

Retrospective Study

Formalin irrigation for hemorrhagic 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 were enrolled. Patients with anorectal strictures, deep ulcerations, and fistulas were excluded. All patients underwent flexible endoscopic evaluation before 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, 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. The mean time from the end of radiotherapy to the onset of bleeding was 11.1 ± 9.0 mo (range: 2-24 mo). Six patients (25.0%) were blood transfusion dependent. The median preoperative Vienna Rectoscopy Score (VRS) was 3 points. Nineteen patients (79.2%) received only one course of topical formalin irrigation, and five (20.8%) required a second course. No side effects were observed. One month after treatment, bleeding cessation was complete in five patients and obvious in

14; the effectiveness rate was 79.1% (19/24). For long-term efficacy, 5/16, 1/9 and 0/6 patients complained of persistent bleeding at 1, 2 and 5 years after treatment, respectively. Three rectovaginal fistulas were found at 1 mo, 3 mo and 2 years after 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 procedure that was well tolerated with long-term effectiveness for refractory hemorrhagic chronic radiation proctitis. The method focused on improving safety and reducing complications. The advantages of the procedure were as follows: protection of internal sphincter (spinal epidural anesthesia and the clasp-knife position provide full anal dilatation instead of dilatation by an anal retractor); protection of proximal normal colonic mucosa (Foley catheter 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 gynecological, rectal and prostate cancer. However, chronic radiation proctitis (CRP) is a common and severe complication in these patients, with 29%-51% developing rectal hemorrhage following pelvic radiotherapy^[1,2]. The underlying causes for this type of complication include endarteritis obliterans and progressive submucosal fibrosis^[3,4].

Refractory hemorrhagic CRP is difficult to manage^[2,5-9], but previous successful experience in treating cystitis has led to the use of formalin as a treatment option^[10]. Topical formalin application has 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^[10-14]. Formalin acts only on the superficial mucosa, which results in rapid deterioration of mucosal blood flow and superficial coagulation necrosis^[3,15,16].

Despite the efficacy, high complication rates after formalin application have been reported, such as anal pain, rectal stricture, and incontinence^[17]. De Parades *et al.*^[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. 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. Exclusion criteria were: (1) patients with large ulcers, mucosal necrosis, or stricture [Vienna Rectoscopy Score (VRS): 4-5 points] due to increased risk of perforation; (2) patients with life-threatening or mild bleeding that could be controlled by medical treatment; (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 (CTCAE) 4.0^[19], and had not responded to previous medical treatment 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 in rectal bleeding, and potential complications 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 evaluation before formalin irrigation and were scored according to VRS criteria^[20] (Table 1). A 30-min water enema was performed, and patients then received topical formalin irrigation in a clasp-knife position under spinal epidural anesthesia in the operating room. First, a

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 cm ²	None	None
4	Any	Any	Superficial, > 1 cm ²	> 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* (%)

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 dosage ¹ , 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 (9 received radiotherapy in other centers). VRS: Vienna rectoscopy score.

Foley catheter was inserted into the proximal sigmoid cavity to prevent formalin backflow. Then, 10-20 mL 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. A semicircular 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 1 wk in the absence of obvious cessation of bleeding.

Follow-up

Patients were followed-up by telephone after 1, 3 and 6 mo, and then every year for 5 years after treatment. Defecation 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 1 mo after 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. 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 χ^2 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. Twenty-four patients were followed-up for a median 20 mo (Table 2); seven patients did not complete follow-up evaluation (survival status unknown). Primary tumors included cervical, endometrial, prostatic, rectal and ovarian cancer. Patients with gynecological cancer received external radiotherapy, intracavity irradiation, or both. Patients with prostate or rectal cancer received external radiotherapy or intensity-modulated radiotherapy.

Ten patients (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 (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 the lithotomy position under general or regional anesthesia

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.

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 1 case). Nineteen patients received only one course of topical formalin irrigation, and five required a second course. No adverse effects were reported after treatment.

Efficacy of formalin irrigation

One month after treatment, five patients showed complete cessation of bleeding, 14 presented only minor bleeding, and five still had bleeding, for a 79.1% (19/24) effectiveness rate. Three months after treatment, 6/22 patients presented with bleeding. One year after treatment, 5/16 patients complained of persistent bleeding, which was reduced to 1/9 patients and 0/6 patients at 2 and 5 years after treatment, respectively.

Rectovaginal fistulas and associated endoscopic findings

A total of three rectovaginal fistulas (RVFs) were reported at 1, 3 and 2 years after treatment (Table 3). Surgical interventions were conducted for these patients, including fecal diversion ($n = 1$) and Parks' operation (a sphincter-saving operation involving resection of the rectum and perianal anastomosis of healthy colon to the anal canal)^[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% to 20%^[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

Table 4 Univariate analysis of endoscopic findings after topical formalin irrigation

Variable	With fistula	Without fistula	<i>P</i> value ¹
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).

results^[23]. Endoscopic treatment with argon plasma coagulation (APC) is an effective and popular option for patients with refractory hemorrhagic CRP; however, it can result in rectal ulceration, stricture, bowel perforation, and RVF^[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]. In this study, modified formalin irrigation was effective in 79.1% of patients after 1 mo, which is similar to previous studies^[10,12-14,25,26]. In our series, 18 (75.0%) patients reported rapid reduction in rectal bleeding at 2 d after 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 2 years. However, resolution of rectal bleeding cannot be entirely attributed to formalin irrigation, because it may reduce spontaneously when the fibrosis of the rectal wall progresses^[27].

With an emphasis on safety, we modified the formalin irrigation procedure, resulting in a low rate of complications compared with previous studies^[17,18,28]. The modified method protects the internal sphincter; spinal epidural anesthesia and the clasp-knife position provided 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. We used a semicircular anal speculum for visual formalin irrigation, therefore, the lesion could be directly targeted, thus preventing damage to the normal rectal mucosa, superficial ulcerations, anal canal, and perianal skin. The volume and time of irrigation are well controlled, thus further reducing the 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 high endoscopic VRS and high ulceration score are associated with risk of 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].

There were several limitations to this study that may have produced 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 cancer. The most common symptom is rectal bleeding, which is difficult to manage. Medical and endoscopic treatments have been tried, with unsatisfactory results. Argon plasma coagulation (APC) 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 that of APC. 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 was 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 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 than application for the technique. Other treatment options like endoscopic plasma coagulation should be discussed.

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