Argon Plasma Coagulation in Radiation-induced Proctitis

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Abstract

Background Argon plasma coagulation (APC) is a non-tactile ablative therapy that helps to stop rectal bleeding in patients who have developed actinic proctitis after exposure to radiotherapy. This approach seems to be more effective than medications or surgical procedures.

Objective To review the literature to verify the effectiveness of APC in the treatment of patients with actinic proctitis induced by radiation therapies.

Methods A systematic search was conducted on the following databases: MEDLINE/PubMed, LILACS, SCIELO, and the Cochrane Central Register of Controlled Trials. We identified 81 studies, and 5 of them fulfilled the inclusion criteria.

Results In the articles included, a total of 236 patients were evaluated. Most of them were men (67.7%) with a mean age of 66.6 years. Prostate cancer was the main cause of actinic proctitis (67.3%), and control of the bleeding was achieved in 83.3% of the cases, after a mean of 1.67 session of APC. Moreover, 66 patients had complications with the treatment, and rectal pain was the most referred.

Conclusions Argon plasma coagulation is a well-tolerated and effective treatment to control rectal bleeding in patients who underwent radiotherapy, and the number of sessions varies from 1 to 2, according to the case.

Keywords
- proctitis
- radiotherapy
- argon plasma coagulation
- bleeding

Introduction

Pelvic cancers are frequently treated through radiotherapy, but although radiation can be beneficial in reducing the tumor and even mortality, it can also lead to adverse injuries, especially due to the proximity and anatomical relationship among pelvic organs. In this scenario, the rectum and the sigmoid colon are the structures most commonly affected, and the most prevalent (and feared) complication after radiotherapy sessions is actinic proctitis.[1]

This condition consists of mucosal inflammation due to radiation toxicity, and it may cause a wide range of intestinal symptoms, such as diarrhea, abdominal pain, mucous discharge, tenesmus, and bleeding.[2–4] Moreover, rectal bleeding affects around one third of patients submitted to radiotherapy,[5] and it is considered a serious complication, not only due

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to its impact on the patient's quality of life, but also because rectal bleeding may require hospitalization and blood transfusion.[4,6–8] Despite that, the treatment of this condition remains uncertain.

Three different therapeutic approaches are currently available: medications, surgery, and endoscopy. However, none of these have been standardized as the ideal treatment.[2,9–12] Surgical procedures seem to have little effect, and they are associated with the occurrence of postoperative complications, which makes them the last resort.[2,4,12–14] On the other hand, medications have been used as the first-line treatment due to their safety, but contemporary studies have suggested that they also have little effect on the resolution of rectal bleeding.[13,14]

In this context, the endoscopic approach, such as argon plasma coagulation (APC), has been frequently recommended as a possible first-line treatment.[15] A non-tactile ablative therapy that consists of thermic coagulation directly into the lesion, it has been suggested that APC reduces rectal bleeding in rates of up to 80%.[16] However, studies on this technique[4,7,10–12,15,16,23] are still controversial, so the aim of the present work is to review the literature to verify the effectiveness of APC in the treatment of patients with actinic proctitis induced by radiation therapies, as well as to evaluate the technique regarding the number of sessions required to control the bleeding and the common complications.

Methods

Literature Search

A systematic search was conducted on the MEDLINE/PubMed, LILACS, SCIELO and Cochrane Central Register of Controlled Trials databases using the following terms: (*proctitis*) and (*radiation*) and (*argon plasma coagulation*) and (*bleeding*), with only a few adaptions for each database. Our search strategy included studies available in English, Portuguese or Spanish published between January 2000 and December 2018.

Study Selection

All articles found were meticulously evaluated, and they were excluded if they: were animal studies; were descriptive studies, such as editorials, case reports or case series; had unavailable text or data; did not investigate APC as a treatment for actinic proctitis; studied the association between different types of treatment; and assessed neither rectal bleeding nor actinic proctitis by scores. Moreover, duplicate papers were also excluded.

The process of article evaluation occurred through a paired selection. Two independent reviewers analyzed each article to determine if it should be included or not. In cases of divergent opinions, the final decision was made in a meeting, after discussion and agreement.

Data Analysis

Randomized clinical trials had their quality assessed through the Consolidated Standards of Reporting Trials (CONSORT)[17] statement, and the following aspects were analyzed: adequate randomization, patient allocation, blinding of the participants, blinding of the investigators, losses, exclusions after randomization, referred limitations, and other sources of potential bias. Furthermore, observational studies were evaluated through the application of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[18]

In both cases, the articles were only included in the present review if they had contemplated at least 70% of the CONSORT or STROBE checklists, and these tools were also independently applied by two reviewers. Divergence was, once again, discussed until an agreement was reached. Moreover, the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[19] statement was used as a guide for the present systematic review.

Variables of Interest

Once included in the protocol, all articles were evaluated, and the following variables were collected: author's information, title, year of publication, sample size, duration of the treatment, APC technique, number of APC sessions performed, complications, and patient's characteristics (age, gender, previous malignancy, diagnosis of anemia, and blood transfusion).

Results

Search Results

After screening the titles and abstracts, we identified 81 studies, 8 of which fulfilled the inclusion criteria. Among those, 3 articles were excluded for reporting less than 70% of the STROBE checklist; therefore, 5 papers were included in the present review. ►**Figure 1** summarizes the PRISMA flowchart for article selection.

Studies Characteristics

Only cohort studies ended up being included in the present review and the characteristics of each one is available in ►**Table 1**.

Moreover, regarding all 5 articles, a total of 236 patients were analyzed. Most participants were men (67.7%) with an average age of 66.6 years; 134 were anemic, 56 of whom required blood transfusion (►**Table 2**).

Additionally, the treatment for prostate cancer was the main cause of actinic proctitis (in 67.3% of the cases), as seen on ►**Figure 2**.

All selected studies reported a predetermined scale to assess the severity of actinic proctitis and/or rectal bleeding. Three studies[11,15,20] reported the same score to assess the severity of actinic proctitis, and categorized their population into "mild," "moderate," and "severe" based on the distribution of telangiectasias, the involved surface area, and the presence of fresh blood. Karamanolis et al.,[21] on the other hand, used a modified scale considering only two factors of the previously-used score: distribution of telangiectasias and involved surface area. Thus, patients were categorized into "mild" or "severe" proctitis.

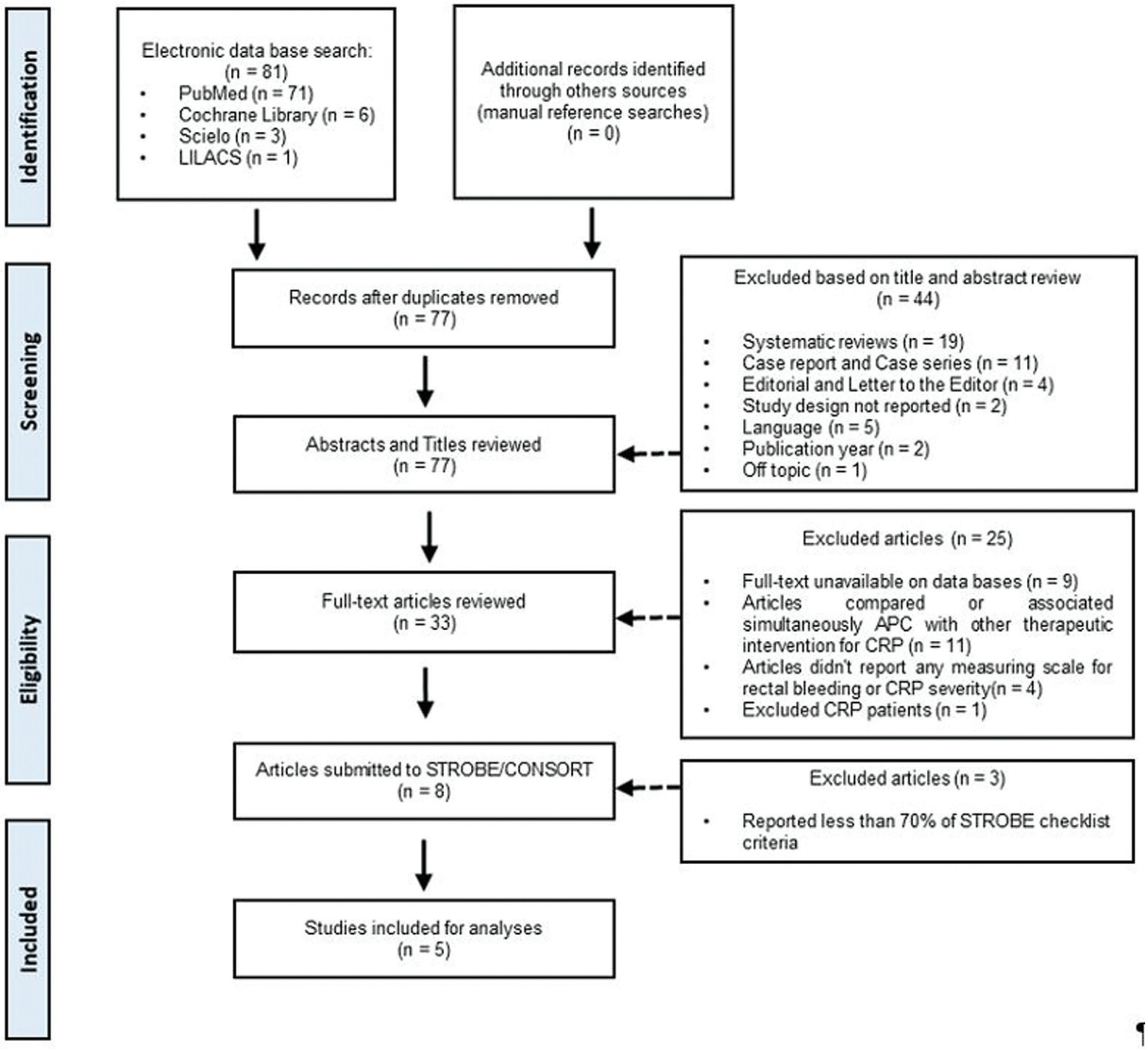

Fig. 1 PRISMA flowchart of the selection of articles.

However, when it comes to the stratification of rectal bleeding, the tool varied according to each study, but all papers regarded the periodicity and volume of the bleeding (►**Table 3**).

Combining the results of the 5 studies, 66 posttreatment occurrences were observed, and rectal pain was the most reported symptom. Moreover, the mean number of sessions performed was 1.67, and bleeding control was achieved in

Table 1 Methodological characteristics of the selected studies

Author	Year of publication	Country	Study design	Average follow-up	Limitations
Sultania et al.[20]	2019	India	Prospective cohort	6 months	It does not compare argon plasma coagulation with other known treatments
Weiner et al.[11]	2017	United States	Retrospective cfohort	112 months	Not reported
Swan et al.[15]	2010	Australia	Prospective cohort	20.6 months	Not a randomized clinical trial
Karamanolis et al.[21]	2009	Greece	Prospective cohort	12 months	Not reported
Sebastian et al.[7]	2004	Ireland	Prospective cohort	14 months	Not reported

Table 2 Patient characteristics

Author	Sample (n)	Mean age (years)	Gender proportion male/female (%)	Malignancy: n (%)	Anemic patients: n (%)	Blood transfusion: n (%)
Sultania et al.[20]	70	51.9	0 / 100	Cervical: 63 (90); endometrial: 7 (10)	65 (92.8)	23 (32.8)
Weiner et al.[11]	35	72.0	100 / 0	Prostatic: 35 (100)	15 (42.9)	15 (42.9)
Swan et al.[15]	50	72.1	90 / 10	Prostatic: 45 (90); endometrial: 2 (4); cervical: 2 (4); vaginal: 1 (2)	21 (42.0)	Not reported
Karamanolis et al.[21]	56	68.4	100 / 0	Prostatic: 56 (100)	15 (26.7)	9 (16.0)
Sebastian et al.[7]	25	69.0	96 / 4	Prostatic: 23 (92); bladder: 2 (8)	18 (72.0)	9 (36.0)

83.8% of the cases. The characteristics of the applied technique are evident in ►**Table 4**.

Discussion

In the present systematic review, we found that APC is a safe and effective endoscopic treatment for actinic proctitis, with a high rate of therapeutic success (83.3%), and these findings support the previous literature[7,15,22] that recommends APC as first-line treatment for patients with actinic proctitis.

However, it is important to mention that there is no consensus about the exact number of APC sessions to achieve bleeding control. In the present review, the mean number was 1.67, which is close to the one reported by Higuera et al.[12] (mean of 1.9 session). Nevertheless, Sudha and Kadambari[10] reported a mean of 5 sessions to achieve bleeding control. The wide variation in the number of sessions required for therapeutic success may include several factors, such as the flow and potential applied during the performance of technique. In addition, Tjandra and Sengupta[23] and Siow et al.[24] suggested a correlation between the number of APC sessions necessary to interrupt the bleeding and the intensity of the bleeding since its onset.

Another important aspect is the absence of a standardized score to evaluate the severity of actinic proctitis and rectal bleeding. The divergence among the scores can lead to an overestimation of some cases, and consequently favor certain studies. Although three[11,15,20] out the five[7,11,15,20,21] selected studies used the same severity score for actinic proctitis (the Total Colonoscopic Severity Score, TCSS), one of the articles (Karamanolis et al.[21]) used a modified version of the tool. With this perspective of different classifications, many patients who could have been categorized as "moderate" ended up being categorized as "mild" or "severe," which influences the statistical analysis.

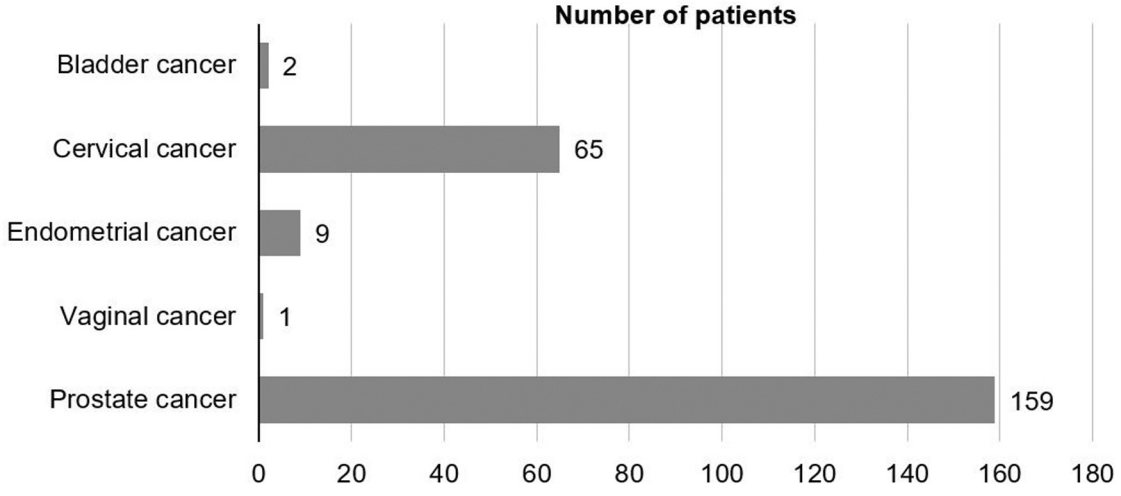

Fig. 2 Most prevalent types of cancer associated with actinic proctitis.

Table 3 Severity scores for rectal bleeding and actinic proctitis

Author	Rectal bleeding		Actinic proctitis	
	Score	Severity	Score	Severity

Sultania et al.[20]	Rectal Bleeding Grade (RBG):
	no bleeding = 0;
	bleeding once a week = 1;
	bleeding 2 or more times a week = 2;
	daily bleeding = 3;
	bleeding requiring blood transfusion = 4
		Median (range):
		3 (2–4)
			Total Colonoscopic Severity Score (TCSS): previously described by Zinicola et al.,[8] based on the distribution of telangiectasias.
			Distal rectum (within 10 cm of the anal verge): 1 point;
			more than 10 cm: 2 points;
			surface area covered by telangiectasias:
			less than 50%: 1 point;
			more than 50%: 2 points;
			presence of fresh blood:
			no: 0 points;
			yes 1 point.
			There are three categories of endoscopic severity for CRP:
			1. grade A (mild): 2 points;
			2. brade B (moderate): 3 points;
			3. grade C (severe): 4 or 5 points
				Grade A (mild):
				23 (32.86%);
				grades B or C
				(moderate or severe):
				47 (67.14%)

Weiner et al.[11]	Not reported	Not reported	Total Colonoscopic Severity Score (TCSS): described previously by Zinicola et al.[8] All items were depicted above.	Not reported
Swan et al.[15]	Modified bleeding scoring system. No rectal bleeding: 0; minor, intermittent: 1; minor, daily: 2; moderate, daily: 3; heavy, daily: 4	Mean (standard deviation): 2.03 ± 0.93	Total Colonoscopic Severity Score (TCSS): previously described by Zinicola et al.[8] All items were depicted above.	Grade A (mild): 17 (34%); grade B (moderate): 23 (46%); grade C (severe): 10 (20%)
Karamanolis et al.[21]	Not reported	Not reported	Modified scoring system based on the aforementioned TCSS.[8] After the total score was calculated according to the distribution of telangiectasias and the surface area covered by them, only 2 categories were established: · mild: 1–2 points; · severe: 3–4 points	Mild: 27 (48%); severe: 29 (52%)
Sebastian et al.[7]	Bleeding severity score. No blood: 0; blood on the toilet paper: 1; intermittent visible bleeding: 2; regular and heavy bleeding: 3; bleeding necessitating blood transfusion: 4	Median score: 3	Not reported	Not reported

Table 4 Characteristics of the protocol for argon plasma coagulation

Author	Protocol		Mean number of sessions	Complications n (%)	Bleeding control rate n (%)
	Flow (L/min)	Wattage (W)			
Sultania et al.[20]	1	45–50	2	Rectal pain and mucous discharge: 12 (21.0); deep ulcers: 8(14.0)	48 (85.70)
Weiner et al.[11]	1	60–70	2	Deep ulcers: 8 (22.9); colovesicular fistulas: 2 (5.7); 1 patient died from this complication	30 (85.70)
Swan et al.[15]	1.4 - 2.0	50	1.36	Rectal pain: 13 (26.0); mucous discharge: 4 (8.0); fecal incontinence: 1 (2.0); fever:1 (2.0); bleeding: 1 (2.0); asymptomatic rectal stricture: 1 (2.0)	49 (98.0)
Karamanolis et al.[21]	2	40	2	Colonic explosion: 1 (1.78%)	50 (89.0)
Sebastian et al.[7]	1.5	25–50	1	Rectal pain: 1 (4.0)	81 (21.0)

The same issue of standardization also affects the interpretation of therapeutic success. Sultania et al.[20] understood the treatment as effective if there was a reduction in the bleeding scale, which was previously documented (from ≥ 2 points to ≤ 1 point). Weiner et al.,[11] on the other hand, defined therapeutic success as the cessation of bleeding, in other words, no evidence of macroscopic rectal bleeding. For Swan et al.,[15] the same aspect was defined as a bleeding severity score ≤ 1 after treatment, while for Karamanolis et al.[21] the definition was the interruption of bleeding or the presence of some occasional traces of bleeding in feces without anemia recurrence. Lastly, Sebastian et al.[7] considered the reduction in the bleeding severity score < 2 points during the minimum period of 6 months. Therefore, the rates of success will diverge when different limits for the establishment of therapeutic success are used.

Furthermore, the present study has some limitations that must be taken into consideration. It only involved cohort studies, which is not an ideal methodology to define treatment options. However, this is a reflection of what is available in the scientific literature. Moreover, we did not perform a statistical analysis with the data extracted from the articles, which could have provided more accurate information about these studies and the role of APC on the treatment of actinic proctitis.

Conclusion

Argon plasma coagulation is a well-tolerated and effective treatment to control rectal bleeding in patients who underwent radiotherapy, and the number of sessions varies from 1 to 2, according to the case. This technique is not exempt from complications, but most of them seem to be short-term occurrences. Nevertheless, further studies are needed before establishing APC as the initial therapy for patients with actinic proctitis.

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Conflict of Interests
The authors have no conflict of interests to declare.

Author's Contributions
Study design: FMAG, GEA;
Data collection: FMAG, RSR, GEA;
Data analysis: FMAG, RSR GEA;
Writing of the manuscript: FMAG, MMP; and
Manuscript review: FMAG, RSR, MMP, GEA.

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