Sex, female/male | 19/5 |
| Primary cancer |  |
| Cervical  | 15 (62.5) |
| Endometrium | 3 (12.5) |
| Prostatic  | 3 (12.5) |
| Rectal  | 2 (8.3) |
| Cervical and ovarian | 1 (4.2) |
| Total irradiation dosage1, Gy  | 75 (44–97) |
| Concomitant chemotherapy | 13 (54.2) |
| History of abdominopelvic operation | 13 (54.2) |
| History of acute radiation proctitis | 19 (79.2) |
| Time from the end of radiotherapy to bleeding, mo | 11.1 ± 9.0 |
| Duration of bleeding, mo  | 10.6 ± 8.0 |
| Grade of bleeding, CTCAE v 3.0 |  |
| II | 20 (83.3) |
| III | 4 (16.7) |
| Preoperative hemoglobin, g/L | 107.6 ± 16.4 |
| Transfusion dependent | 6 (25.0) |
| Preoperative VRS | 3 (1–5) |

1data from 15 patients (nine patients received radiotherapies in other centers). CTCAE: Common Terminology Criteria for Adverse Events; VRS: Vienna Rectoscopy Score.

**Table 3 Demographic and clinical parameters of three patients with rectal fistulas after topical formalin irrigation**

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter** | **Case 1** | **Case 2** | **Case 3** |
| Preoperative VRS score  | 5 | 5 | 4 |
| Preoperative ulcer score | 3 | 2 | 2 |
| Formalin concentration | 4% | 4% | 4% |
| Time of formalin exposure | 30 s | 1 min | 2 min |
| Courses of formalin irrigation | 1 | 1 | 1 |
| Postoperative VRS score  | Unknown | 5 | 5 |
| Time from the end of radiotherapy to fistula formation, mo | 3 | 20 | 1 |
| Therapy for rectal fistula | Diversion | Parks operation | Parks operation |

VRS: Vienna Rectoscopy Score.

**Table 4 Univariate analysis of endoscopic findings after topical formalin irrigation**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **With fistula** | **Without fistula** | ***P-*value1** |
| VRS scores | 5 (4–5) | 3 (1–5) | 0.012 |
| Friable mucosa  | 1 (0–1) | 1 (0–3) | 0.374 |
| Telangiectasis | 2 (1–2) | 2 (1–3) | 0.231 |
| Ulcer | 0 (0–5) | 4 (0–5) | 0.022 |
| Necrosis | 0 (0–5) | 0 (0–5) | 0.556 |

1Wilcoxon rank sum test; data are presented as median (range).