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ORIGINAL PAPERS

Is argon plasma coagulation an effective and safe treatment option for patients with chronic radiation proctitis after high doses of radiotherapy?

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ABSTRACT

Introduction: In severe cases refractory to medical treatment, APC appears to be the preferred alternative to control persistent rectal bleeding of patients with chronic radiation proctitis. Although successful outcomes have been demonstrated in patients previously treated with moderate doses of radiotherapy, there is reluctance towards its indication due to the concern of severe adverse events in patients treated with high doses of radiation.

Objectives: The aim of this study was to assess the efficacy and toxicity of APC in the management of bleeding radiation-induced proctitis in patients treated with high doses of radiation for prostate cancer.

Methods and materials: Data from 30 patients were treated with APC due to chronic radiation proctitis, were reviewed retrospectively. All cases had prostate cancer and 9 of them (30 %) underwent previous radical prostatectomy. The median dose of conformal 3D External Beam Radiotherapy (EBRT) delivered was 74 Gy (range 46-76). Median rectal D1cc and D2cc was 72.5 and 72.4 Gy respectively. Median rectal V70, V60 and V40 was 12, 39.5 and 80 %. Cardiovascular and digestive disease, diabetes, smoking behaviour, lowest haemoglobin and transfusion requirements were recorded. Indications for treatment with APC were anemia and persistent bleeding despite medical treatment. Argon gas flow was set at 1.8 l/min with an electrical power setting of 50 W.

Results: Median age of all patients was 69.6 years. The median lowest haemoglobin level was 9.6 g/dL. Median time between completion of radiotherapy and first session of APC was 13 months. Ninety-four therapeutic sessions were performed (median 3 sessions). Median time follow-up was 14.5 months (range 2-61). Complete response with resolved rectal bleeding was achieved in 23 patients (77 %), partial response in 5 (16 %) and no control in 2 (6 %). No patients required transfusion following therapy. Two patients developed long-term (> 6 weeks) grade 2 rectal ulceration and grade 2 rectal incontinence, respectively.

Conclusions: The argon plasma coagulation is an effective and safe management option in patients with medically refractory rectal bleeding after high doses of radiation for prostate cancer.

Key words: Argon plasma coagulation. Radiation proctitis. Prostate cancer. External beam radiation therapy.

INTRODUCTION

Chronic radiation proctopathy (CRP) is a complication occurring in 5 %-20 % of patients following pelvic radiotherapy with curative intent for carcinoma of the prostate, rectum, urinary bladder, cervix and uterus. The most frequent form of clinical presentation of chronic radiation proctitis is rectal bleeding and typically manifests about 12 to 24 months after pelvic irradiation (1-3).

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.

CRP resolves spontaneously in many cases, but sometimes can lead to persistent rectal bleeding and iron deficiency anaemia requiring blood transfusion (1). Current treatment of late rectal bleeding includes steroid enemas, topical sucralfate, 5-ASA enemas, short chain fatty acids and antioxidants such as vitamin E and pentoxifylline. These have been used with limited success and healing can be a very prolonged process. When medical therapies fail,

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invasive treatments could be used such as topic formalin, the heater probe, bipolar electrocoagulation, neodymium: Yttrium-aluminium-garnet (Nd:YAG) laser and potassium titanyl phosphate (KTP) laser.

Other options are hyperbaric oxygen therapy (HBO) and newer endoscopic techniques such as cryotherapy and radiofrequency. Surgery is reserved for severe cases grade 4 or refractory to previous treatments although high rates of morbidity and mortality have been reported (4).

In the last few years, argon plasma coagulation (APC) has been reported to be a useful treatment for CRP in limited series of patients, and some authors consider it the standard treatment for patients with CRP refractory to medical therapies because of its advantages based on coagulation depth control, easy use, and low cost (5). However, there is still reluctance towards its indication due to the concern of severe adverse events (such as rectal ulcers and recto-urethral fistulas) in patients treated with high doses of radiation.

The aim of the present study is to report the efficacy and safety of APC for late rectal bleeding in a group of patients treated with high doses of radiotherapy for prostate cancer with curative intent.

METHODS AND MATERIALS

From 2005 to 2012, thirty men with prostate cancer treated with pelvic radiotherapy experienced chronic radiation proctitis that was refractory to conservative approaches. Patient characteristics are detailed in table I. The retrospective review of medical records was approved by the local ethics committee.

The main indications for endoscopic treatment were persistent rectal bleeding and recurrent anaemia despite several treatment attempts with various topical agents including 5-aminosalicylic acid, corticosteroids, and sucralfate enemas.

All cases had previous diagnoses of prostate cancer and 9 of them (30 %) had undergone previous radical prostatectomy. The median dose of 3D Conformal External Beam Radiation Therapy (EBRT) delivered was 74 Gy (range 46-76). Median rectal D1 cc and D2 cc (maximum dose received by 1 cc and 2 cc of rectum) was 72.5 Gy and 72.4 Gy respectively. Median rectal V70, V60 and V40 was 12 %, 39.5 % and 80 %, where Vn is the fractional volume of the organ that receives ≥ n Gy. One patient underwent combined treatment of EBRT and brachytherapy.

Table I. Baseline features of patients

	n	*Percentage (%)*
Cancer site: Prostate	30	100
Risk factors		
Smoking	10	33
Diabetes	22	73.3
Gastrointestinal disease	11	36.6
Anticoagulant therapy	9	30
Bloody transfusion dependence	11	36.6
Cardiovascular disease	15	50

Patients received treatment with APC after standard bowel preparation and sedation with midazolam and propofol if required. In few patients preparation with enemas was carried out. An ERBE APC 300 (ERBE Elektromedizin, Tübingen, Germany) argon delivery unit and a 2.3 mm diameter front-firing APC probe, inserted through the working channel of the flexible sigmoidoscope, were used for APC application. The argon gas flow rate and the electrical power were set at 1.8 L/min and 50 W, respectively. During the procedure, adequate endoscopic aspiration was performed to avoid patient discomfort because of argon gas introduction. Repeat procedures were usually carried out at intervals of 3-4 weeks until bleeding remission. Anticoagulants and 5-aminosalicylic acid were discontinued 1 week and 3 days before treatment, respectively.

Study endpoints

The primary endpoint was bleeding control. Complete response was defined either as cessation of bleeding or only occasional traces of blood in the stools, and no recurrence of anaemia. Partial response was defined as only a slight improvement in bleeding intensity and frequency, but no further blood transfusions required after APC was initiated.

Proctitis was clinically defined as irritation or pain in the rectum or anus, fecal urgency, or passage of blood or mucus. The diagnosis was based on the typical endoscopic appearance of rectal telangiectasia, friability and contact bleeding in a patient who had prior radiotherapy and where other causes of rectal bleeding were excluded at colonoscopy. The clinical severity of radiation proctitis and rectal bleeding was measured according to CTCAE version 3.0 scale (7). All patients were considered to have severe endoscopic proctitis or grade 3 clinical proctitis and rectal bleeding, which means that they had severe symptoms, needed transfusion and endoscopic intervention was indicated.

The endoscopic severity of radiation proctitis was measured using the scale of Zinicola et al. (6). Two factors were evaluated, telangiectasia distribution (telangiectasias involving the distal rectum -10 cm from the anal verge, or the entire rectum with/without sigmoid) and surface area involved (less than 50 %, or more than 50 %). All 30 were offered APC.

Complications were divided into short term (< 6 weeks 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.

The follow-up evaluations consisted of a history and physical examination. Blood tests and PSA were obtained every 3 months for the first year after treatment, every 6 months for 2 years, and annually thereafter during follow-up. Imaging and additional studies were obtained at the discretion of the treating physician.

RESULTS

Median age was 70 years (range, 56-78 years) and the median interval between completion of radiotherapy and development of the soft tissue ulceration was 13 months (range 4-41 months).

Morbidities affecting refractory bleeding included smoking (10/30), diabetes (22/30), cardiovascular disease (15/30), anticoagulant therapy (9/30) and gastrointestinal disease (11/30). All patients had grade 3 radiation proctitis and 11 of them were repeated blood transfusions-dependents. The median lowest haemoglobin level was 9.6 g/dL (range 5.1-14.1) before APC and the median improvement in haemoglobin level after treatment was 2.05 g/dL (range 0.5-5.1). Ninety-four therapeutic sessions were performed to stop rectal bleeding (median 3 sessions). Patients were regularly followed after completion of APC and cautioned to avoid intensive exercise and to follow a high fibre diet plan.

Median time follow-up since last APC session was 14.5 months (range 2-61). Complete response with resolved rectal bleeding was achieved in 23 patients (77 %), partial response in 5 (16.6 %) and no control in 2 (6 %). None of 30 patients required blood transfusion following therapy.

APC was well tolerated and no short-term (< 6 weeks) side effects were described. However, 2 patients developed long-term (> 6 weeks) rectal ulceration and rectal incontinence grade 2 respectively.

DISCUSSION

Our study shows encouraging results with APC in the management of rectal bleeding related to CRP after pelvic irradiation in cases refractory to conventional medical treatments, with responses in up to 93 % of the patients.

When late radiation injury occurs, tissues undergo a progressive deterioration characterized by endothelial dysfunction, reduced vascularity, intimal damage and fibrin thrombus of small arteries and arterioles leading to ischemia, fibrosis and the development of neovascular lesions (2,3).

Factors related to the radiotherapy technique have been associated to the frequency and severity of CRP, being the dose of radiation and area of exposure the most important factors. It is generally agreed that doses < 45 Gy cause very few side effects, doses between 45 and 70 Gy, cause more complications, but complications tend to be of lesser intensity. And doses above 70 Gy cause significant and long standing injury to the surrounding area (11). In our series, 87.7 % of patients received radiation doses higher than 70 Gy.

Most of the previous studies either, do not report the radiation doses administered or these doses were in the moderate dose range (< 70 Gy) (8,9). To the best of our knowledge the present study is the first reporting efficacy and safety results of APC in patients treated with high doses of radiotherapy.

To date, the basis of evidence for the therapy of CRP is generally scarce. Medical measures appear as the first treatment choice in mild cases. Sucralfate enemas seem to be the best available "medical" therapy and are safe and well tolerated.

Steroid enemas and derivatives of 5-ASA have shown subjective improvement of symptoms. Short chain fatty acids and antioxidants such as vitamin E and pentoxifylline have been used with limited success (10). Patients with refractory CRP to previous treatments and grade 2-3 chronic radiation proctitis may benefit of endoscopic treatments. Formalin therapy is effective in up to 48 % of patients with CRP, however, high rates of complications have been reported including rectal pain, incontinence, diarrhoea, formalin-induced colitis, anal and rectal strictures, rectal ulcerations, and rectal perforation (11). Other endoscopic modalities such as bipolar electrocoagulation, KTP and Nd:YAG laser have shown certain efficacy but also significant adverse effects (10).

Another described therapeutic modality is HBO which is reported to be a safe and effective treatment for problematic wound healing and soft tissue necrosis of other aetiology (12). The response to HBO-mediated tissue hyperoxygenation is stimulation of angiogenesis and reduction of tissue oedema. These changes lead to normalized tissue metabolism and tissue regeneration. Alvaro Villegas et al. (9) in a prospective study of 31 patients comparing HBO and APC reported similar rates of bleeding control but faster clinical response with APC. Historically, HBO has been an uncommon therapeutic consideration. The reasons for this have purportedly been cost and, for cancer patients, concern for possible worsening of coexisting malignancy. Furthermore, HBO is only available in specialized centres.

Although successful results have been obtained for CPR with newer endoscopic techniques such as cryotherapy and radiofrequency, both approaches are still considered experimental (10).

The theoretical advantages of APC include its ease of application, speedy treatment of multiple lesions in the case of angiodysplasias or wide areas, safety due to reduced depth of penetration (0.5-3 mm), and lower cost compared to laser. Another known benefit of APC is that the probe can be applied axially and radially, allowing tangential coagulation of lesions around rectal bends.

Most studies on the use of APC in the management of CRP have demonstrated some benefit. Nevertheless the number of patients included in those studies is limited (Table II).

We report encouraging results with APC in the management of rectal bleeding related to CRP after pelvic irradiation in cases refractory to conventional medical treatments, with responses in up to 93 % of the patients. These results are consistent with data published in literature and suggest that APC is highly effective in control of late rectal bleeding unresponsive to medical therapies, achieving complete response in 80-100 % of cases (5,8,11,13-19).

The median improvement in haemoglobin level after treatment was 2.05 g/dL (range 0.5-5.1), previous reports support this circumstance (5,11,13,14,19-22).

Overall APC has a good safety profile although the data recorded are highly variable. The most common complication is the anal or rectal pain with or without urgency, and more likely after treatment near the dentate line (13,21), but often it resolves spontaneously in a few days.

Table II. Results of the 30 patients of our study

n	*Age (years)*	*EBRT dose (Gy)*	*Hb level (g/dL) before APC*	*Follow-up since last APC session (mo)*	*Interval EBRT and APC (mo)*	*Number APC sessions/ patient*	*Improvement Hb levels (g/dL)*	*Response to APC (%)*	*Late toxicity (> 6 weeks) after APC*
1	75	76	13.8	7	10	1	0.5	Partial > 50 %	
2	70	74	12.7	15	17	3	0.6	100	
3	63	70	8	39	13	6	5.1	100	
4	68	74	7.7	2	11	2	1	100	
5	66	74	8.9	18	21	3	2.8	100	Ulceration grade 2
6	71	66	9.5	2	9	1	1.2	Partial > 50 %	
7	73	76	13.4	3	18	2	1.2	100	
8	69	74	12.5	37	8	5	2.6	100	
9	75	66	7.1	58	9	9	2	100	
10	78	76	12.3	3	17	3	2.2	No control	
11	76	74	9.6	25	6	3	1.3	100	
12	63	68	15.4	23	13	1	2.9	100	
13	68	70	11.8	3	12	1	1.7	Partial > 50 %	
14	72	74	5.1	34	15	6	1.2	100	Incontinence grade 2
15	58	74	12.8	5	20	4	2.1	100	
16	70	72	8.8	10	41	2	2.9	100	
17	74	74	6.4	4	28	1	1.3	100	
18	70	46*	6.6	14	7	6	3.9	No control	
19	56	74	9.6	47	14	5	3	100	
20	68	76	8.6	6	19	2	1.9	100	
21	74	72	7.3	30	27	3	1.4	100	
22	72	74	13.4	6	11	3	3.4	100	
23	67	74	13.5	23	15	1	1.4	100	
24	74	72	13.7	4	13	1	2.7	Partial < 50 %	
25	66	70	9.1	2	18	5	1.3	Partial > 50 %	
26	67	72	12.6	61	10	1	2.1	100	
27	58	76	6.8	23	8	4	1.7	100	
28	70	68	14.1	9	12	4	2.9	100	
29	60	70	11.1	15	4	1	4.3	100	
30	74	72	6.8	20	15	5	2.2	100	

*Patient treated with combination of high dose rate brachytherapy (15 Gy) and 46 Gy of EBRT.

Like any coagulation method, severe complications can occur, particularly rectal perforation. Additional reported complications are asymptomatic and symptomatic pneumoperitoneum and subcutaneous bubbling of gas. It is likely that these problems are caused by either over-distension within the cecum or unintentional direct contact of the probe to the thin bowel wall during pulses resulting in deeper monopolar cautery.

Although the severity of toxicity after APC is usually mild, Canard et al. (15) in a study of 30 patients observed an overall morbidity of 47 % including 3 severe cases (bleeding, necrosis and perforation). Karamanolis (18) described one case of colon explosion without perforation and Rotondano (23) recorded a recto-vaginal fistula.

Reports in literature support these outcomes. In fact, Tjandra (22), Sebastian (5), Karamanolis (18) and Venkatesh (8) recorded complications in 0 %, 4 %, 5.3 % and 7.5 % of patients respectively.

After a median follow-up of 14.5 months (range 2-61), only 2 patients (6 %) developed APC related toxicity in our study.

The toxicity observed in our 2 patients was grade 2 (rectal ulceration and incontinence), it was successfully treated with conservative methods, and both experienced symptoms improvement. The healing of the rectal ulcer was complete after 6 months, and now is 18 months since the procedure without any symptoms, and the patient with rectal incontinence persisted with a grade 1 toxicity following 34 months.

Moreover, a power setting higher than 45 W (15) has been reported to be a risk factor of post APC complications. In our study, a setting of 50 W has not demonstrated higher rates of toxicities compared to previous reports.

We acknowledge several limitations of our study. First, the study is a retrospective single-centre experience of a small group of prostate patients who had been treated with APC, rather than being treated prospectively on a well-defined treatment protocol. Second, factors such as high radiation doses and the percentage of rectum irradiated may have influenced the onset of chronic GI toxicity.

At the University Hospital of Cruces about 180 patients are treated annually with radiotherapy for prostate cancer. Half of them, receive high doses of radiation (external beam radiotherapy alone or in combination with brachytherapy). Since severe radiation proctitis rates occurs in 5-10 % of the cases, the number of patients in the present study (30 patients) treated with argon plasma coagulation is the expected number over a period of 7 years. The sample size of 30 patients in our study is meaningful according to the previous reported articles on APC used in CRP. Moreover our results are comparable with the literature either in efficacy and toxicity.

Although the follow-up is relatively short, clinical outcomes of APC for CPR are excellent, with high rates con bleeding control. Acute and late APC related events are rare without severe late side effects.

Multicenter trials in larger cohorts of patients and randomized trials comparing APC with other treatment modalities are required to confirm it as the "gold standard" therapy for late rectal bleeding related to CRP refractory to medical treatment. However, currently available data would suggest that the treatment of APC for CRP in patients treated with high doses of radiotherapy for prostate cancer is effective, feasible and safe.

CONCLUSION

Men with late rectal bleeding associated with chronic radiation proctopathy treated with argon plasma coagulation have experienced excellent bleeding control rates with acceptably low toxicity. The argon plasma coagulation has proven to be a very effective management option in patients with medically refractory rectal bleeding after high doses of radiation for prostate cancer.

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