Comparison of Endoscopic Therapies for Chronic Radiation Proctitis: A Systematic Review and Meta-Analysis

Abstract

Background: Radiation injury to the lower intestine may result following treatment of cancers of the pelvis. The rectum is most often affected. Argon plasma coagulation (APC), bipolar electro coagulation (BEC) and topical formalin are recognized as effective treatments.

Objectives: This study aimed to determine in a systematic review and meta-analysis the most effective endoscopic therapy in the treatment of complications secondary Chronic Radiation Colo-Proctopathy (CRCP).

Data sources: A systematic review of English and non-English articles using MEDLINE, COCHRANE, EMBASE, EBSCO, LILACS, Library University of Sao Paulo, BVS, and SCOPE.

Criteria: The main outcome measures while undergoing endoscopic therapies are as follows: mean hemoglobin level before and after treatment, complications, and success in patients with chronic radiation Colo-Proctopathy (CRCP).

Results: Three comparative studies were selected: one was a cohort study comparing APC with Formalin; the other two were unblinded randomized clinical trials with different comparisons (i.e., APC with BEC and APC with formalin). Based on the power of evidence from clinical trials and cohort studies, we can say that the APC seems to have the same efficacy as formalin and the BEC.

Conclusions: The evidence for treatment modalities of CRCP is insufficient, although for endoscopic therapy APC appears to be the most promising treatment.

Keywords: Analcanal; Rectum; Radiation injuries; Argon plasma coagulation; Coagulation; Formaldehyde

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Objectives

This study aimed to evaluate in a systematic review and meta-analysis the most effective endoscopic therapy (i.e., Argon plasma coagulation versus formalin and Argon plasma coagulation versus bipolar electro coagulation) for controlling bleeding. Also, the study aimed to determine which intervention would be better for the treatment of complications from secondary chronic radiation Colo-Proctopathy (CRCP).

Introduction

Chronic radiation Colo-Proctopathy (CRCP) is a well-recognized complication of radiotherapy that occurs as a delayed negative outcome in up to 20% of patients who undergo pelvic radiotherapy [1-3]. Rectal bleeding is the most common presentation [4-6]. Risk factors for radiation proctitis include the dose of radiation, area of exposure, and method of delivery. Doses of radiation <45 Gy are associated with few long-term radiation side effects [7,8]. It is frequently refractory to conservative management, but the optimal endoscopic treatment of bleeding secondary to CRCP is still controversial [9].

Acute radiation proctitis is caused by direct mucosal damage. Chronic radiation proctitis results from progressive epithelial
atrophy and fibrosis associated with chronic mucosal ischemia [10,11]. Symptoms include diarrhea and uncommonly bleeding. Histologic findings include eosinophilic infiltrates, epithelial atypia, and fibrosis [7,12,13].

In patients with chronic radiation proctitis, treatment should be based on the pattern and severity of symptoms [14]. Enemas with the short-chain fatty acids (SCFAs) butyrate, Sucralfate enema, and oral sulfasalazine with prednisolone enemas may accelerate healing in patients with acute radiation proctitis [15-17].

Argon plasma coagulation (APC) and topical formalin are recognized as effective treatments for rectal bleeding associated with chronic radiation proctitis (CRCP) [18-20]. Between the endoscopic therapies available, argon plasma coagulation is effective in reducing short-term symptoms (<6 weeks) of chronic radiation proctitis [21,22] as suggested in several case series [23-25]. Other effective therapies described are the argon and Nd: YAG laser, cryoaolation, bipolar electrocoagulation (BiCap), heater probe, hyperbaric oxygen therapy (HBO), hormonal therapy, antioxidants and metronidazole [26,27]. Several studies including systematic reviews have reported an improvement in symptoms, but it is still not sufficiently clear which therapy is better [28,29].

Methods

This systematic review of the literature was conducted in accordance with the PRISMA Statement (Preferred Reporting Items of Systematic Reviews and Meta-Analyses) [30] and was registered on the PROSPERO 2015: CRD42015016482 [31].

Eligibility criteria

Types of studies: randomized controlled trial, controlled clinical trial, comparative study.

Types of participants: patients diagnosed with chronic radiation colo-proctopathy (CRCP) with bleeding symptoms.

Types of intervention

Argon plasma coagulation versus topical formalin, and Argon plasma coagulation versus bipolar electrocoagulation.

Types of outcome measures: The main outcome measures were mean hemoglobin levels before and after treatment as well as complications and success of the therapy. In this review, we recovered the full text of the selected studies.

Information sources

Were searched for reports published in English, Spanish and Portuguese between January 1st 1990 and March 2016, with a combination of Medical Subject Headings terms or free text word MEDLINE, COCHRANE, EMBASE, EBSCO, LILACS, Library University of Sao Paulo, BVS, and SCOPE (details on the search strategy are displayed in the appendix).

Study selection: References cited in the research articles extracted from databases were also evaluated. Eligibility assessment and selection of relevant studies were performed independently by two reviewers (C.N. and F.A.B.). Studies selected were read in their entirety and were excluded according to criteria from Methodology Check List SIGN [32]. Studies that did not report the results in absolute numbers and those not written in English, Spanish, or Portuguese were excluded. Disagreements between reviewers were resolved by consensus.

Data collection process: We extracted data from a detailed reading of the results of each study. We only included absolute numbers reported in the text of the article or with the analysis of graphs. One review author extracted data from the included studies, and the second author checked the extracted data. We not contacted authors for further information.

Data items: We selected populations with chronic radiation colo-proctopathy (CRCP). We compared the following endoscopic therapies: Argon plasma with formalin and electrocoagulation with bipolar. The characteristics compared included mean hemoglobin level before and after treatment, complications, and procedure success.

Risk of bias in individual studies: Since both cohort and randomized studies were included, the risk of bias in individual studies was assessed using the Newcastle-Ottawa quality assessment for cohort studies [33], the JADAD scale for randomized trials [34].

We extracted data into a table of all studies and identified all potential bias of each study. Then, different factors were identified as individual generators of biases, including age, comorbidities, techniques used, prevalence, and experience.

Synthesis of results: Using the software CAT maker, response and side effects were qualitatively analyzed [35].

We performed a meta-analysis with the software RevMan5 [36]. with the following characteristics: dichotomous data type, statistical method of Mantel-Haenszel, fixed effect model analysis, effect measure risk difference, study confidence interval 95%, total confidence interval 95%, and organized by year of study.

Risk of bias across studies: To identify true heterogeneity and cause for publication bias between studies, we conducted both graphic funnel plot and I^2 analysis. We noted a value of I^2 greater than 50% as high heterogeneity, and if the study was outside the funnel plot it was regarded as publication bias, but if it was inside the funnel plot it was considered to be true heterogeneity.

Results

1744 records were identified through database searching PUBMED, and 76 records were identified through database searching COCHRANE, EMBASE, EBSCO, LILACS, Library University of Sao Paulo, BVS, and SCOPE. 36 duplicates were removed. We recovered 1784 and selected 24 studies (Figure 1) [30].

“RCTs were assessed with Scottish Intercollegiate Guidelines Network, Methodology checklist 2 [32]. Non-randomized studies were assessed with Scottish Intercollegiate Guidelines Network, Methodology checklist 3” as we can see at Critical appraisal: Notes and checklists [37]. Three studies were used in the qualitative analysis (Table 1). For the meta-analysis, we included...
two clinical trial studies. We excluded the cohort study because it was a retrospective study [38,39].

Study characteristics

Among those selected for data extraction and analysis, we found two randomized clinical studies and a single cohort study; the distributions were homogeneous in these studies. The response to treatment results were presented as absolute numbers in all studies. The level hemoglobin post treatment and complications were evaluated in only two of the three studies. Hemoglobin was expressed in mean without standard error, preventing meta-analysis (Table 2).

Risk of bias within studies

We identified biases selected for qualitative analysis studies and evaluated them according to the criteria of JADAD [34] and NEWCASTLE OTTAWA [33]. Although the rate was not optimal for the characteristics of the studies (i.e., they were a retrospective cohort study and non-blind clinical trials) by consensus of reviewers only use clinical trials in the quantitative analysis.

Results of Individual Studies and Synthesis of Results

Qualitative analyses

Using the software CAT maker, response and side effects were analyzed and are shown in Table 3.

Response to treatment: Three studies reported response to treatment [40-42], shows no difference between therapies. Unfavorable results were found for formalin therapy, as reported by the cohort study Alfadhli [40] (Table 3).

Adverse effects: Two studies reported adverse effects between endoscopic therapies [40,41], shows differences between the therapies with a lower rate of adverse effects of therapy with APC (Table 3).

Mean hemoglobin before and after treatment: Mean hemoglobin before and after treatment was reported in two studies that used different designs [40,42], this prevented us from performing a quantitative analysis and we were unable to...
perform sensitivity analysis. Therefore, we decided to perform percentage improvement in order to identify conflicting results. In the clinical trial we can see a reduction of 2.8% of the mean hemoglobin using APC, and the study cohort improved more than 19%, leaving inconclusive this major label clinical bleeding. A similar phenomenon occurred with the treatment of formalin (Table 2).

Quantitative analyses (meta-analysis)

**Response to treatment:** Meta-analysis response to treatment was the only result expressed in absolute numbers included in the clinical trials; this allowed us to perform a dichotomous analysis (Figure 2).

**Response to treatment for APC, formalin, and BEC endoscopic therapies:** Two studies reported response to treatment [41,42], the heterogeneity test indicated $\chi^2$ to be 0%, suggesting homogeneity. Therefore, the fixed-effects model was adopted, and the RD was -0.10 (95% CI: -0.24, 0.05) (Figure 2). Analysis of the pooled data revealed no differences between the therapies.

**Risk of bias across studies:** Although qualification is acceptable for those selected for the qualitative analysis studies, the fact that we had only one retrospective study was considered by consensus of reviewers unfit for meta-analysis given the difference in design was excluded the study [40].

We only evaluated results expressed in absolute numbers for the quantitative analysis and excluded those variables expressed without standard errors. Although it is important to note that many of these variables expressed in median without standard errors can generate biases, mean hemoglobin is different between studies, and the numbers of treatment sessions are different between the groups. Finally, we identified that a generator of bias across studies is the concept of a successful treatment. This concept is completely different between studies. These differences will greatly influence the other outcomes assessed across studies (Table 4).

### Table 1

| Author's names and publication year | Population | Intervention | Mean Hb-pre | Mean Hb-post | Resp | Adv effect |
|-----------------------------------|------------|--------------|-------------|-------------|------|------------|
| Alfadhli A. Can J Gastroenterol February 2008 cohort study [40] | CRCP N 22 May 1998 April 2002 | APC N14 | 105 | 125.5 | 11 | 5 |
| | | 4% Formalin n =11 | 106 | 120.1 | 3 | 9 |
| Lenz L. Endoscopy 2011 randomized without blinding [41] | CRCP N 30 Aug 2005 Apr 2008 | APC n = 15 | 117 | 12 | 5 |
| | | BEC n = 15 | 117 | 14 | 13 |
| Eric Yeoh Int J Radiation Oncol Biol Phys 2013 randomized without blinding [42] | CRCP N 30 Jan 00 April 2010 | APC n = 17 | 140 | 136 | 16 |
| | | 4% Formalin n = 13 | 135 | 137 | 13 |

- **Mean Hb-pre:** mean Hb pre-procedure mg/dl
- **Mean Hb-post:** mean Hb post-procedure mg/dl
- **Resp:** response
- **Adv effect:** adverse effect

### Table 2

| Author’s names and publication year | Population | Intervention | Resp | EER | NNT | Adv effect | EER | NNT |
|-----------------------------------|------------|--------------|------|-----|-----|------------|-----|-----|
| Alfadhli A. Can J Gastroenterol February 2008 cohort study [40] | APC n=14 | 11 | 0.786 | 2 | 5 | 0.357 | 2 |
| | 4% Formalin n =11 | 3 | 9 |
| Lenz L. Endoscopy 2011 randomized without blinding [41] | APC n =15 | 12 | 0.800 | 8 | 5 | ; | 0.333 | 2 |
| | BEC n =15 | 14 |
| Eric Yeoh Int J Radiation O. B. Phys 2013 randomized without blinding [42] | APC n =17 | 16 | 0.941 | 17 | | |
| | 4% Formalin n = 13 | 13 | |

- **EER:** Experimental event rate
- **NNT:** Number needed to treat
- **Resp:** response
- **Adv effect:** adverse effect

### Table 3

| Work | Intervention | Resp | EER | NNT | Adv effect | EER | NNT |
|------|--------------|------|-----|-----|------------|-----|-----|
| Alfadhli A. Can J Gastroenterol February 2008 [40] | APC n=14 | 11 | 0.786 | 2 | 5 | 0.357 | 2 |
| | 4% Formalin n =11 | 3 | |
| Lenz L. Endoscopy 2011 [41] | APC n =15 | 12 | 0.800 | 8 | 5 | ; | 0.333 | 2 |
| | BEC n =15 | 14 |
| Eric Yeoh Int J Radiation O. B. Phys 2013 [42] | APC n =17 | 16 | 0.941 | 17 | | |
| | 4% Formalin n = 13 | 13 | |
**Discussion**

In patients with chronic radiation Colo-Proctopathy (CRCP), prognosis depends on the disease severity [30-33]. Up to 20 percent of patients with acute radiation proctitis will have symptoms that are severe enough to necessitate an interruption in radiation treatment [16,28,29]. In patients with persistent or severe bleeding due to chronic radiation Colo-Proctopathy (CRCP) and that fail to respond to sucralfate therapy for four weeks, endoscopic therapy with (APC, formalin, and BEC) are indicated [43-45].

The available literature comparison between endoscopic therapies for CRCP is scarce, in the present work, the characteristics of the selected studies do not allow for a statistical assertion, but it seems that the three therapies (APC, formalin, and BEC) are equally effective. Based on the power of evidence from clinical trial and cohort studies, we can say that the APC have the same efficacy as formalin or BEC. However, the side effects of therapy with APC seem to be smaller than other endoscopic therapies studied, including stenosis, anal pain, abdominal discomfort, and bleeding ulcers. Showing that the endoscopic therapies available the APC may be the first choice.

This study has important limitations, mainly, scarcity of comparative studies of endoscopic therapies for CRCP. Three comparative studies were selected: one was a cohort study that compared APC with formalin, and the other two were randomized clinical trials with different comparisons (APC with BEC and APC with formalin), which greatly limits the possibility to conduct a meta-analysis, mainly by the difference in the evaluation of the results of successful therapy. Population analysis was able to identify differences in mean hemoglobin before treatment for each study, showing that the state of blood loss (most important symptom), as well as the number of sessions that was required was heterogeneous across studies, it is allowing us to make qualitative conclusions with a measurable result by meta-analyses (Figure 2) (Response to treatment for APC, formalin, and BEC endoscopic therapies). Prospective, controlled, blinded randomized trials for the treatment of CRP are needed to provide statistically meaningful conclusions, with better quality of evidence.

![Figure 2](Response to treatment for APC, formalin, and BEC endoscopic therapies.)

**Table 4** Heterogeneity between studies.

| Study | Population | Intervention | Hb-pre mg/dl | Age and Sessions numbers | Response to treatment |
|-------|------------|--------------|--------------|--------------------------|-----------------------|
| Alfadhli A. Can J Gastroenterol February 2008 [40] | CRCP N 22 May 1998 April 2002 | APC N14 4% Formalin N11 | 105 106 | 74.1 y 1.7 sessions 71.7 y 1.8 sessions | better hb 10% and hb normal eradication telangiectasia's |
| Lenz L. Endoscopy 2011 [41] | CRCP N 30 Aug 2005 Apr 2008 | APC N15 70 y 3.7 sessions | 117 | 64 y 2.9 sessions | reduction bleeding <1 x month |
| Eric Yeoh Int J Radiation Oncol Biol Phys 2013 [42] | CRCP N 30 Jan 00 April 2010 | APC N17 73 y 2 sessions | 140 | 73 y 2 sessions | |

CRCP Chronic radiation coloproctopathy  
APC Argon plasma coagulation  
BEC Bipolar electro coagulation  
N Number of patients
Conclusions

Although the literature is sparse to draw conclusions with quality in their evidence, in this systematic review we can conclude that the endoscopic therapies are effective for the treatment of (CRCP) difficult to control and with persistent symptoms, placing the (APC) as therapy more successful, especially in the control of bleeding with fewer adverse effects.
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