



Original research article

Formalin therapy for hemorrhagic radiation proctitis



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ABSTRACT

Background: Radiotherapy within pelvis is a vital component of curative therapy for urological, gynecological and rectal malignancies. Rectum is especially vulnerable to secondary radiation injury resulting in proctitis. The most common and life-threatening symptom is rectal hemorrhage. Formalin application into the rectum causes local cauterization of telangiectatic mucosal vessels. The aim of our study was to assess the efficacy of local formalin application in patients with hemorrhagic radiation proctitis.

Methods: A solution of 4.0% formalin was used in the treatment of 20 patients with clinical and proctoscopic evidence of radiation proctitis. Treatment involved direct application of 4.0% formalin into the rectum. All patients were followed-up in terms of complete resolution of symptoms or recurrences of bleeding.

Results: A total of 20 patients with a mean age of 69.7 (range, 57–80) years were followed for 51.2 (range, 1–93) months. The mean duration of symptoms was 4.5 (range, 1–10) months and the interval between the end of radiotherapy and symptoms was mostly between 5 and 30 months. Patients required an average of 2 (range, 1–5) formalin treatments. Of the 20 patients, 10 had complete resolution of their symptoms after their first treatment. In 10 patients bleeding recurred and they were offered another formalin instillation and/or 5-ASA suppositories and argon therapy. Complete resolution of symptoms was achieved in all patients.

Conclusions: Topical formalin instillation is effective, safe, and well-tolerated method for the patients with radiation proctopathy. This therapy may be repeated in case of recurrent bleeding and combined with other methods of treatment.

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Introduction

Gastrointestinal tract may be affected by radiation-induced injury that leads to a variety of symptoms [1]. Pelvic radiotherapy is a vital component of curative treatment for many urological, gynecological and gastrointestinal tract cancers. Particularly, the rectum is the site most frequently affected within the gastrointestinal tract [2]. Because of the close proximity to the prostate, cervix and uterus, rectum is especially vulnerable to secondary radiation injury resulting in proctitis. Radiation-induced proctopathy occurs in 2.0–5.0% of patients having had pelvic radiation. Two forms of radiation proctitis are distinguished, acute and chronic. In spite of the fact that the acute form concerns almost all patients, it is rather

self-limiting condition. Chronic radiation proctopathy ranges from 1.0 to 20.0%. Chronic radiation proctitis may be both a continuation of early symptoms 3 months after the completion of radiation therapy and symptoms may begin 3 months after the initiation of radiation therapy. The median onset of symptoms is 8–12 months, but symptoms may happen as late as 30 years. The prevalence of severe adverse events such as fistulation, stricture formation, transfusion-dependent bleeding or secondary cancers after pelvic radiation is not fully known but has been estimated to be 5% at 10 years. The most common and bothersome of all symptoms in patients with radiation-induced proctitis is rectal bleeding. Rectal hemorrhage requires hospitalization as well as quite often blood transfusion. In some patients, fibrosis of the rectal wall may lead to rectal structure. Moreover, such fibrosis may be the cause of a loss of distension of the rectum, thus may result in difficulty in defaecation or even obstruction [2–13]. A progressive vasculitis, thrombosis and finally ischemia and even necrosis may be the

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consequences of transmural injury of the bowel wall [14]. Quality of life as well as daily routines are impaired in 6.0% patients with rectal bleeding after pelvis radiation [1]. What's more, ischemia gives rise to telangiectatic neovasculation. Such vessels are fragile and prone to bleeding which is caused by rupture of telangiectatic vessels and friable mucosa. Such rectal bleeding may be extremely difficult to stop and up to now there is no ideal option to cope with all these patients successfully. The therapeutic methods comprise topical corticosteroids, pentoxifylline, 5-aminosalicylic acid, sucralfate or short-chain fatty acid enemas, as well as hyperbaric oxygen treatment with its angiogenic effect, endoscopic therapy (YAG laser, argon laser, bipolar cautery, heater probes, argon plasma coagulation) or even temporary fecal diversion [8,9,15–18]. Kim et al. used rebamipide enemas in patients with chronic radiation proctopathy. Rebamipide as a cytoprotective agent is used for mucosal protection that leads to the healing of gastroduodenal ulcers [19]. Surgery is a last resort and performed only in the presence of stricture, fistula, abscess, perforation, necrosis or life-threatening rectal hemorrhage [4,20,21]. Formalin treatment is also recommended as an effective therapy in patients with radiation-induced proctitis. Brown, in 1969, was the first who used formalin for radiation-induced hemorrhagic cystitis. In 1986, Rubinstein et al. successfully used formalin therapy in one patient with radiation-induced hemorrhagic proctitis. This patient did not rebleed during 14 months of follow-up [10]. Applied topically formalin solution causes local chemical cauterization of telangiectatic mucosal vessels. Direct application of formalin to the rectum is performed either by direct enema or with formalin-soaked gauze. According to the literature, the success of this method in patients with radiation proctitis in terms of cessation of bleeding is 60.0–100.0% [9].

The aim of our study was to assess the efficacy of local formalin instillation in patients with radiation-induced proctitis.

Patients and methods

We performed a retrospective study from October 2005 to November 2012 and analyzed 20 patients who were treated for radiation-induced hemorrhagic proctitis at the Department of General and Colorectal Surgery, Medical University of Lodz. Data collected included the gender of the patient, symptoms, hemocrit, hemoglobin and red blood cells values, time period between radiotherapy and symptoms as well as duration of symptoms, concomitant treatment with antiplatelet or anticoagulant, type of malignancy, other therapies before and after formalin instillation, and also number of formalin treatments, response to treatment, complications, and length of follow-up. Twelve out of twenty patients had undergone unsuccessful previous therapy for radiation proctitis (5-ASA tablets or suppositories, argon beam therapy, hydrocortisone enemas) and therefore they were referred to formalin treatment. All patients presented symptoms of refractory radiation-induced proctitis and typical proctoscopic findings as well as past history of pelvic radiotherapy. All procedures were performed in the lithotomy position under general anesthesia without bowel preparation. A solution of 4.0% formalin was drawn up into a 100 ml syringe and then instilled into the rectum through Foley catheter under general anesthesia. The total mucosal contact time for the formalin was around 1–2 min. After chemical cauterization had been performed, the rectum was rinsed with saline. Patients were admitted to the hospital for the procedure because of general anesthesia and they were monitored for blood cell counts, hemocrit and hemoglobin levels. A complete response was defined as no episodes of recurrent bleeding and that was regarded as therapeutic success. Recurrence was defined as a rebleed event requiring one or more additional formalin

application or any other treatment during follow-up period. All patients were discharged on the next day after procedure and followed-up to assess their response to the treatment and to check for any complications. Formalin application was repeated if bleeding persisted or recurred. In 8 out of 10 patients with recurrent bleeding also received both argon plasma therapy or 5-aminosalicylic acid (5-ASA) suppositories.

Results

During the study period we treated 20 patients with radiation-induced proctitis. The mean age of patients was 69.7 (range, 57–80) years. Ten patients were male, all with prostatic cancer. Of the ten female patients, nine had cervical cancer, one had vaginal cancer. The interval between the end of radiotherapy and the onset of radiation proctitis symptoms was between 5 and 12 months in 13 patients and between 14 and 30 months in 6 patients. One female developed rectal bleeding after 360 months after irradiation for cervical cancer. She underwent sigmoid resection for radiation-induced stenosis 8 months prior to formalin therapy. One male patient who underwent prostatectomy for cancer in 1998, followed by radiotherapy for cancer recurrence in 2006, had sigmoid resection due to sigmoid cancer in 2002. One female who underwent panhysterectomy for cervical cancer followed by irradiation in 2010, five months later developed radiation-induced small intestine stenosis and for this reason she underwent side-to-side anastomosis of the ileum to the transverse colon that was one month prior to formalin therapy. Before formalin application, all patients complained of rectal bleeding, two patients experienced rectal pain, in two cases diarrhea was present, and two patients reported rectal tenesmus. The mean duration of symptoms was 4.5 (range, 1–10) months. Twelve patients had undergone prior treatment ($n = 2$, 5-aminosalicylic acid tablets; $n = 6$, argon beam therapy; $n = 4$, 5-aminosalicylic acid suppositories, argon beam therapy and hydrocortisone enemas). Patients required an average of 2 (range, 1–5) formalin applications to achieve cessation of bleeding. The mean follow-up period was 51.2 (range, 1–93) months. The mean hemoglobin level was 10.1 (range, 6.1–13.9) g/dl and four patients required blood transfusion on the day of admission, before treatment. One patient was on the long-term anticoagulant treatment due to previous coronary bypass surgery. A summary of patient demographics and characteristics is presented in Table 1.

Of the 20 patients, 10 had complete resolution of their symptoms after their first treatment. In ten patients bleeding recurred after 2 days to 8 months after initial formalin application. Four of these patients had one recurrence, in four patients bleeding recurred twice, and in two cases we observed three recurrences. In the patients with one recurrence, formalin treatment was repeated in two patients successfully, and the other two received 5-aminosalicylic acid suppositories as they refused further formalin application. In the patients with two recurrences, two patients received formalin treatment again and during the second recurrence formalin instillation was supported by 5-ASA suppositories. The other two patients received formalin treatment during his first recurrence, and formalin treatment with argon beam therapy during the second recurrence. The patient with three recurrences received formalin instillation during first, argon beam therapy during second and again formalin therapy during third recurrence (Fig. 1). Finally, complete resolution of the symptoms was achieved in all patients regardless of single or repeated formalin therapy and/or eventually combined treatment (argon beam therapy, 5-ASA suppositories).

No serious complications related to the formalin treatment were observed.

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