World Journal of Gastrointestinal Surgery

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DOI: 10.4240/wjgs.v8.i2.151

World J Gastrointest Surg 2016 February 27; 8(2): 151-160
ISSN 1948-9366 (online)

MINIREVIEWS

Chronic radiation proctopathy: A practical review of endoscopic treatment

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Author contributions: All of the authors contributed to this manuscript.

Conflict-of-interest statement: None.

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Received: June 28, 2015
Peer-review started: July 11, 2015
First decision: August 16, 2015
Revised: November 20, 2015
Accepted: December 13, 2015
Article in press: December 14, 2015
Published online: February 27, 2016

Abstract

Chronic radiation proctopathy (CRP) is a troublesome complication of pelvic radiotherapy. The most common presentation is rectal bleeding. CRP symptoms interfere with daily activities and decrease quality of life. Rectal bleeding management in patients with CRP represents a conundrum for practitioners. Medical therapy is ineffective in general and surgical approach has a high morbid-mortality. Endoscopy has a role in the diagnosis, staging and treatment of this disease. Currently available endoscopic modalities are formalin, potassium titanyl phosphate laser, neodymium:yttrium-aluminum-garnet laser, argon laser, bipolar electrocoagulation (BiCAP), heater probe, band ligation, cryotherapy, radiofrequency ablation and argon plasma coagulation (APC). Among these options, APC is the most promising.

Key words: Endoscopic treatment; Radiation proctopathy; Proctitis; Argon plasma coagulation; Cryotherapy; Radiofrequency ablation; Formalin; Laser; Bipolar probe; Pelvic radiotherapy

Core tip: The objective of this review is to critically analyze the available data and our experience with this disease, with suggestions for daily practice and further research. In our view, laser treatment is an obsolete technology and can be abandoned. The bipolar probe (BiCAP) is very well indicated for patients with implantable electronic devices. The best way to use formalin is still unknown. More studies with band ligation, cryotherapy and radiofrequency ablation are still needed. Argon plasma coagulation has emerged as the front-runner, due to its ease of use, affordability, better-defined settings, effectiveness and low risk of complications.

Lenz L, Rohr R, Nakao F, Libera E, Ferrari A. Chronic radiation proctopathy: A practical review of endoscopic treatment. *World J Gastrointest Surg* 2016; 8(2): 151-160 Available from: URL: http://www.wjgnet.com/1948-9366/full/v8/i2/151.htm DOI:

http://dx.doi.org/10.4240/wjgs.v8.i2.151

INTRODUCTION

Chronic radiation proctopathy (CRP) is recognized as injury to the rectum and/or colon due to radiotherapy for the treatment of pelvic malignancies; it occurs when clinical symptoms persist or appear months to years after therapy (median 6-12 mo). The sigmoid colon may also be affected[1,2]. The term radiation proctitis is a misleading term since epithelial damage to the rectum due to radiation is associated with minimal or no inflammation[1,3]. Cancers of the cervix, prostate, rectum, bladder, testicles and uterus are commonly treated with pelvic irradiation. Among these, prostate malignance is the most frequent[1].

The incidence of CRP has yet to be ascertained due to the lack of prospective studies and variability in the definition and classification systems used for the condition[1,2]. However, it is estimated to range from 2% to 20%[3,4]. The method of radiation delivery is an important predictor of the risk for radiation proctopathy[2,5]. The rate of colorectal complications with brachytherapy is lower compared to external beam radiation[6]. The use of newer conformal radiation therapy techniques maximizes the dosage directed to the tumor while minimizing the dosage of radiation to the rectum[6,7]. CRP may be more frequent in patients with inflammatory bowel disease, diabetes, hypertension or peripheral vascular disease and in those who develop severe acute proctopathy[2].

CRP should be suspected in patients who develop symptoms such as diarrhea, urgency, tenesmus or bleeding, usually 6 mo or more after pelvic radiation exposure. Hematochezia occurs due to oozing from a friable, ischemic mucosa, and the rupture of radiation-induced telangiectasias and can lead to anemia and the need for blood transfusions[1-3,8]. Symptoms are non-specific and the diagnosis requires exclusion of other etiologies of colitis[3,4]. Diagnosis can be confirmed by colonoscopy or sigmoidoscopy[7]. Endoscopic findings of CRP are mucosal pallor, telangiectasias, spontaneous hemorrhage, edema and friability. Less frequent findings are ulcers, strictures and fistulas[9]. A scoring system has been developed for the endoscopic evaluation of radiation proctopathy severity, based on three factors: The presence of fresh blood, the telangiectasia distribution and the surface area involved[10]. Although biopsies are not diagnostic, they can rule out other causes of proctopathy such as inflammatory bowel disease or infection and can grade the mucosal damage[11,12].

TREATMENTS FOR CRP

In patients with CRP, the management should be based upon the severity and pattern of symptoms and experience within the treatment center[13].

Therapy for CRP includes medical, endoscopic and surgical therapies. Medical therapy includes: Use of non-steroidal anti-inflammatory drugs, sucralfate, short chain fatty acids, metronidazole, pentoxifylline, vitamins (A, C and E), and hyperbaric chamber treatment; all have been described with limited success. In a small study, vitamin A also showed some benefits on functional symptoms[14], although the effect of retinol on rectal bleeding was not evaluated[15]. Enemas of sucralfate are safe and well tolerated and have become the best medical therapeutic option[7,15,16].

The management of patients with symptomatic CRP remains essentially empirical because there are only a few randomized trials, in addition to the difficulty of grading symptoms, endoscopic severity and response to therapy. However, some concepts regarding the management of these patients have been suggested: Treatment for hematochezia is in general better if it involves a sclerosing agent or a topical cautery to obliterate telangiectatic mucosal vessels; non-steroidal anti-inflammatory drugs have a limited role in treatment; large rectal ulcers, strictures, fistulas, abscesses and intractable bleeding generally require surgical management[1,15]. However, surgical therapy has high morbidity and mortality rates[16].

ENDOSCOPIC TREATMENTS FOR CRP

The main objective of endoscopic therapies of CRP is to achieve control of blood loss, leading to improvements in quality of life by reducing the requirement for blood transfusions, iron replacement and hospital admissions, resolving anemia and hematochezia[10,16]. Endoscopic therapy using potassium titanyl phosphate (KTP) laser, argon laser, neodymium:yttrium-aluminum-garnet (Nd:YAG) laser, BiCAP, heater probe, endoscopic band ligation (EBL), cryotherapy, radiofrequency ablation (RFA) and argon plasma coagulation (APC) have been reported[15,16]. Formalin is a miscellaneous technique with aspects of medical and endoscopic approaches. However, Cullen *et al*[17] described instilling formalin into the rectum during flexible sigmoidoscopy, and it shall be included in the endoscopic treatment group. Endoscopic treatment can also be used for radiation-related strictures[7].

Formalin therapy

Formalin therapy for CRP is based on its use in patients with hemorrhagic cystitis[18]. Since Rubinstein's work, in 1986, reported the first successful CRP treatment using a rectal wash with formalin, many authors have published on the treatment of hemorrhagic CRP using this therapy[19]. Formalin functions as a local sclerosant and causes chemical cauterization of telangiectasias.

According to an email survey with members of the American Society of Colon Rectal Surgeons, formalin is the most popular method to treat CRP. Of the 327 respondents, 85% favored to formalin, while 42% used APC. Only 25% of practitioners reported using sucralfate (more than one modality could be chosen)[20].

Success rates vary from 27% up to 100%[16-23]. This

difference can be explained by the wide variability in application technique and concentration[21]. Formalin can be administered as an enema, irrigation in small aliquots, or soaked pledgets of cotton wool applied under rigid sigmoidoscopic, proctoscopic or flexible endoscope guidance[17,22]. Sedation may be needed, but because of pain due to the procedure, most authors reported the use of general anesthesia for this procedure. Formalin therapy can be repeated for two or three more applications until symptomatic improvement, especially with the cessation of rectal bleeding. Ulcers due to formalin application preclude repeating the procedure[18].

Patel *et al*[19], in a retrospective study, evaluated the combination of oral vitamin A with formalin application. The addition of vitamin A led to a significant decrease in the number of formalin sessions and a significantly shorter time for resolution. Supplementation with vitamin A also has a better success rate in controlling rectal bleeding than formalin alone (94% *vs* 64%).

There are also two small studies comparing formalin with APC. Yeoh *et al*[21] suggested that formalin and APC had similar success in managing hemorrhagic CRP. Nevertheless, Alfadhli *et al*[22] concluded that APC was significantly more effective (78.5% *vs* 27.2%, P = 0.017) and safer (P = 0.001) than formalin.

The advantages of formalin application include low cost, wide availability and good efficacy in general[23]. Despite this, high rates of complications have been reported, including chemical colitis, anorectal pain, anal and rectal strictures, rectal perforation, fissures, incontinence and diarrhea[16,18]. Further studies are needed to determine the optimal method of delivery.

Laser therapy

Lasers cause thermal destruction by tissue absorption of laser light and have been used to coagulate radiation proctopathy related vascular lesions in small retrospective series. The KTP laser, the Nd:YAG laser and the argon laser have been effectively used for CRP. A laser fiber is advanced into the working channel of a regular endoscope and is activated by the endoscopist, generating several laser pulses. The depth of thermal effect is dependent on the duration of pulses, power setting and light wavelength. Multiple sessions are generally required. Laser therapy usually decreases rectal bleeding, transfusion dependence and the frequency of hospitalization[24,25].

Complications secondary to deeper thermal injury, which include strictures, transmural necrosis, perforations and fistulas, occur in up to 15% of patients. Intervals between sessions of at least a few weeks and using the least amount of energy for ablation are recommended to avoid complications[26].

Chapuis *et al*[24] described the combination of formalin and Nd:YAG laser in 34 patients with CRP. The patients underwent an endoscopic Nd:YAG laser session and then were treated with formalin application. The authors reported that bleeding ceased in 25 patients (74%) with no major complications.

Compared with other ablative devices, lasers are unwieldy and far more expensive. Other considerations include availability, safety issues and limited portability[25]. The use of lasers in the treatment of CRP has declined[27].

Heater probe and BiCAP - contact therapy

BiCAP and heater probe and are contact methods for CRP treatment. The heater probes have Teflon-coated heating components at the extremity of a plastic catheters that deliver standardized energy over set times. The BiCAP probes have pair of electrodes (negative and positive) at its end through which current is passed using the tissue as a conduction surface[3,16]. No current is passed through the tissues to either a distant or local electrode; for this reason, the induced electromagnetic field is insignificant[28]. Both devices are directed in the setting of active bleeding[16]. In contrast to BiCAP, heater probe mucosal injury is based on direct heat application rather than electrical current. Both probes have an irrigation port[25].

The heater probe and BiCAP have advantages. They cause less tissue injury (in comparison to laser therapy), permit tangential application of cautery, and are both are relatively inexpensive and widely accessible[11]. They are also considered the best methods to use in patients with electronic devices, such as pacemakers and defibrillators[28]. The disadvantage of both methods is char formation on the tip of the probe, requiring catheter retrieval and repeated cleaning[7,11,16].

In a randomized prospective trial by Jensen *et al*[29], 21 patients with chronic recurrent hematochezia and anemia due to CRP were followed for 12 mo. Nine patients were treated with heater probe and 12 with BiCAP (power of 10-15 W). A median of four sessions was required. Severe bleeding episodes were significantly reduced after BiCAP (75% *vs* 33%) and heater probe (67% *vs* 11%) treatment without a statistically significant difference between the methods. The decreased rate of bleeding was accompanied by hematocrit improvement in both groups. There were no major complications.

A retrospective study evaluated 55 patients treated with three sessions of BICAP (power of 30 W) and sucralfate enemas. The authors concluded that BICAP was effective in stopping bleeding from telangiectasias, decreasing recurrence, hospital stay and blood requirements (especially in the group of more severe patients). Unfortunately, there were no comments about complications and follow-up in this study[30].

We recently published a prospective randomized trial comparing APC and BiCAP for rectal bleeding due to CRP. Fifteen patients were enrolled in each group. BiCAP was performed using a 7Fr Gold probe (Wilson-Cook, Winston-Salem, United States) and a high frequency generator (ERBE ICC 200; Electromedizin, Tubingen, Germany). The power setting was 50 W. Coagulation was achieved by applying light pressure with the

probe directly into each telangiectasia. Success was considered as the eradication of all abnormal vessel, and failure as the requirement for more than seven sessions or the need for other therapeutic modality. The complete eradication success rate was 93.3% for BiCAP after a mean of 2.9 sessions, *vs* 80% at 3.7 sessions for APC ($P > 0.05$). Ten of 15 (66.7%) patients had minor complications, mainly transitory anal and abdominal pain. One developed symptomatic stenosis (successfully managed with a fecal emollient). Five patients presented major or hemorrhagic complications (two patients had both minor and major complications). There were no statistical differences between the groups regarding complications when categorized as major ($P = 0.169$) or minor ($P = 0.068$). Nevertheless, the total rate of complications was significantly higher in the BiCAP group ($P = 0.003$, with power 97.4%). No other more severe adverse events, such as fistulas, extensive necrosis, bowel explosion or perforations were noticed in this study. The frequency of complications was evidently superior than those reported so far. Many potential factors can account for such a difference: Most prior studies have been retrospective and underestimated the real incidence of complications; in our study, BiCAP was used at a higher power setting; our patients had a meticulous follow-up; most of the complications were minor and all of them were managed on an outpatient basis. We concluded that APC and BiCAP are both effective for hemorrhagic CRP. There are probably no significant differences between the two methods. Even though, APC seemed to be safer than BiCAP in our study, further research with a larger sample size is necessary to assess complication rates and determines the best therapeutic choice[31].

Endoscopic band ligation

Endoscopic band ligation (EBL) was introduced in 1986 and is currently considered the endoscopic method of choice for the prevention of esophageal varices bleeding[32]. As far as we know, there is only one paper published on the use of EBL as a treatment for CRP[33]. The authors reported one patient who had been treated with APC sessions with no success. EBL was performed with a gastroscope and a standard multiband ligation kit. Three bands were placed in the first session and two during the second session (interval of 20 d between the first and second sessions). The procedure was well tolerated. A lower gastrointestinal endoscopy 45 d after the completion of treatment showed no evidence of ongoing CRP[33]. This was the first experience using this technique, and more data are needed to make further conclusions.

Cryotherapy

Cryospray ablation, similar to APC, is a non-contact therapeutic method by the application of liquid nitrogen or carbon dioxide gas at extremely cold temperatures[8,16]. Cryoablation has been used to treat esophageal early cancer and high-grade dysplasia[8]. Limited data exist on the efficacy of this technique for treating vascular lesions[25]. In a few studies, endoscopic cryoablation was performed in patients with CRP[34-38].

Cryotherapy is performed with a catheter passed through the working channel and its tip is positioned around 0.5 to 1.0 cm from the end of the scope. The spray is applied for 5 s directly onto the mucosa. The freeze/thaw cycle is repeated for a total of three series (total of 15 s) per involved area. A decompression tube with ports spanning the distal 35-40 cm is inserted over a Savary-like guide wire. Suction *via* the decompression tube is applied for the period of cryospray application to protect against over-insufflation[8,35]. Despite this care, one patient was reported with a cecal perforation caused by malfunction of the decompression tube. For this reason, the procedure was adapted to reduce treatment time and carry out full colonoscopy after the cryotherapy for bowel decompression[35]. Difficulties include the field of view with frosting of the lens, and management around the decompression tube. Using a friction-fit mucosectomy cap reduces the chance that the catheter will adhere to the surface and improves access to difficult areas[39].

The required number of sessions ranges from one to four. In one study, the endoscopic score considerably improved, as well as hematochezia and rectal pain. Symptomatic improvement was observed in 80% of patients[35].

The cryospray generators currently on the market are more cumbersome and less mobile than most APC and the radiofrequency units, and need maintaining a supply of liquid nitrogen, which lasts around 2 wk in the holding tank. Therefore, therapies for rare findings, mainly in a lower volume service, may be more difficult. One possible advantage of cryospray over the heat-generating ablative techniques is that colonic lavage is not required to reduce the probability of gas ignition. However, studies in animals showed that the depth of tissue destruction may be deeper with cryospray than that achieved by RFA, and it is unknown whether this could lead to fistulas, abscesses and strictures or whether cryospray is inherently less prone to such complications. Furthermore, the quickly expanding gas requires adequate venting, which may be difficult for proximal lesions in the sigmoid[16].

Studies using cryospray for CRP remain experimental and anecdotal. These initial case reports support the use of cryotherapy for the treatment of CRP. In spite of this, there has been no prospective study comparing cryotherapy with other methods such as APC, regarding the durability of results, safety and efficacy. Supplementary research is required to confirm the superiority or even utility of cryospray[16].

RFA

RFA is a newer endoscopic technique. The Halo RFA system uses two different types of probes with a closely spaced arrangement of electrodes, which thermally ablate tissue. The depth of injury (0.5-1 mm)

is dependent on the power, density and duration of contact. A generator connects to either a 360° Halo catheter or a 90° Halo catheter to provide circumferential or more focused ablation[40]. The FDA (United States Food and Drug Administration) approved the RFA for the treatment of Barrett's esophagus and for gastric hemostatic applications. RFA reaches large areas in a superficial way, suggesting that analogous benefits could be applied in the rectum and colon[41].

Recently, a number of studies have evaluated the safety and efficacy of RFA for CRP treatment[40-45]. RFA is generally performed on outpatients using a single use Halo90 electrode catheter (BARRx/Covidien, Sunnyvale, United States) that is passed through a standard gastroscope. A gastroscope is used instead of a colonoscope because Halo devices are designed for a gastroscope, and because retroflexion is easier using a gastroscope, especially with the RFA catheter attached. During the ablation procedure, the Halo90 catheter is mounted in the 6 o'clock position (as opposed to the 12 o'clock location usually used for the ablation of Barrett's esophagus). To promote hemostasis, the coagulum in treated areas is not scraped off. The endoscope and device are removed for cleaning every eight applications in order to preserve electrode surface effectiveness for subsequent areas treatment. Ablations are performed about 1 mm proximal to the dentate line (to prevent sensory injury to the anal mucosa) and restricted to a short length (less than 6 cm to the dentate line). The procedure is repeated as needed until complete rectal mucosa ablation is achieved. Based on prior studies, an energy density of 12-15 J/cm^2 at a power density of 40 W/cm^2 was selected, which showed no transmural damage at these settings[8,41,43].

Generally, the procedure is well tolerated with mild anorectal pain was reported in 12% of sessions. One of 39 patients presented with significant anorectal bleeding (endoscopic exam demonstrated arterial-like hemorrhage from a vessel in a shallow erosion at a place of excessive ablation) and was treated with a single hemostatic clip[41]. After one or two RFA sessions, hemostasis was achieved with a significant decrease in clinical symptoms and an increase in the hemoglobin concentration[8,41,43]. Thus, RFA seems to be safe and effective to treat CRP. The benefits of RFA include re-epithelialization with the prevention of rebleeding without stenosis and ulceration that may be more frequently observed in other thermal methods. The narrowly spaced bipolar array of the RFA catheter confines the radiofrequency energy penetration, restricting the RFA lesion to the superficial mucosa, in this manner avoiding deep tissue injury. In conclusion, RFA permits much broader areas of tissue to be treated at the same time compared to the point-by-point approach required with the bipolar or heater probes, or even with APC. Similar to APC, the equipment is transportable and can be utilized in different places. The BARRx units also deliver a consistent energy to the surface by using a well defined and a reproducible ramp-up of energy. This diminishes the likelihood of over-treatment and operator-dependence that may lead to ulcerations or perforations[16]. However, despite these theoretical advantages, some statements should be made before RFA is considered the treatment of choice for CRP. First of all, these studies were retrospective and conclusions are limited by the lack of a control group. They were also non-powered and even considering all published works, only a few dozen patients with CRP have been treated with RFA. Another important limitation is that no sigmoid or proximal rectal lesions were ablated, thus safety in those areas (with a thinner wall) remains uncertain. The cost of the RFA energy generator (applicable in only a few indications) and the price of the Halo catheter can be another drawback. Therefore, additional controlled studies are required to compare RFA to other therapeutic modalities for CRP.

APC

APC is a non-contact thermal method using ionized argon gas to deliver a monopolar high-frequency current, which efficiently coagulates tissue. APC is applied to tissue until a white coagulum appears, and then the endoscope and catheter are maneuvered in a vertical or circumferential linear pattern to coagulate additional tissue. The depth of tissue destruction is limited due to increased resistance and decreased current flow through coagulated tissue[39]. Once the tip makes contact with the target tissue, it works as a monopolar probe and it can cause deeper damage. And contact between the tissue and tip may also result in the infusion of extraluminal or submucosal gas. Due to repeated contact with the mucosa, a coagulum may also develop on the extremity of the catheter, which needs intermittent removal of the probe for manual cleaning[25].

The second-generation equipment (VIO/APC2) integrates numerous improvements over the first-generation device. The total effectiveness of the method was improved by 30% ± 50%, so lower power settings can be utilized to create the same thermal effects and, conversely, the same power settings may produce deeper and more extensive tissue injury than expected. Three different modes are now available on the apparatus: Forced, pulsed and precise. Forced mode provides continuous output and corresponds to the settings on the earlier system. Pulsed mode delivers an intermittent current with two alternative effects: Effect 1 pulses nearly every second with a higher energy output following each pulse, while effect 2 pulses around 16 times per second with a lower energy output *per pulse*. The latter may be preferred when superficial treatment of large surface areas is desired. Precise mode uses an integrated regulation system to control the flow. This results in a more superficial depth of damage compared to the other settings[39].

APC has been used to treat a wide spectrum of bleeding lesions in the gastrointestinal tract[25]. However, CRP is really a niche for APC[46]. An impressive

number of studies evaluated APC efficacy and safety for the treatment of CRP, with more than 500 patients enrolled[15,21,31,47-52]. Thus, APC is certainly the best-studied technique in the management of this disease. Nevertheless, until now, there has been no consensus regarding the best APC settings (gas flow rate and power). Power settings reported in the literature range from 25-80 W and flow from 0.6-2.5 L/min[8,15]. Gheorghe *et al*[53] compared two different power settings: 23 patients were treated with 60 W and 19 patients with 50 W. They concluded that there was no statistical significance concerning the efficacy and safety of APC application between the 60 W and 50 W power setting, although rectal stenosis was described only in patients treated with the higher power setting. Sato *et al*[52] using a porcine rectal wall *ex vivo*, found that the optimal setting was 40 W with 1.2 L/min gas flow and a two-s application, which was enough to treat submucosal vessels but did not affect the muscle layer.

More spread lesions commonly need repeated applications per session and several treatments. The mean number of sessions varies from 1 to 3.7 with a calculated overall cumulative mean of 2.13 sessions per patient (median: 2)[16,31]. APC session intervals range from every 2 d to every 8 wk[15,16]. APC improves rectal bleeding in 80%-90% of cases as well as symptoms of tenesmus, diarrhea and urgency in 60%-75% of cases[16]. Follow-up ranged from 2 to 60 mo[15]. Recurrences have been reported, which responded to additional rounds of APC therapy[16,31].

Ulcers after APC can be considered an effect of thermal injury to already damaged, compromised more fragile and tissue, with poorer healing. Ulcer incidence may be affected by the flow rate and power settings of the argon gas, way of application, interval between sessions, and number of sessions subsequent to ulcer development, which may delay ulcer healing due to repeated thermal damage. The fact that rectal ulcers are not clinically problematic denotes they should not be considered a complication or an absolute contraindication to APC, nor do they necessarily need any further endoscopic follow-up[16,54]. However, it is advisable that in the presence of a large ulcer (> 1.0 cm), treatment should be delayed.

The overall reported complication rate with APC has been variable[16], probably due to the lack of a standard technique, variation in the criteria for defining complications and different follow-up periods. The most common procedure-related complication is rectal or anal pain with or without tenesmus, which is most probable to occur following treatment near the dentate line, and habitually resolves spontaneously within a few days, with or without regular analgesics[16,31]. A method described by Coriat *et al*[55], using a transparent cap attached to colonoscope tip, improved visualization of the upper part of the anal canal and of low rectal lesions without retroflexion and a proper distance for safe and effective APC use. Vagal symptoms, cramping and abdominal bloating related to luminal distension have also been reported. One potential drawback of using APC is the risk of excessive bowel distention from the quick instillation of argon gas. It is recommended that, whenever available, a two-channel endoscope should be utilized so that the insufflated argon gas can be removed periodically, associated with a low flow rate[16].

Overall, the frequency of asymptomatic rectal strictures is 4.3%[16]. Although some eschew treating in a circumferential manner to avoid stricture formation, the results of Villavicencio *et al*[56] seem to indicate otherwise. It is likely that the long trawl back technique is more associated with rectal strictures than single-shot procedures with separated spots[57-59]. Ben-Soussan *et al*[59] reported three cases of colonic explosion in two poorly prepared patients. The pathophysiology of the explosion remains unclear but an accumulation of bowel gas (methane and hydrogen) at potentially explosive concentrations due to poor preparation could be the cause. Theoretically, intestinal gas production could also be influenced by the presence of fermentable products in the administered enema. In the Ben-Soussan study[59], the enema used (disodium phosphate and monosodium phosphate) did not contain any fermentable agent likely to increase gas production and facilitate colonic explosion. Thus, these authors concluded that rather than the type of preparation, the presence of stools above the telangiectasias constituted the main risk. In our previous study, we also used enema preparation before the APC session and did not encounter any colonic explosions[31]. As far as we know, no other explosions have been recently reported in the literature.

Bacterial translocation of endogenous microbial flora into the bloodstream may occur during any endoscopic procedure. We prospectively evaluated the frequency of bacteremia following APC during CRP treatment. A total of 21 patients were included and 30 APC sessions were performed. Bacteremia was found in two patients (6.67%). In one case, the isolated bacterium was *Staphylococcus hominis,* and regarded as a contaminant. Another patient had two different microorganisms (*Rhodotorula sp.* and *Streptococcus bovis).* None had infectious symptoms[50].

There are few comparative studies using APC. One of them compared two different power settings[53] and the other compared oral sucralfate with placebo following APC; the authors stated that additional sucralfate treatment did not influence clinical or endoscopic outcomes[49]. Only four studies have compared APC with other therapy for CRP. Two compared APC with formalin (vide formalin section)[21,22], one with hyperbaric oxygen[48] and our study assessed APC *vs* BiCAP (see contact method)[31]. The results of these preliminary studies show that APC is at least as effective and safer than other treatments. However, more comparative studies with larger series, especially between APC and the newest techniques (RFA and cryotherapy) are needed for definite conclusions.

DISCUSSION

CRP is a troublesome complication with an adverse effect on quality of life. The most common complaint is rectal bleeding. Most available data come from uncontrolled, undersized studies with short-term follow-up. Satisfactorily powered, randomized trials comparing different modalities are lacking, and an optimal management strategy has yet to be determined.

Vitamin A had some benefits on functional symptoms, but has not been studied regarding blood loss. Sucralfate enema seems to be the best medical therapy and is well tolerated and secure[15,16]. There is not enough data to support the use of other medical options in daily practice[1-3,8]. Surgical management is associated with high morbidity and mortality and should be considered a last resort. Fewer than 10% of patients eventually require surgery, which is usually for intractable bleeding, perforations, strictures and fistulas[6,7]. In this scenario, endoscopic treatment is becoming increasingly popular[31].

Besides the therapeutic aspects, endoscopy plays a role in diagnosis and grading and in ruling out another sources of bleeding, especially malignancy[3,4,11] Full colonoscopy is recommendable for all patients with rectal bleeding. Due to the risk of fistula formation, rectal biopsies should be performed judiciously. If necessary, they should be directed to the lateral and posterior walls to avoid irradiated areas[11].

Patients considered to be ideal candidates for endoscopic treatment are those with transfusion dependency, chronic hematochezia, refractory to medical management, no tumor recurrence, no other bleeding source, and no fistulas, ulcerations or strictures[18]. It is still controversial that patients with occasional hemorrhage without anemia should be treated endoscopically. We think that at least one endoscopic session during the first diagnostic colonoscopy is a reasonable approach. Presumably, it will resolve once and for all these milder cases[60]. Of course, this and subsequent treatments (if necessary) should be tailored to the patient's preferences.

Nowadays, we agree with other authors in advocating a four to 6 wk interval between sessions[46,59,61]. It is likely that the ischemic rectal mucosa needs this minimal amount of time to recover from thermal or chemical injury[1-3,8]. We agree with John Lee[46] that repeating endoscopy is not necessary in the absence of symptoms.

Good bowel preparation is crucial for endoscopic therapy. We currently recommend complete anterograde bowel preparation for all treatment sessions. Because enemas can cause trauma to a friable mucosa, and many patients with CRP have fecal incontinence[21], retrograde preparation may be more difficult and provide worse results. Because feces above the lesions are the main risk for bowel explosion[59], in cases of poor preparation, the procedure should be postponed or vigorous washing must be done. In the presence of significant oozing, adrenaline solution (1:10000) should be sprayed over the mucosal surface[31].

Like other invasive procedures, there is a debate about antibiotic, antiplatelet and anticoagulant prophylaxis with endoscopic therapy for CRP. The current American Society for Gastrointestinal Endoscopy guidelines do not mention the use of antibiotics in this patient condition (CRP) nor in this procedure (endoscopic ablation)[62]. Tam *et al*[57] suggested the use of antibiotics for immunocompromised patients before APC for CRP. Postgate *et al*[63] made this recommendation for all patients. However, in our study, the incidence of bacteremia after APC for CRP was low (6.67%), similar to the mean frequency of bacteremia associated with colonoscopy in the literature (4.4%). Therefore, APC for CRP may be considered a low-risk method regarding infectious complications, and does not demand the prophylactic administration of antibiotics[50]. Unfortunately, until now, no other study like ours has been done with other endoscopic techniques for CRP. Chruscielewska-Kiliszek *et al*[47] suggested that antiplatelet drugs can play a protective role against ulcer formation after APC. In our study, we found a negative impact of antiplatelet medication, with a statistically significant higher number of APC sessions being required to eradicate telangiectasias in patients using aspirin (P = 0.047) (unpublished data). Kaassis *et al*[61] also reported a higher number of treatments in patients using anticoagulants. In the Karamanolis *et al*[64]'s study recurrence was higher in those using an anticoagulant or aspirin (P = 0.02). The present European Society of Gastrointestinal Endoscopy guidelines recommend that clopidogrel or aspirin can be continued in patients undergoing APC for vascular lesions (recommendation grade C). In the lack of appropriate studies, no recommendation can be made for patients taking a combination of thienopyridines and aspirin[65].

Another issue is whether concomitant medical treatment improves the results of endoscopic treatment. Patel *el al*[19] demonstrated that adding vitamin A enhances the effectiveness of formalin application (see the section on formalin treatment). On the other hand, combined oral sucralfate for 4 wk with APC was not better than APC alone in improving the overall disease severity score (see APC section)[49]. Two possible reasons for the absence of an effect of sucralfate are the short-term period of use and the oral route. Kochhar *et al*[66] identified a good response with enemas with a 77% response in 4 wk and 92% response in 16 wk. Studies using oral vitamin A and sucralfate enemas (or both) for longer periods in association with different endoscopic modalities are welcome, especially in patients with intractable bleeding.

Intractable bleeding is traditionally managed surgically. Nonetheless, when surgery is needed, most studies have demonstrated poor outcomes (because a diversion rarely controls the bleeding completely), as well as high complication (15%-80%) and mortality (3%-9%) rates[6]. Therefore non-surgical strategies

are desirable. Some authors described the success of a second endoscopic modality when the first one had failed[22,33,56,67]. So a cross-over (two endoscopic methods) or a combined (medical plus endoscopic treatments - see above) schemes may avoid surgery in some patients.

A variety of endoscopic techniques for treating CRP were evaluated and discussed in this review. The choice of treatment should be based on the availability and experience of each center[13]. If there is more than one method at hand, some considerations can be made. Laser therapy is an obsolete technology and should be abandoned. Contact methods, especially BiCAP, are very well indicated for patients with pacemakers and other implantable devices. The best way to use formalin is still unknown. More studies with EBL, cryoablation and RFA are still needed. APC has emerged as the front-runner due to its ease of use, affordability, better-defined settings, efficacy and safety. Perhaps in the future, the results of the second generation APC device will improve further.

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