
CONSERVATIVE THERAPIES FOR HEMORRHAGIC RADIATION PROCTITIS: A REVIEW

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Chronic radiation proctitis represents a challenging condition seen with increased frequency due to the common use of radiation for treatment of pelvic cancer. Hemorrhagic radiation proctitis represents the most feared complication of chronic radiation proctitis. There is no consensus for the management of this condition despite the great number of clinical approaches and techniques that have been employed. Rectal resection represents an available option although associated with high morbidity and risk of permanent colostomy. The effectiveness of nonoperative approaches remains far from desirable, and hemorrhagic recurrence represents a major drawback that leads to a need for consecutive therapeutic sessions and combination of techniques. We conducted a critical review of published reports regarding conservative management of hemorrhagic chronic radiation proctitis. Although prospective randomized trials about hemorrhagic radiation proctitis are still lacking, there is enough evidence to conclude that topical formalin therapy and an endoscopic approach delivering an argon plasma coagulation represent available options associated with elevated effectiveness for interruption of rectal bleeding in patients with chronic radiation proctitis.

DESCRIPTORS: Proctitis. Radiation. Hemorrhagic. Conservative. Treatment.

Radiotherapy (RDT) techniques have become primary treatments for pelvic organ cancer, subsequent to improvements in these techniques over the past few decades. After pelvic irradiation, the rectum is one of the most commonly injured organs due to its fixed position¹⁻³. Its anatomic relationships with the uterine cervix and prostate make it impossible not to irradiate the rectum during RDT regardless of the target organ⁴. Radiation proctitis (RP) is an adverse effect of RDT to the rectum, and its prevention and treatment have become topics of debate. The main purpose of this review is to discuss current therapies for radiation-induced injury to the rectum, mainly in its hemorrhagic form.

GENERAL CONSIDERATIONS

Radiation proctitis can be classified as acute or chronic. Acute radiation proctitis (ARP) can begin during or shortly after irradiation but usually resolves in up to 6 months. It is characterized by diarrhea, intermittent bleeding, nausea, abdominal pain, mucous discharge, and constipation or even urinary symptoms. Histological alterations are usually confined to the mucosa⁵, and in general, has a short

duration and improves with conservative measures. However, about 20% of the patients with RP require interruption of the treatment for 1 to 2 weeks in order to improve clinical status. Following this acute episode most of the patients remain asymptomatic, but up to 20% of this contingent will develop chronic radiation proctitis (CRP)⁶. The development of CRP may take up to 2 years and has no relationship with the occurrence of ARP⁷.

During the course of radiotherapy, virtually all patients present symptoms related to ARP. However, such symptoms usually subside from 2 to 3 months after the end of RDT⁸. Nevertheless, 2% to 10% of the patients develop CRP, usually 6 to 24 months af-

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ter RDT, but clinical symptoms may appear up to 30 years after treatment^{9,10}.

Chronic radiation proctitis has several forms of clinical presentation, including mucous rectal discharge, diarrhea, urgency, pain, and bleeding. Recto-vaginal fistula, enteric fistula, cutaneous fistula, perforation, and rectal stenosis can rarely occur. Histological alterations are mainly of a vascular nature, such as subintimal fibrosis and platelet thrombi in the arterioles of the submucosa with fibrosis of connective tissue⁵.

The development of RP is directly related to the dose of radiation, the irradiated volume, type of radiation exposure, dose fraction regimens, and the interval between sessions. Smith *et al.* reported a 20% incidence of RP with a radiation dose up to 7.500 Cgy and a 60% incidence of RP with doses greater than 7.500 Cgy¹¹.

Other factors predispose to RP, including previous abdomino-pelvic surgery, obesity, diabetes mellitus, hypertension, atherosclerosis, and simultaneous chemotherapy. In 1997, Bertuccelli *et al.* studied the effect of the combination of chemotherapy with RDT in the treatment of rectal cancer and observed an increase in incidence of severe diarrhea in the group that received RDT plus chemotherapy when compared to the group that underwent RDT alone (20% versus 10%)¹².

Endoscopic findings of RP are also variable. Since 1923, when the first endoscopic findings were reported, there have been many attempts to establish a standardized endoscopic approach to its diagnosis¹³. Paleness, erythema, vascular abnormalities, and ulcerations are easily recognized alterations. However, in order to correlate the clinical picture to endoscopic findings, Wachter *et al.* proposed a score for RP based on terminology of the World Organization of Digestive Endoscopy (OMED) and its

5 main alterations, namely telangiectasias, congestion, ulcerations, stenosis, and necrosis¹⁴.

The prognosis of RP remains obscure. Gilinsky *et al.*, in 1983, reported on 88 patients with RP followed for more than 8 years. Fifty percent presented slight to moderate symptoms with distinct endoscopic findings that resolved spontaneously in 2 years¹⁰. Nevertheless, 17 patients presented refractory symptoms. Cho *et al.* observed that 19 out of 101 patients developed RP after radiation therapy for prostate cancer¹⁵.

Despite the fact that the incidence of RP tends to increase with time, RP still lacks research and attention. It should be noted that no consensus exists about its clinical and endoscopic evaluation and its natural history. Its behavior and prognosis are not completely known.

Rectal bleeding due to RP usually represents a chronic condition, and anemia is a common finding; sometimes bleeding may be severe. Several treatments for this presentation have been used, and as a result of its high recurrence rate, they were rarely utilized in a cyclic manner, which makes their evaluation difficult. We opted to review and analyze the results of conservative treatments of hemorrhagic CRP.

Steroids

In 1976, Goldstein *et al.* observed clinical improvement of a patient with radiation-induced proctitis who received salicylazosulfapyridine in combination with prednisone¹⁶. Subsequently, other studies were developed in an attempt to evaluate the use of steroids as a therapeutic alternative for RP, alone and also in combination with other modalities.

In 1984, Ben Bouali *et al.* demonstrated clinical and endoscopic improvement in 4 out of 33 patients treated with daily rectal administration

of 5 mg of betamethasone in combination with diphenoxylate¹⁷. In 1977, Pajares *et al.* also observed a decrease of rectal bleeding after administration of prednisone¹⁸. More recently, Triantafillidis *et al.* reported 5 patients treated for RP with enemas containing 5 mg of betamethasone without any clinical improvement¹⁹.

In a prospective randomized study, Kochhar *et al.* compared the use of enemas containing prednisolone and 3 g of oral sulfasalazine in 18 patients to the use of enemas containing sucralfate in combination with an oral placebo in 19 patients for 4 weeks²⁰. Clinical improvement was appraised by a score based on the number of bowel movements, bleeding, and tenesmus. Therapy with sucralfate was more efficient, better tolerated, and cheaper.

Another prospective randomized study in mice analyzed administration of 90 mg of hydrocortisone and showed endoscopic improvement and better tolerance when compared with betamethasone enemas²¹.

Steroids have been used for many years in the treatment of RP despite the absence of larger and well-designed studies²². Moreover, steroids were not able to achieve sustained resolution of symptoms for patients with CRP.

Aminosalicylates

Derivatives of 5-aminosalicylic acids (5ASA), also known as aminosalicylates, have been the object of research in treatment of RP since the studies of Menie *et al.* in 1975 showed efficiency of the 5-aminosalicylic acid drugs versus placebo in the prevention of diarrhea in patients undergoing pelvic RDT, as well as studies for their previous use in the management of inflammatory proctitis. Aminosalicylates act in reducing the production of prostaglandins in the intestinal mucosa²⁰.

Goldstein *et al.* demonstrated the effectiveness of oral sulfasalazine in combination with steroid enemas in 1 patient¹⁶. Bem Bouali *et al.* demonstrated that administration of sulfasalazine, in oral or enema form, provided clinical and endoscopic improvement in 60% of patients¹⁷. In 1989, Ladas *et al.* demonstrated that administration of sulfasalazine in combination with sucralfate enemas was effective in controlling rectal bleeding and promoted endoscopic improvement in 1 patient with CRP.²³

On the other hand, in 1989, Baum *et al.* showed that daily administration of enemas containing 5ASA for a period of 2 to 6 months was not able to induce clinical, endoscopic, or histological improvement in 4 patients with CRP²⁴. Another study of 5 patients performed by Triantafillidis *et al.* demonstrated no improvement over 5ASA enemas.¹⁹

We believe that multicenter prospective randomized studies of aminosalicylates are needed to confirm their role in the management of RP, but available evidence suggests that they are not effective.

Sucralfate

Sucralfate is an aluminum salt that adheres to the mucous membrane, promoting the formation of a protective barrier that has been used for many years in the treatment of peptic ulcers. Its possible effectiveness for inflammatory proctitis and for colonic bleeding after endoscopic polypectomy is also under investigation.

The cytoprotective action of sucralfate seems to be derived from the production of prostaglandins and promotion of epithelial cell proliferation. In animal models of colitis in mice, rectal administration of sucralfate induced high E2-prostaglandin levels and increased cellularity of the colonic mucosa²⁵.

The best route for sucralfate administration remains controversial. In 1988, Kochhar *et al.* used enemas containing 2 g of sucralfate in 4 patients with hemorrhagic RP and demonstrated reduced bleeding²⁶. A previous study by Henriksson *et al.* in 1987 showed the usefulness of oral sucralfate administered for 2 to 6 weeks after RDT in the reduction of bowel movements, mucous discharge, and rectal bleeding after 1 year²⁷. Another study by Kochhar in 1991 demonstrated the superiority of topical sucralfate over steroid enemas administered in combination with sulfasalazine²⁰.

In 1996, Stockdale and Biswas reported that administration of enemas containing 2 g of sucralfate in a patient with hemorrhagic RP resulted in long-term control of CRP as revealed from 4 years of follow-up²⁸. Again in 1996, Tada *et al.* demonstrated endoscopic improvement of CRP in 6 out of 7 patients treated with 2 g sucralfate enemas.²⁹

In 1997, O'Brien *et al.* published the negative effect of a sucralfate suspension for prevention of ARP³⁰. In this multicenter Australian study, 86 patients were randomized into 2 groups: 1 group received 3 g sucralfate enemas and the other group received a placebo. Enemas were administered once daily for a period of 2 weeks after RDT. Sucralfate enemas did not reduce symptoms associated with ARP and therefore should not be recommended in clinical practice.

In 1998, Sasai *et al.* published 3 cases of patients with hemorrhagic RP who had undergone previous sulfasalazine and steroid treatment without success. They experienced significant improvement of rectal bleeding after daily administration of 4 g of sucralfate during 1 to 2 months³¹. The authors emphasized the advantages of oral sucralfate, which include good tolerance and few side effects associated with control of the symptoms for a long period.

More recently in 1999, Kochhar *et al.* demonstrated that topical sucralfate produced sustained resolution of symptoms, in agreement with previous authors³². Stockdale and Biswas²⁸ studied 26 patients with hemorrhagic RP that were treated with 2 g sucralfate enemas twice daily. The patients were examined every 4 weeks in the first 16 weeks of treatment and after that at an interval of 8 to 12 weeks. Twenty patients had a significant reduction of bleeding in the first 4 weeks of treatment, as did another 4 patients after 16 weeks. At a mean of 45 weeks, 7 patients had some kind of symptomatic recurrence. However, bleeding ceased soon after the sucralfate treatment was reintroduced.

Short-Chain Fatty Acids (SCFA)

During the past few years, many studies have been performed on short-chain fatty acids (SCFA) so that knowledge regarding these substances has increased. Short-chain fatty acids are organic acids containing from 1 to 6 carbons that are a product of bacterial metabolism of some carbohydrates in the colon; they are the main source of energy for colonocytes. Butyrate is the most important SCFA and is preferentially metabolized by colonic mucosa when compared to propionate and acetate. The dependence of the colon related to the oxidation of SCFA increases towards the rectum, and 70% of the oxygen consumed by the colonic epithelial cells is used in the oxidation of SCFA³³.

The effect of SCFA on rectal and colonic mucosa has been tested in patients with RP in an attempt to obtain healing of mucous lesions^{33,34}. In 1999, Pinto *et al.* in a double-blind randomized placebo-controlled trial studied 19 patients with CRP³⁵. They demonstrated a beneficial effect from administration of 2 daily enemas with 60 mmol SCFA for 5 weeks in compari-

son with the administration of an isotonic solution. There was a significant decrease of rectal bleeding with SCFA as well as an endoscopic improvement. In 1995, Mamel *et al.* also demonstrated the efficacy of enemas containing 60 mL of SCFA twice daily for 4 weeks in the improvement of 6 patients with CRP³⁶. In 1996, Al Sababagh *et al.* using the same solution described in the previous studies achieved clinical, endoscopic, and histological improvement in 7 patients with hemorrhagic RP³⁷.

These results were not reproduced by Chen *et al.* in a prospective study, where they evaluated the evolution of 12 patients with hemorrhagic CRP for 2 weeks and did not find any significant difference in clinical, endoscopic, and histological aspects of patients treated with SCFA³⁸.

More recently, Talley *et al.* compared daily administration of 2 enemas with 60 mL of butyrate in a concentration of 40 mmol to placebo for 2 weeks in a randomized double-blind study of 15 patients with CRP. They found no benefit from SCFA³⁹.

In 1998, Cook and Sellin performed a literature review about SCFA in the management of colitis³³. Regarding RP, the authors observed that studies showed early reduction of bleeding episodes, but SCFA had no influence in other symptoms such as chronic pain and tenesmus.

In spite of the great progress in the knowledge of the structure, metabolism, and action of SCFA, there is still need for additional data to confirm its effectiveness. Because of these conflicting data, there are no commercial preparations available for clinical use.

Formalin

The use of formalin in the management of RP emerged from its use in the treatment of bleeding tumors of the bladder and radiation cystitis^{40,41}.²

In 1986, Rubinstein *et al.* successfully used a rectal wash with formalin for the first time in the treatment of RP⁴². The authors reported a 71-year-old patient irradiated for bladder cancer who developed diffuse hemorrhagic RP. The patient underwent general anesthesia and the rectum was irrigated with two liters of 3.6% formalin for 15 minutes, followed by irrigation with saline. An insufflated vesical probe was used in order to protect the sigmoid colon. The procedure was repeated after 2 weeks and after 3 months. Bleeding episodes immediately ceased and the patient was asymptomatic after 14 months.

After these results, many authors initiated treatments of hemorrhagic CRP with formalin. In 1993, Seow-Choen *et al.* used formalin in 8 patients with hemorrhagic CRP refractory to steroids and with a constant need for blood transfusions⁴³. In this study, a 4% solution-soaked gauze was applied to the rectum through a rectoscope. Patients underwent regional anesthesia and had their perianal skin protected to avoid direct contact with the formalin. Contact between the gauze and rectal mucosa was maintained until the bleeding stopped (from 2 to 3 minutes). Bleeding ceased in 7 patients after a single session, while another patient needed an additional application.

In 1995, the same authors confirmed the effectiveness of direct application of formalin solution soaked

gauze in 29 patients followed for 12 months⁴⁴. In this study, rectal bleeding ceased right after application in 17 patients. Four patients needed a second application (72% success rate). The 5 remaining patients obtained only partial improvement.

The instillation technique proposed by Rubinstein *et al.* was modified by 2 groups. One of them used rectal instillation with 4% formalin after placement of a Foley catheter in order to delineate the superior limit of the instillation and protect the normal intestine in 14 patients resistant to steroid and/or sulfasalazine treatment⁴⁵. Treatment was well tolerated, and 11 patients needed 2 applications while other 3 patients needed 3 sessions. After 6 months, 9 patients were asymptomatic (64%), 3 patients had incomplete resolution of symptoms, and 2 had no improvement. Saclarides *et al.* reported a study in which aliquots of 50 mL of 4% formalin were instilled into the rectum for 30 seconds each, with a total of 400 to 500 mL per session in 16 patients. They achieved complete symptom control in 81% of after 1 or 2 applications⁴⁶. Four patients developed fissures in the anal verge and 1 developed tenesmus.

The technique of soaked gauze proposed by Seow-Choen was revised by 5 groups, with a total of 41 patients. Complete success rate ranged from 80% to 100% after 1 to 4 sessions (Table 1)^{43,47-51}.

Recently, in an Australian study, a

Table 1 - Summarized results of patients with hemorrhagic radiation proctitis treated with formalin instillation.

Author	Number of patients	Follow-up (months)	Response
Seow-Choen <i>et al.</i> ⁴³ , 1993	8	4	88%
Biswal <i>et al.</i> ⁴⁷ , 1995	16	11	81%
Isenberg <i>et al.</i> ⁴⁸ , 1994	2	3	100%
Salvati <i>et al.</i> ⁴⁹ , 1996	10	Not reported	100%
Roche <i>et al.</i> ⁵⁰ , 1996	6	12	100%
Faragher <i>et al.</i> ⁵¹ , 1997	7	10	100%

combination of formalin and Nd:YAG (neodymium yttrium-aluminum-garnet) laser was used in 14 patients⁵². First, the patients underwent an endoscopic Nd:YAG laser procedure and then were treated with a formalin application as described by Seow-Choen. A single session was enough for 9 patients, 2 sessions were necessary for 3 patients, and 3 sessions for the other 2 patients. After a 3-year follow-up, 10 (71%) patients had no rectal bleeding, and another one had a significant decrease in bleeding episodes. Two patients required an operation to manage their symptoms.

After these first published series with formalin as a therapeutic alternative for hemorrhagic RP, investigators have been trying to determine the best concentration and form of its application as well as its side effects. In low concentrations, formalin is not toxic. However, high concentrations can result in severe toxic effects. Additionally, the nutritional state and smoking can alter blood levels of formalin. The only reported case of intoxication after rectal irrigation occurred due to accidental infusion of 100 mL of 10% formalin. The patient developed chronic colitis that resolved after 2 months⁵³.

Evidence suggests that formalin is very effective in the treatment of hemorrhagic CRP, mainly in cases in which the 2 distal thirds of the rectum are affected. Other advantages of formalin application are low cost, low incidence of side effects, availability, and its easy manipulation.

Endoscopic

Endoscopic management of CRP is based on endoscopic coagulation induced by Nd:YAG laser, electrocoagulation, or argon plasma coagulation (APC).

The first description of Nd:YAG laser use in CRP was published by Leuchter in 1982. The author reported the success of this technique for the

control of rectal hemorrhage after 4 applications in 1 patient in which he used 30 shots driven to the endoscopically identified vascular alterations⁵⁴.

The effectiveness of the Nd:YAG laser was confirmed by other authors in series with a total of 98 patients. One of the most important was published by Viggiono *et al.* in 1993 reporting on 47 patients. After an average of 2 sessions (7950 joules each), a 79% control rate of rectal bleeding was achieved⁵⁵.

In 1998, Swaroop *et al.* described the technique for therapy with a Nd:YAG laser⁵⁶. Initially, the patient should undergo a complete colonoscopy to determine the extent of the lesion. With an initial energy of 40 W and a maximum pulse duration of half a second, the laser is applied without direct contact to the mucosa, but with its tip less than 1 cm away from it. All visible lesions should be coagulated in the distal direction. A white clot should be obtained as a final effect, avoiding cavities in the intestinal mucosa. Complications of Nd:YAG laser therapy include tenesmus, abdominal pain, rectal stenosis, prostatitis, and recto-vaginal fistula^{55,57}.

Laser therapy for hemorrhagic CRP was supplanted by argon plasma coagulation (APC) because it is more readily available, cheaper, and requires fewer safety precautions, while still yielding excellent results. Argon plasma coagulation is a diathermy method in which there is no direct contact between the electrode and the patient, and high frequency energy is

applied to the tissue through the ionized argon. This technique is very suitable for coagulation of large bleeding surfaces and features the advantage of limited penetration (2 to 3 millimeters), minimizing the risks of perforation, stenosis, and fistulization. The char generated with APC promotes an interruption of the current passing through the tissue while Nd:laser continues to penetrate the tissue until it is switched off.

Since the first use of APC with a flexible endoscope described by Grund *et al.*⁵⁸ in 1994, it has gained a wide popularity. Silva *et al.* in a study of 28 patients obtained good results⁵⁹ and emphasized the possibility of application of the argon plasma in any direction, resulting in excellent access to vascular lesions. Gas flow eliminates oxygen from the coagulation area, avoiding carbonization of the tissue and smoke production. Moreover, light produced by gas ionization promotes good visual control of the procedure. Those authors also propose the use of 50 W of energy and a 1.5 L/min flow for the procedure. Fantin *et al.* demonstrated the effectiveness of APC in 7 patients after 2 to 4 applications, using as parameters an energy of 60 W and a flow of 3 L/min⁶⁰.

Other authors have also obtained good results with APC. Taylor *et al.* used APC in 14 patients with hemorrhagic CRP⁶¹. Bleeding episodes ceased in 10 patients (71%), although they needed complementary applications. The summarized series are reported in table 2⁶¹⁻⁶³.

Table 2 - Series and summarized results of patients with hemorrhagic radiation proctitis treated with argon plasma coagulation.

Author	Number of patients	Follow-up (months)	Complete Response	Partial Response
Buchi <i>et al.</i> ⁶² , 1987	3	7	66%	100%
Taylor <i>et al.</i> ⁶³ , 1993	14	35	50%	50%
O'Connor <i>et al.</i> ⁶⁴ , 1989	5	5	100%	-

Argon plasma coagulation has proven beneficial in almost all available studies. Use of argon plasma technology for other applications especially in surgery increases the usefulness of the equipment.

Endoscopic treatment through electrocoagulation is simple, widely available, and cheap. Bipolar electrocoagulation may be safer than monopolar. Electrocoagulation and heater probes are readily available at most hospitals without significant additional cost. Because of its ready availability, it is one of our first options for hemorrhagic CRP. Distal telangiectasias can be treated conveniently by this method. All visible lesions should be treated in a single session. The most important technical aspect of telangiectasias ablation is to use the smallest possible amount of energy for coagulation, avoiding formation of deep ulcers. After the initial session of coagulation, an interval should be intervene before reexamination, since coagulated areas need time for healing.

Hyperbaric Oxygen Therapy

Hyperbaric oxygen (HBO) has been used in the treatment of the RP after previous experiences with other radiation-induced lesions (cystitis and dermatitis) with satisfactory results.

Its mechanism of action is based on the decrease of tissue hypoxia with consequent acceleration of healing process, restoration of local anti-infectious defenses, and directly toxic effects to bacteria.

Four publications reported excellent results with the use of HBO in 8 patients with hemorrhagic RP⁶⁴⁻⁶⁷. However, 2 recent studies demonstrated more modest results. The first of these obtained a 56% rate of good results for 18 patients⁶⁸. The other was able to achieve 64% good results in 14 patients⁶⁹. These studies were retrospective with controversial results. There may be recurrences, and it may take a long period of treatment for symptoms to resolve. In addition to the lack of scientific support, HBO is an expensive technique that is still restricted to specialized centers.

CONCLUSIONS

Many alternative techniques and research with other possible therapeutic agents for the treatment of hemorrhagic CRP, the most frequent chronic complication of radiation injury to the rectum, are currently under investigation⁷¹⁻⁷³. The effectiveness of many therapeutic options has still not been shown with solid scientific evidence from controlled trials, and basic research may open a new perspective. Nowadays, the best alternatives for management of hemorrhagic CRP seem to be topical formalin and APC.

Despite all therapeutic strategies available for the management of CRP, the best one remains its prevention. Use of more advanced radiation techniques in the past few decades and introduction of less toxic regimens are good examples that may contribute to a decrease in incidence of CRP. However, the prevalence of CRP may increase as result of widespread use of radiotherapy for cancer treatment.

RESUMO

COTTI G e col. - Tratamento conservador da retite actínica hemorrágica: uma revisão. **Rev. Hosp. Clín. Fac. Med. S. Paulo** 58(5): 284-292, 2003.

A retite actínica crônica é uma condição cada vez mais frequentemente observada como resultado do crescente emprego da radioterapia no tratamento do câncer de órgãos pélvicos. A manifestação hemorrágica da retite actínica é a complicação mais comum dessa doença e seu tratamento é desafiador. Diversas técnicas foram empre-

gadas para o tratamento dessa condição e não há evidência satisfatória acerca da melhor forma de controlar os episódios de sangramento de forma eficaz e duradoura. A necessidade de se realizar múltiplas sessões de tratamento conservador bem como a associação de técnicas frequentemente observada no manejo desses pacientes dificulta a interpretação dos resultados. O objetivo dessa revisão foi avaliar a segurança e a eficácia das alternativas clínicas mais frequentemente empregadas no controle da retite actínica hemorrágica. Ainda que a falta de es-

tudos prospectivos e randomizados comparando duas ou mais alternativas terapêuticas impeça uma conclusão mais definitiva, concluímos que existe suficiente evidência acerca de elevada eficácia e segurança associadas ao emprego da formalina tópica e da coagulação por plasma de argônio no controle do sangramento em pacientes com retite actínica crônica.

DESCRITORES: Retite. Actínica. Hemorrágica. Tratamento. Conservador.

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