Efficacy and safety of single-session argon plasma coagulation in the management of chronic radiation proctitis

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Background: Chronic radiation proctitis (CRP) manifests as rectal bleeding 12 to 24 months after pelvic radiotherapy. No criterion standard of treatment has been established, although argon plasma coagulation (APC) has increasingly become the treatment of choice. Previous studies have applied APC over multiple sessions, necessitating increased numbers of treatments.

Objective: To assess the safety and efficacy of large-volume APC application in the treatment of CRP with the intention of a single-session treatment protocol.

Design: Prospective study.

Setting: Tertiary referral hospital.

Patients: Over an 8-year period, consecutive patients with CRP with rectal bleeding were prospectively enrolled.

Intervention: Large-volume APC application to affected rectal mucosa.

Main Outcome Measurements: Number of treatments, bleeding scores, complications.

Results: Fifty patients (mean age 72.1 years; range 51-87 years) were treated; 45 were men (prostate cancer). The mean period between radiotherapy and initial APC treatment was 23 months (range 4-140 months). Seventeen (34%) patients had grade A endoscopic severity, 23 (46%) grade B, and 10 (20%) grade C. Other therapies failed in 16 (32%) patients. The mean number of treatments was 1.36 (range 1-3) with a mean follow-up of 20.6 months (range 6-48 months). Sixty-eight percent of patients were successfully treated after 1 session and 96% after 2 sessions. Bleeding scores improved in all patients ($P < .001$). Seventeen (34%) patients experienced short-term, self-limiting complications; 1 (2%) patient experienced a long-term complication.

Limitations: Nonrandomized study.

Conclusions: Large-volume APC treatment was successful in the treatment of CRP, including those in whom other therapies had previously failed, and resulted in a decreased number of treatments compared with other published studies. The benefits were offset by an increased incidence of short-term complications but no increase in long-term complications. (Gastrointest Endosc 2010;72:150-4.)

Chronic radiation proctitis (CRP) occurs in 5% to 15% of patients after pelvic radiotherapy and typically manifests as rectal bleeding 12 to 24 months after pelvic radiation.[1] CRP can be a debilitating and chronic condition. In the case of prostate cancer radiotherapy, the rectal mucosa is susceptible to radiation damage because of the close proximity to the prostate. The likelihood of its development is dependent on the dose and method of radiotherapy delivery as well as patient factors including previous proctocolitis, history of smok-

Abbreviations: APC, argon plasma coagulation; CRP, chronic radiation proctitis.

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ing, diabetes mellitus, and medications. The exact pathophysiology of radiation proctitis is not fully understood; however, a combination of radiation-induced ischemia and fibrosis is the currently accepted hypothesis.[2] The endoscopic appearance is characterized by the presence of multiple telangiectasias in the distal rectal mucosa associated with a combination of mucosal pallor and friability; uncommonly strictures and ulcerations may also be seen.

Medical, endoscopic, and surgical approaches have been evaluated for the treatment of CRP, with varying success and complications. Argon plasma coagulation (APC), a nontouch thermoablative therapy, is increasingly recommended as first-line management. APC is traditionally not applied to the entire affected area in 1 treatment session, particularly if there is widespread involvement, because of the concern regarding the creation of strictures and other local complications. As such, previous publications reported multiple sessions to treat the total affected surface area. Generally, APC treatment of CRP results in success rates of 80% to 100%, with variable long-term complications rates of 0% to 18%.[3] We evaluated the long-term efficacy and safety of APC therapy for chronic hemorrhagic radiation proctitis to assess the feasibility and safety of a single treatment session.

Take-home Message

- Argon plasma coagulation (APC) can be applied to the affected area in a widespread manner with the intent of a single-session treatment with a resultant reduced number of treatments. This can result in short-term self-limiting complications without an increase in long-term complications. Pretreatment symptoms are a better guide to response to APC treatment for chronic radiation proctitis than endoscopic markers.

METHODS

Patients

The Southern Health Human Research Ethics Committee approved the study. All patients were referred for management of chronic bleeding secondary to chronic hemorrhagic radiation proctitis, were naïve to APC therapy, and were enrolled prospectively over an 8-year period between January 2001 and January 2009. Patients previously treated with modalities other than APC were included. All patients had a complete colonoscopy either before referral or at the time of first intervention to confirm the diagnosis of radiation proctitis and to exclude other pathology. Patients were included only if the characteristic endoscopic appearance of CRP was present without other potential colorectal bleeding sources. Biopsies were not routinely performed to confirm the diagnosis per current clinical recommendations.[3] All patients were treated on an outpatient basis, with written discharge instructions including recommendations for stool softeners or laxatives.

Full bowel preparation was used if a complete colonoscopy was required; otherwise, it was at the discretion of the endoscopist. Enema purgatives were avoided because of the potential for mucosal trauma to obscure the extent and degree of the proctitis. Colonoscopy was performed by using a single-channel Pentax adult colonoscope (EC-3831) or a Pentax single-channel gastroscope (EG-2931) (Pentax Medical Co, Montvale, NJ). APC was applied at an average power of 50 W by using an ERBE APC generator (Tübingen, Germany) with flow rates between 1.4 and 2.0 L/min.

The goal of treatment was to ablate all the visible telangiectasias during a single endoscopic procedure (Fig. 1). The total affected surface area was assessed and treated with both forward-viewing and retroflection in the rectum. If required, APC was applied to the level of the dentate line.

CRP was endoscopically graded by assessing the area and length of affected mucosa and the presence of active bleeding by using a previously described scale[4]: distribution of telangiectasia: less than 10 cm from the anal verge (1 point), more than 10 cm (2 points); surface area affected: less than 50% (1 point), more than 50% (2 points); presence of fresh bleeding: no (0 points), yes (1 point). The total score was calculated and patients categorized into 3 groups: grade A (mild), 2 points; grade B (moderate), 3 points; grade C (severe), 4/5 points.

Symptoms were assessed before and after APC therapy by using a modified bleeding scoring system: 0, no rectal bleeding; 1, minor, intermittent; 2, minor, daily; 3, moderate, daily; 4, heavy, daily.[5] Demographic data were collected including previous treatments for CRP bleeding. Hemoglobin levels were collected if available before the procedure and repeated at an interval not less than 3 months during follow-up to assess response to treatment. Information on the site of malignancy requiring radiation therapy, the time interval between radiation therapy and symptom onset, and radiation dose was obtained where possible. Follow-up was performed for at least 6 months after treatment by clinical or telephone interview.

Study endpoints

The primary endpoint was bleeding measured as a reduction in symptom score; secondary endpoints were the number of treatments required and symptoms after APC therapy. Treatment success was defined as a symptom score of 1 or less after treatment; treatment failure was defined as a clinical symptom score of 2 or more. Anemia was defined as serum hemoglobin less than 130 g/L. Proctitis was clinically defined as irritation or pain in the rectum or anus, fecal urgency, or passage of blood or mucus. Complications were divided into short term (<6 weeks,

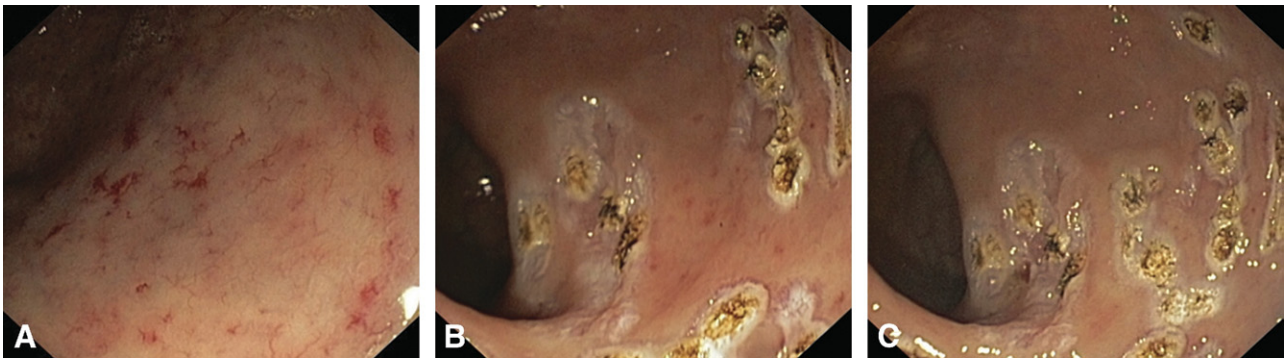

Figure 1. CRP appearance before, during, and after single-session APC.

self-limiting) and long term (persisting >6 weeks). Follow-up endoscopy was not routinely performed unless indicated by ongoing symptoms, patient preference, or other unrelated indications.

Statistical analysis

Mean and median values were calculated for continuous data. A paired *t* test was used to compare the means before and after treatment (SPSS for Windows version 15; SPSS Inc, Chicago, Ill). $P < .05$ was considered significant.

RESULTS

Over an 8-year period between January 2001 and January 2009, 50 consecutive patients (45 men, 5 women) were referred and treated endoscopically for CRP at a single center. The mean age was 72.1 years (range 51-87 years). Prostate cancer composed 90% of the initial malignancy requiring radiotherapy; the remaining 5 patients were all female with gynecological malignancy (2 uterine, 2 cervical, 1 vaginal). All patients underwent external beam radiotherapy; the mean duration between cessation of radiotherapy and treatment of radiation proctitis was 23 months (range 4-140 months).

Sixteen (32%) patients had been treated previously; formalin application (6 patients), 5-aminosalicylate enemas (6 patients), and prednisolone enemas (4 patients).

At enrollment, 17 (34%) patients had grade A endoscopic severity, 23 (46%) patients had grade B, and 10 (20%) patients had grade C. The mean symptom score at enrollment was 2.03 (standard deviation 0.93), indicating that the average patient experienced daily rectal bleeding. Hemoglobin levels before and after treatment were available in 27 (54%) patients. Anemia before treatment was present in 21 patients (78% with available hemoglobin determinations).

Sixty-eight treatment sessions were required in the 50 patients (mean 1.36 sessions; range 1-3 sessions) for symptom control. APC was successful in reducing clinical symptoms in all patients and achieved the primary endpoint of a posttreatment score of 1 or less in 49 (98%) patients.

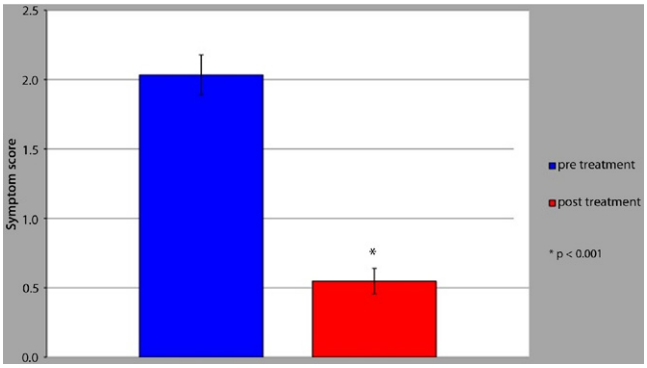

Figure 2. Mean symptom score before and after APC treatment.

Complete resolution of bleeding was achieved in 36 (72%) patients; 13 patients had minor intermittent bleeding after treatment that did not require further therapy; 1 patient continues to have minor daily (grade 2) bleeding compared with a baseline of grade 4 bleeding. The majority (68%) of patients achieved treatment success after only 1 treatment session, a further 14 (28%) patients required 2 sessions. Posttreatment symptom scores demonstrated a statistically significant improvement compared with pretreatment levels (Fig. 2). After APC treatment, 26 of 27 patients had improved hemoglobin levels compared with pretreatment levels, with a mean increase of 19 g/L.

All 16 patients in whom previous treatment for CRP failed responded to endoscopic APC therapy without a significant difference in symptoms, endoscopic grade, or number of treatment sessions compared with naïve CRP patients.

The endoscopic grade did not correlate with the severity of bleeding (Fig. 3) and did not predict the likelihood of success or posttreatment symptom score. Pretreatment symptom score was predictive of outcome; a higher score (3-4) was significantly associated with a higher posttreatment bleeding score ($P < .008$), and a there was a trend toward a higher mean number of treatment sessions (1.7 for a score of 3-4 compared with 1.25 for a score of 1-2) ($P = .06$).

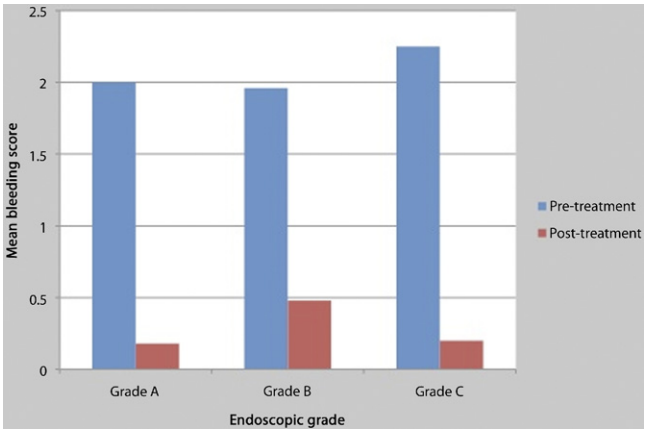

Figure 3. Comparison of CRP bleeding score and CRP endoscopic grade.

During a mean follow-up period of 20.6 months (range 6-48 months), 2 distinct types of complications were identified: (1) short-term complications presenting within hours to days after therapy and resolving within 2 to 6 weeks and (2) long-term complications persisting longer than 6 weeks. Seventeen (34%) patients had short-term symptoms (proctalgia in 13 patients, rectal mucous discharge in 4, incontinence in 1, fever in 1, and bleeding in 1). All of the aforementioned symptoms resolved spontaneously within 6 weeks. One (2%) patient had a long-term complication, an asymptomatic rectal stricture, diagnosed at a follow-up colonoscopy 3 years after treatment for an unrelated indication (screening colonoscopy for family history of bowel cancer) and did not require dilation. There were no deaths among the enrolled patients during follow-up. During follow-up, there was no observed deterioration of bleeding symptoms after the treatment course.

DISCUSSION

The findings of this single-center study demonstrate that APC treatment is highly effective in the treatment of patients with CRP including those in whom other therapy failed. All 50 patients with clinically apparent and debilitating rectal bleeding, with or without anemia, experienced improvement in bleeding symptoms that lasted during long-term follow-up.

One of the main aims of the study was to look at the efficacy and safety of large-volume APC application. In the current study, 68% of patients required only 1 session for bleeding resolution with no recurrence. The mean treatment/session number of 1.36 per patient is one of the lowest reported currently in the literature. Most previous studies[6-8] required at least 2 treatment sessions because of concern that treatment of all affected mucosa in 1 session would result in circumferential rectal mucosal damage with subsequent higher stricturing rates. In the current study, there was no increase in the long-term complication rate compared with other studies,[3] despite the extent of APC treatment.

The short-term complications of APC treatment have been previously reported only once, in a 2002 study by Villavicencio et al.[9] This similar, smaller series of 21 patients had an identical regimen of ablating all visible telangiectasias in a single session. Three (14%) patients experienced short-term side effects of bloating, proctalgia, and tenesmus, respectively, with resolution within 24 hours. There was a reported high long-term complication rate of 19% in this study. However, 2 of the 4 patients defined as having long-term complications resolved within the current study's time frame for short-term complications (<6 weeks). Therefore, using our definitions, the Villaviecencio et al study had a similar short-term self-limiting complication rate of 24% (compared with 34% in the current study). Despite the change in classification applied, the Villavicencio et al study had a higher long-term complication rate (9.5%) compared with other studies.[10] Combining these 2 studies to assess the complications of large-volume APC application, the rate of short-term reversible complications was 31%, with a long-term complication rate of 4%. Given the intention to treat all of the affected mucosa in 1 session as distinct from the majority of other studies, these short-term complications may be unique to this technique. Alternatively, these short-term complications may be the result of close monitoring of all symptoms of proctitis, not just recurrent bleeding. Although concerning at first glance, the rate and degree of short-term complications need to be considered along with the need, cost, and inconvenience of further endoscopies as well as the continued bleeding symptoms.

In the current study, the clinical course of CRP was better predicted by the bleeding score than the endoscopic grade. A higher bleeding score (3-4) before treatment was associated with a higher mean symptom score after treatment as well as a higher mean number of treatment sessions. The endoscopic grade of CRP did not correlate with bleeding score nor did it assist in the prediction of success of a single-session APC treatment. In contrast, 2 studies indicate that the endoscopic grade is predictive of APC treatment success. The original description of the endoscopic grade by Zinicola et al[4] suggested a predictive component, hence its incorporation into this study. However, that study has several limitations because only 14 patients were included and the design was retrospective. Importantly, the grading scale was based on the assumption that APC was less effective on extensive and confluent disease, which was not found in this study and which may explain why this scale was not predictive of outcome in our patients. The second study suggesting a correlation was a more recent series of 56 patients by Karamanolis et al.[11] The association was statistically significant, although a modified 2-grade scale was assessed rather than the 3 grades used in this study, and in the original study by Zinacola et al, it is possible that suggest-

ing fewer grades may be a better discriminator for treatment success. An added problem with the endoscopic grading score is the lack of data regarding interobserver variability, which may explain the differences observed. Further research is needed to assess the accuracy of the endoscopic grading scale for CRP; however, in our opinion, it remains a useful descriptive tool for CRP.

CRP is a common complication of pelvic radiation therapy, occurring in as many as 5% to 15% in long-term follow-up of prostate cancer patients. Localized prostate cancer is the most common indication for pelvic radiotherapy; therefore, middle aged and elderly men predominate in this condition. Women may present with CRP after radiotherapy for local control of gynecological cancers (cervical, ovarian); however, in most Western populations, they constitute a small minority.[6] Unlike our study, others have enrolled a higher proportion of female patients,[1,7,12,13] and therefore caution should be exercised in the interpretation and comparison of these studies because the technique and dose of radiotherapy differ significantly among different malignancies. Consequently, differences in demographics may contribute to the overall efficacy and complications of all treatments, including APC therapy, for radiation proctitis. In addition, modifications to the delivery of radiotherapy such as more accurate contouring and brachytherapy have dramatically reduced the incidence and severity of CRP after prostate cancer treatment.[14,15]

The efficacy of APC in the treatment of CRP exists mainly in multiple case series and has not been evaluated in the context of a randomized, controlled trial or compared directly with other treatment modalities. Our study is similarly limited, although the prospective nature does increase the relevance compared with other studies. Importantly, previous treatment modalities had failed in one third of the patients in this study, and all improved with APC. Newer modalities of treatment such as cryotherapy,[16] hyperbaric oxygen treatment,[17] and radiofrequency ablation[18] may offer novel treatment options for CRP, in which a randomized trial may allow direct comparison with APC treatment. At present, APC is considered by many to be the criterion standard treatment for CRP.

In conclusion, the use of large-volume, single-session application of APC for the treatment of CRP is highly effective without significant long-term consequences for the majority of patients, although a proportion may experience short-term self-limiting symptoms. Despite the short-term complications, we believe that large-volume APC should be considered as standard practice.

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