Diseases of the Colon & Rectum

Original Contributions

A Prospective, Randomized, Double-Blind, Placebo-Controlled Trial of Retinol Palmitate (Vitamin A) for Symptomatic Chronic Radiation Proctopathy

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PURPOSE: This study was designed to determine whether oral retinol palmitate (vitamin A) can reduce the symptoms of radiation proctopathy. METHODS: A randomized, double-blind trial comparing retinol palmitate (10,000 IU by mouth for 90 days) to placebo was conducted. Eligible patients were more than six months postpelvic radiotherapy and had significant symptoms as measured with the Radiation Proctopathy System Assessments Scale. Nineteen patients were randomized in total: ten to retinol palmitate and nine to placebo. The Radiation Proctopathy System Assessments Scale scores before and every 30 days for 90 days were measured. Five placebo nonresponders were crossed over to the retinol palmitate for another 90 days. Response was defined as a reduction in two or more symptoms by at least two Radiation Proctopathy System Assessments Scale points. RESULTS: Seven of ten retinol palmitate patients responded, whereas two of nine responded to placebo (P = 0.057). Mean pre-post-treatment change in Radiation Proctopathy System Assessments Scale (Δ Radiation Proctopathy System Assessments Scale) in the retinol palmitate group was 11 ± 5, whereas Δ Radiation Proctopathy System Assessments Scale in the placebo group was 2.5 ± 3.6 (P = 0.013, Mann-Whitney U test). Additionally, all five placebo nonresponders who were crossed over to treatment with retinal palmitate responded to treatment. CONCLUSIONS: In our trial, retinol palmitate significantly reduced rectal symptoms of radiation proctopathy, perhaps because of wound-healing effects. The current results can serve as the foundation for future trials examining retinol palmitate in the multi-institutional setting. [Key words: Radiation proctopathy; Retinol palmitate; Vitamin A; Randomized, controlled trial]

Chronic radiation proctopathy is a clinical condition that develops at least six months after completion of pelvic radiation therapy.[1] The rectum is a common site of injury during and after pelvic irradiation because of its close proximity to other pelvic organs. Two distinct types of symptoms, each with unique pathophysiologic mechanisms, occur in patients with chronic radiation proctopathy. Bleeding, the most common of these, develops from mucosal neovascularization, a consequence of persistent endarteritis and tissue ischemia.[2] Rupture of thin-walled telangiectasias from mechanical disruption is the cause of rectal bleeding under these circumstances. Functional symptoms, including rectal urgency, pain, disordered evacuation, and fecal incontinence develop secondary to loss of compliance of the rectal wall, presumably caused by ischemic injury, fibrosis, and diminished motor function.[3] Treatment of rectal

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Table 1.
Characteristics of Study Subjects

Patient	Age	Gender	Primary Tumor	Radiation Type	Time Post-RT
Placebo group					
1	66	M	Prostate	EBRT + BT	1 year
2	72	M	Prostate	EBRT	8 months
3	68	M	Prostate	EBRT + BT	1.5 years
4	82	M	Rectal	EBRT	19 years
5	71	M	Rectal	EBRT	1 year
6	72	M	Prostate	EBRT	7 years
7	75	M	Prostate	EBRT	1.5 years
8	80	M	Prostate	EBRT	9 years
Retinol palmitate group					
1	87	M	Prostate	EBRT	3 years
2	50	M	Anal	EBRT	6 years
3	70	F	Uterine	EBRT + BT	4 years
4	77	F	Uterine	EBRT	10 years
5	60	M	Prostate	EBRT	2 years
6	60	M	Prostate	EBRT	1 year
7	64	M	Prostate	EBRT	1 year
8	81	M	Prostate	EBRT	5 years
9	70	M	Prostate	EBRT	1.25 years

RT = radiotherapy; EBRT = external beam radiotherapy; BT = brachytherapy M = male; F = female.

bleeding, especially when severe, is best accomplished by obliterating telangiectasias using cautery techniques such as the Argon plasma coagulator[4] or direct application of topical formalin solution[5] Symptom-based therapies including bulking agents and antidiarrheals are the only currently recommended treatments for symptomatic relief of the functional symptoms of chronic radiation proctopathy. To date, few, randomized, controlled trials have been performed to investigate therapies for chronic radiation proctopathy despite the apparent increase in prevalence of this condition.[6]

Retinol palmitate has been demonstrated to accelerate wound healing after burn injury and surgeries in laboratory animals.[7] The mechanism of this effect is not been fully elucidated, but increased cross-linking of collagen and myofibrils[8] have been demonstrated to occur after retinol palmitate administration. Our group recently described a dramatic case of a patient with AIDS and anal carcinoma who developed a large radiation-induced anal ulceration.[9] This patient was greatly disabled and required high-dose opioid therapy for control of anal pain. After a 12-week course of orally administered retinol palmitate, the patient experienced complete wound healing and symptomatic relief that persisted for more than six months.

We performed the following study to investigate the use of retinol palmitate for the treatment of chronic radiation proctopathy, with particular emphasis on improvement of the aforementioned functional symptoms.

PATIENTS AND METHODS

All patients were recruited from the primary care, gastroenterology, and radiation oncology clinics at the University of Chicago. For inclusion in the study, patients were required to have completed external beam radiation or seed implantation for a pelvic malignancy, including cancer of the prostate, cervix, or uterus at least six months before enrollment. Patient characteristics are described in Table 1. Patients were seen in the gastroenterology clinic and underwent a general physical examination and laboratory testing by a single physician (EDE).

Before randomization, a questionnaire of the six most common symptoms of chronic radiation proctopathy using a Likert system for the grading of severity and frequency was performed. These symptoms were diarrhea, rectal urgency, rectal pain, tenesmus, rectal bleeding, and fecal incontinence. Scores for severity and frequency ranged from one to five. Our group developed this scale, termed the Radiation Proctopathy System Assessments Scale (RPSAS). Symptom evaluation using a similar Likert grading system, termed the Nepean Dyspepsia Index, has been previously validated in patients with functional dyspepsia by Talley *et al.*[10] The components of the

RPSAS

Severity

1) No problem
2) Mild problem-can be ignored when you don't think about it
3) Moderate problem-cannot be ignored; no effect on daily activities
4) Severe problem-influences your concentration on daily activities
5) Very severe problem- markedly influences your daily activities and/or requires rest

Frequency

1) Monthly
2) Weekly
3) Several times per week
4) Daily
5) Throughout the day

	Severity	Frequency
Diarrhea		
Urgency		
Rectal pain		
Tenesmus		
Rectal bleeding		
Fecal incontinence		

Figure 1. Radiation Proctopathy Symptom Assessment Scale (RPSAS).

RPSAS are shown in Figure 1. It should be noted that the RPSAS score for a completely asymptomatic patient was 6. To meet enrollment criteria for the study, patients were required to have at least two symptoms with a severity score of 3 (moderate problem-cannot be ignored; no effect on daily activities) on at least a weekly basis.

Because the primary focus of the study was directed at the relief of functional symptoms of chronic radiation proctopathy, not rectal bleeding, patients were excluded from the study for hemoglobin level at the time of enrollment < 10 gm/dl or if they had received two or more units of packed red blood cells as treatment for anemia secondary to rectal bleeding. In addition, patients also were excluded if they had rectal ulcerations, strictures, or fistulization. Patients also were excluded from the study if they had clinically significant liver disease or were deemed unable to understand or unable to sign consent for research study.

Retinol palmitate 10,000 IU (Nature's Bounty Inc., Bohemia, NY) and identical placebo capsules were

placed in containers of 100 capsules each by the Investigational Pharmacy at the University of Chicago. The pharmacy developed a random number system for treatment assignment. Neither the investigators nor patients were aware who was receiving retinol palmitate or placebo. After meeting enrollment criteria, patients signed the consent form and investigators initiated a call to the pharmacy and collected the treatment bottles, which were then given to the patient. Patients who ingested at least one dose of medication were included in the intent-to-treat analysis.

The initial RPSAS scores on enrollment were considered the baseline scores for patients. Patients were then contacted by telephone every 30 days by the same investigator for a total of 90 days. RPSAS score was obtained during each follow-up evaluation. Response to treatment was defined as a reduction of at least two symptoms by at least two points on the RPSAS. These response criteria were established before initiation of the study. Secondary end points of the study included a comparison of total RPSAS score before and after treatment in the retinol palmitate and placebo groups. Final scores for patients dropping out of the study before the first 30 days were the initial score. Final scores for patients dropping out of the study between 30 and 90 days were the last collected score. After 90 days, investigators and patients were unblinded to the treatment that the patient had received.

The study was concluded in patients who responded to placebo or did not respond to retinol palmitate. Patients who received placebo and had not responded were offered treatment with retinol palmitate on its open-label basis. These subjects were given 200 capsules of retinol palmitate and were contacted every 30 days to complete the RPSAS for a total of 90 additional days. The study was approved by the University of Chicago institutional review board.

Statistical Analysis

Cross-table analysis comparing responders and nonresponders in the retinol palmitate and placebo groups was performed using Fisher's exact test. Change in RPSAS scores before and after treatment (Δ RPSAS) in patients receiving retinol palmitate *vs.* placebo were compared using the Mann-Whitney *U* test. Wilcoxon matched-pairs, signed-rank test was used to compare the pretreatment and posttreatment RPSAS scores in the subset of patients crossed over from placebo to retinol palmitate after their initial placebo course.

RESULTS

A total of 19 patients originally agreed to participate in the study. Ten of these were randomized to retinol palmitate and nine to placebo. One patient from each group enrolled in the study but did not take a single dose of medication and was therefore excluded from analysis. Clinical characteristics of patients included in the study are shown in Table 1. Patient 4 in the retinol palmitate group took approximately five doses of the medication and then dropped out of the study. This patient was included in the final data analysis.

Baseline RPSAS for the retinol palmitate and placebo groups were not statistically different. Based on the criteria established for therapeutic response, seven patients treated with retinol palmitate responded to therapy and two patients did not.

Two patients treated with placebo responded to treatment, and six patients were nonresponders. This difference demonstrated a trend toward statistical significance ($P = 0.057$, Fisher's exact test). Mean pre-post-treatment change in RPSAS (Δ RPSAS) in the retinol palmitate group was 11 ± 5, whereas Δ RPSAS in the placebo group was 2.5 ± 3.6 ($P = 0.013$, Mann-Whitney *U* test). Figure 2A and 2B demonstrate total RPSAS scores for study patients in the retinol palmitate and placebo groups before and after treatment. Of the six patients who did not respond to placebo, five were enrolled in the open-label retinol palmitate treatment arm. All five of these met criteria for response to therapy. Thus for the entire study, a total of 12 patients responded to retinol palmitate, whereas only 2 responded to placebo.

Figure 3 shows the median RPSAS before and after 90 days in the five placebo nonresponders that were crossed over to receive retinol palmitate. Median RPSAS in this group was 25 at baseline and 17 after 90 days of retinol palmitate treatment ($P < 0.05$).

DISCUSSION

Chronic radiation proctopathy is a common and important clinical problem. Estimates suggest that from 5 to 36 percent of patients receiving pelvic radiation therapy eventually develop symptoms of chronic radiation proctopathy.[6,11] Recommended therapies for chronic radiation proctopathy have included anti-inflammatory agents (5-aminosalicylic acid, corticosteroids), sucralfate, antioxidants (vitamins C and E), sodium pentosan polysulfate, and short-chain, fatty-acid enemas. At present, little clini-

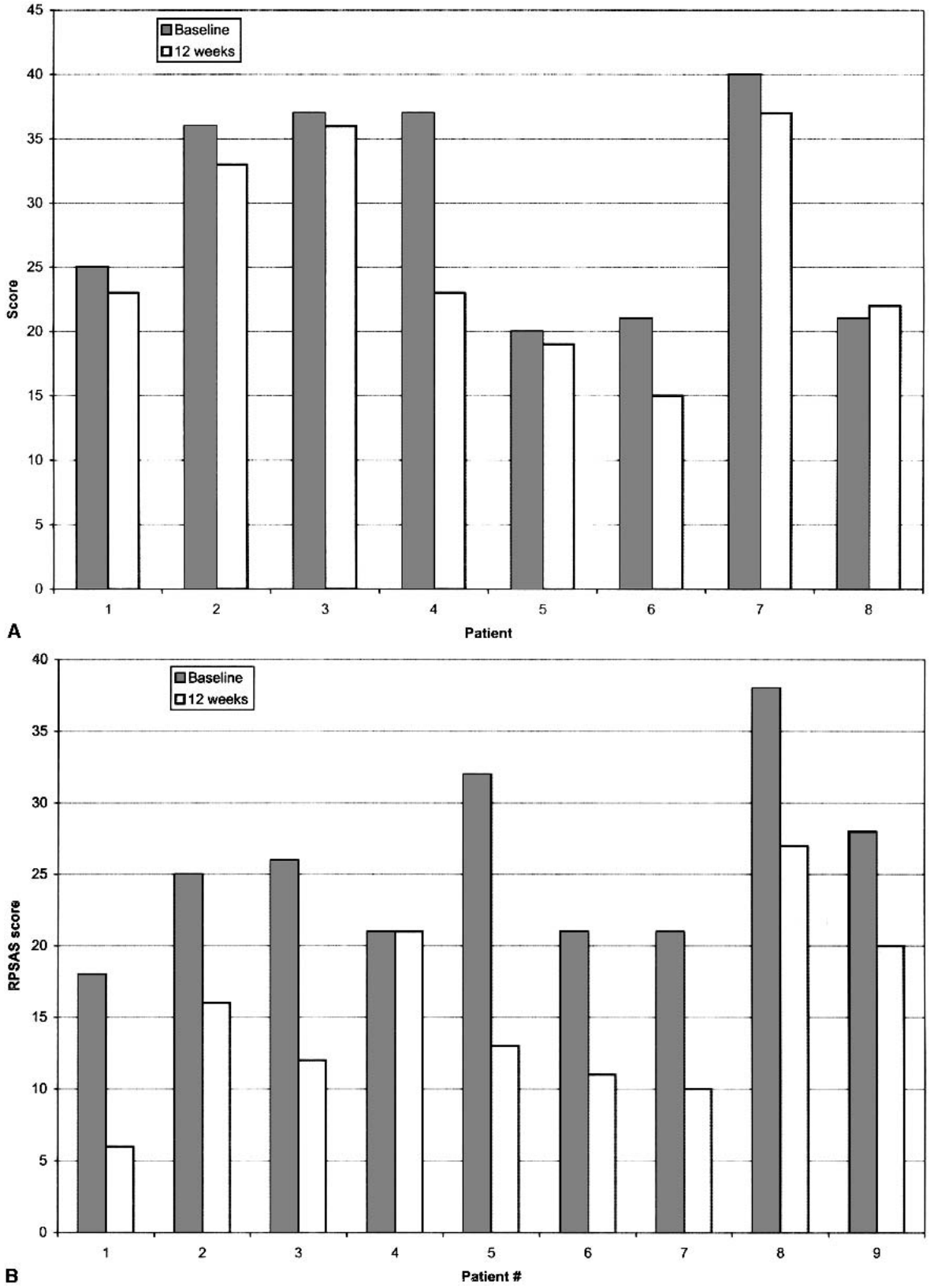

Figure 2. A. RPSAS scores for individual patients in the placebo group before and after 12 weeks of treatment. Median RPSAS was 30.5 before and 23 after treatment. B. RPSAS scores for individual patients in the retinol palmitate group before and after 12 weeks of treatment. Median RPSAS was 25 before and 13 after treatment. RPSAS = Radiation Proctopathy Symptom Assessment Scale.

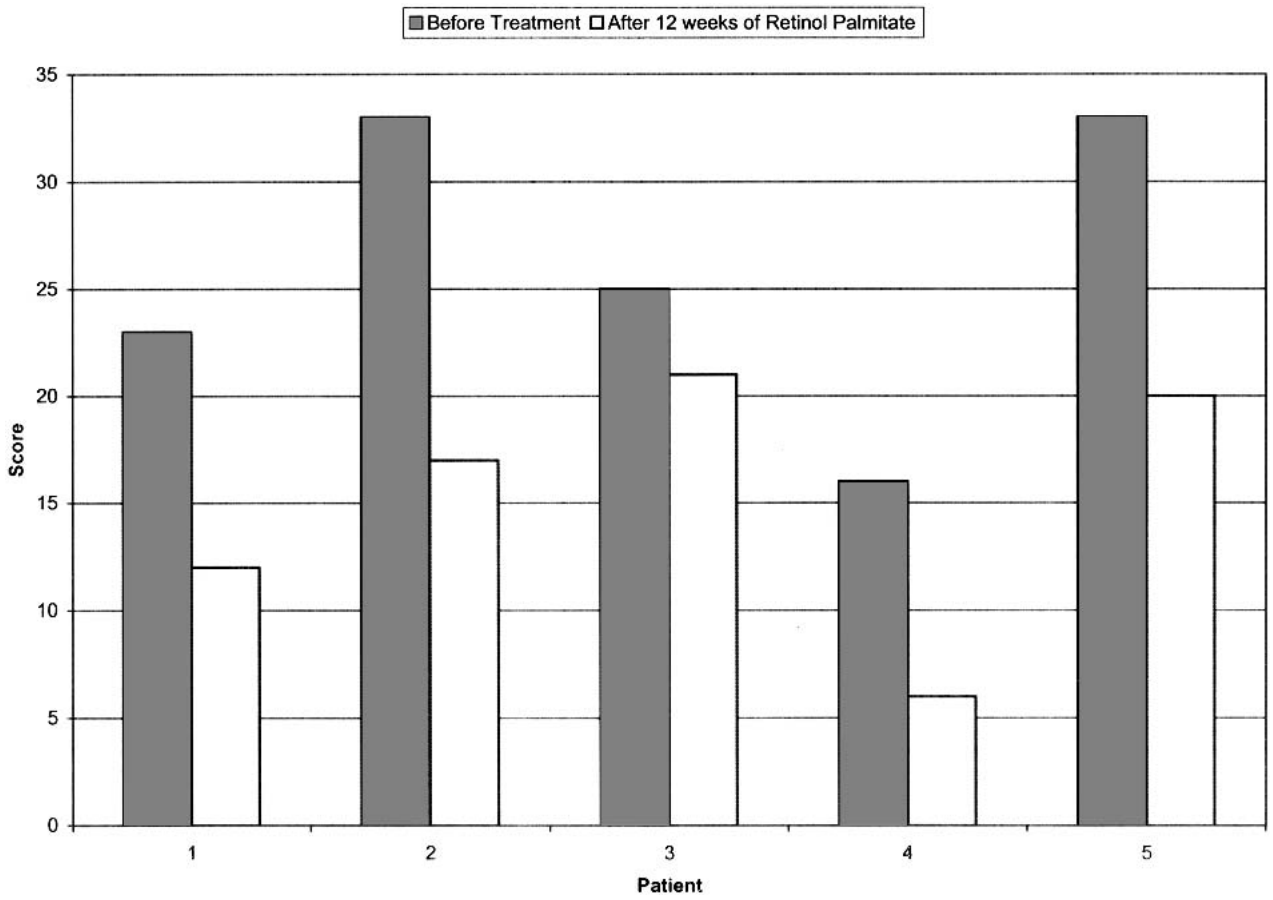

Figure 3. RPSAS scores before and after 12 weeks of treatment with retinol palmitate in placebo nonresponders who were crossed over to active treatment. Median RPSAS scores (25 before, 17 after) were statistically different ($P < 0.05$, Wilcoxon matched-pairs, signed-rank test). RPSAS = Radiation Proctopathy Symptom Assessment Scale.

cal evidence supports the use of these therapies. The vast majority of currently available information on therapies for chronic radiation proctopathy is based on case reports and a few open-label trials.[6] Placebo-controlled trials of treatment of chronic radiation proctopathy have only been performed for the evaluation of short-chain, fatty-acid enema therapy.[12] Short-chain, fatty-acid enema therapy seems to reduce the severity of rectal bleeding in chronic and acute settings.[13]

Retinol palmitate, a form of vitamin A, seems promising as a treatment for chronic radiation proctopathy, in part because of potential benefits in wound healing.[14] Vitamin A has been demonstrated to enhance the repair of skin wounds that had been inhibited by corticosteroid administration.[15] Additional work has shown that vitamin A stimulates the secretion of mucopolysaccharides, collagen, and fibronectin by fibroblasts.[8] These substances have been demonstrated to enhance the wound-healing process. Vitamin A also has been administered in animal studies before and during intra-abdominal radiation treatments and has been shown to limit the severity of radiation-induced inflammation, ulceration, and fibrosis of the gastrointestinal tract.[16,17] On the other hand, retinol palmitate does not seem to have potent antioxidant properties as occurs with beta carotene administration. Based on an open-label trial, antioxidants have been suggested as potential treatments for chronic radiation proctopathy.[18]

Our group recently reported a case of a large, symptomatic, anal ulceration that developed in an HIV-infected patient who had received high-dose radiation therapy for anal squamous cell carcinoma. This ulceration resulted in the development of severe anal pain requiring large doses of opioid medication for relief. In addition, the patient had fecal incontinence with complete loss of bowel control. Treatment with retinol palmitate, 8,000 IU twice per day, resulted in complete healing of the ulceration. Improvement of anorectal function including resolution of fecal incontinence also was documented.[9]

Because rectal bleeding is the most common symptom in patients with chronic radiation proctopathy,[19] patients with bleeding were included in the study. Nonetheless, the primary focus of the study was to determine the effects of retinol palmitate on functional symptoms of radiation proctopathy. For this reason, we excluded patients who were having frequent rectal bleeding and/or evidence of marked blood loss. The pathophysiology of rectal bleeding seems primarily to be caused by the presence of multiple telangiectasias located superficially in the rectum and anus.

Topical therapy with formalin, laser, or Argon plasma coagulation seems to be an effective treatment for bleeding secondary to chronic radiation proctopathy.[4,5,20] Open-label trials of these treatments have demonstrated their efficacy for rectal bleeding in patients with chronic radiation proctopathy.[6]

For inclusion in the study, we selected patients who were moderately symptomatic with at least one other common symptom of radiation proctopathy, occurring at least on a weekly basis. The pathophysiology of functional anorectal symptoms in patients with chronic radiation proctopathy is poorly understood. These functional symptoms, including difficulty with evacuation, increased stool frequency, fecal incontinence, and rectal urgency seem to develop as a consequence of abnormalities of the rectal wall and anal sphincters. For example, physiologic studies of anorectal function have demonstrated that pelvic irradiation results in the reduction of rectal compliance as well as decreased anorectal pressures.[3] In addition, pelvic irradiation seems to lower the threshold volume of the perception of distention of the rectum using rectal balloon installation technique.[21] Decrease compliance of the rectal wall and increased anorectal sensation with distention will result in the development of clinical symptoms such as urgency and other evacuation difficulties that are experienced by patients with chronic radiation. These pathologic occurrences may occur, at least in part, as a consequence of fibrosis of the rectal wall and ongoing ischemia of the anus and rectum.[22] At present, recommended treatment of these functional symptoms with antispasmodic agents and fiber supplementation is directed at symptom relief alone. These treatments, which have not undergone formal study, would not be expected to reverse the pathophysiology of the condition.

We chose to use a modified Likert scale to measure the effects of retinol palmitate in our patient group. A review of studies in the medical literature measuring the effects of treatments in patients with radiation proctopathy does not indicate a single commonly used technique for measuring symptoms of the condition. The Likert scale has been demonstrated to result in consistent, objective effects of drug therapy in patients with nonulcer dyspepsia.[10] Our group recently used a similar system for measuring effects of thalidomide in patients with mesenteric panniculitis.[23]

We encourage the use of the RPSAS as a tool for measuring symptoms in this population and for studying the effects of drug therapy on symptoms. Further studies will be performed to determine whether changes in RPSAS values correlate with improvement in altered anorectal function in patients with chronic radiation proctopathy.

The dose of retinol palmitate used in the study (20,000 IU per day) is well below the reported toxic range of retinol palmitate and other forms of vitamin A (>50,000 IU per day). To ensure the safety of the patients in our study, we excluded individuals with a history of liver disease. In our clinical practice, patients responding to the dose of 10,000 IU retinol palmitate twice per day are changed to a dose of 10,000 IU daily after completion and response to a 12-week course of therapy. No change in liver enzyme testing has occurred in any patients receiving retinol palmitate.

CONCLUSIONS

This randomized, double blind, placebo-controlled trial demonstrated that retinol palmitate, a safe, readily obtainable form of vitamin A, significantly reduced the symptoms of chronic radiation proctopathy. This effect may be because of the wound-healing properties of retinol palmitate. The positive results from this initial study will serve as the basis for a larger, multicenter trial that is planned for the future.

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REFERENCES

1. Wang CJ, Leung SW, Chen HC, *et al*. The correlation of acute toxicity and late rectal injury in radiotherapy for

cervical carcinoma: evidence suggestive of consequential late effect (CQLE). Int J Radiat Oncol Biol Phys 1998; 40:85–91.
2. Hasleton PS, Carr N, Schofield PF. Vascular changes in radiation bowel disease. Histopathology 1985;9:517.
3. Yeoh EK, Russo A, Botton R, *et al*. Acute effects of therapeutic irradiation for prostatic carcinoma on anorectal function. Gut 1998;43:123–7.
4. Silva RA, Correia AJ, Dias LM, Viana HL, Viana RL. Argon plasma coagulation therapy for hemorrhagic radiation proctosigmoiditis. Gastrointest Endosc 1999;50: 221–4.
5. Counter SF, Froese DP, Hart MJ. Prospective evaluation of formalin therapy for radiation proctopathy. Am J Surg 1999;177:396–8.
6. Hong JJ, Park W, Ehrenpreis ED. Review article: current therapeutic options for radiation proctopathy. Alim Pharmacol Ther 2001;15:1253–62.
7. Elson ML. The role of retinoids in wound healing. J Am Acad Dermatol 1998;39:S79–81.
8. Hein R, Mensing H, Muller PK, Muller PK, Braun-Falco O, Krieg T. Effect of vitamin A and it's derivatives on collagen production and chemotactic response of fibroblasts. Br J Dermatol 1984;111:37–44.
9. Levitsky J, Hong JJ, Jani AB, Ehrenpreis ED. Oral vitamin A therapy for a patient with a severely symptomatic postradiation anal ulceration: report of a case. Dis Colon Rectum 2003;46:679–82.
10. Talley NJ, Verlinden M, Jones M. Validation of a new quality of life scale for functional dyspepsia: a United States multicenter trial of the Nepean Dyspepsia Index. Am J Gastroenterol 1999;94:2390–7.
11. Buchi K. Radiation proctopathy: therapy and prognosis. JAMA 1991;265:1180.
12. Pinto A, Fidalgo P, Cravo M, *et al*. Short chain fatty acids are effective in short-term treatment of chronic radiation proctopathy: randomized, double-blind, placebo-controlled trial. Dis Colon Rectum 1999;42:788–95.
13. Vernia P, Fracasso PL, Casale V, *et al*. Topical butyrate for acute radiation proctitis: randomized crossover trial. Lancet 2000;356:1232–5.
14. Winsey K, Simon RJ, Levenson SM, Demetriou AA. Effect of supplemental vitamin A on colon anastomotic healing in rats given preoperative irradiation. Am J Surg 1987;153:153–6.
15. Ehrlich HP, Hunt TK. Effects of cortisone and vitamin A on wound healing. Ann Surg 1968;167:324–8.
16. Wiseman JS, Senagore AJ, Chaudry IH. Methods to prevent colonic injury in pelvic irradiation. Dis Colon Rectum 1994;37:1090–4.
17. Beyzadeoglu M, Balkan M, Demiriz M, *et al*. Protective effect of vitamin A on acute radiation injury in the small intestine. Radiat Med 1997;15:1–5.
18. Kennedy M, Bruninga K, Mutlu EA, Losurdo J, Choudhary S, Keshavarsian A. Successful and sustained treatment of chronic radiation proctitis with antioxidant vitamins E and C. Am J Gastroenterol 2001;96:1080–4.
19. Moore EM, Magrino TJ, Johnstone PA. Rectal bleeding after radiation therapy for prostate cancer: endoscopic evaluation. Radiology 2000;217:215–8.
20. Viggiano TR, Zinghelboim J, Ahlquist DA, Gostout CJ, Wang KK, Larson MV. Endoscopic Md:YAG laser coagulation of bleeding from radiation proctopathy. Gastrointest Endosc 1993;39:513–7.
21. Iwamoto T, Nakahara S, Mibu R, Hotokezaka M, Nakano H, Tanaka M. Effect of radiotherapy on anorectal function in patients with cervical cancer. Dis Colon Rectum 1997;40:693–7.
22. Berthrong M, Fajardo LF. Radiation injury in surgical pathology. Part 2. Alimentary tract. Am J Surg Pathol 1981;5:153.
23. Ginsburg PM, Ehrenpreis ED. A pilot study of thalidomide for patients with symptomatic mesenteric panniculitis. Aliment Pharmacol Ther 2002;16:2115–22.