

Exploring the Management of Radiation Proctitis in Current Clinical Practice

NUPUR BANSAL¹, ABHISHEK SONI², PARAMJEET KAUR³, ASHOK KUMAR CHAUHAN⁴, VIVEK KAUSHAL⁵

ABSTRACT

Introduction: Radiation proctitis is radiation induced rectal mucositis, occurring as a consequence to radiation therapy of the pelvic organs for various pelvic region malignancies. The management of radiation proctitis is extremely challenging as no recommended guidelines are available and limited number of studies are there in the literature involving the various treatment options.

Aim: The aim of the study is the in-depth review of published literature to see the role of various treatment modalities in the management of radiation proctitis.

Materials and Methods: An integrative review was undertaken within PubMed, MEDLINE, PMC, GOOGLE SEARCH databases and articles published upto February 2015 were reviewed and analysed. A total of 54 studies were included.

Results: Literature suggests that non surgical therapies are the first line of treatment and surgery is reserved for advanced or refractory cases. Endoscopic therapies form the mainstay of treatment in managing the patients of radiation proctitis. Argon plasma coagulation and laser therapies are preferred. Radiofrequency ablation, cryoablation and mesenchymal stem cell therapy are the upcoming modalities. Medical therapy can be tried alone or in conjunction to endoscopic therapies. In the resistant or refractory cases, surgery can be looked for in the form of diversion or resection with or without anastomosis.

Conclusion: Though, a number of options are available, still a lot can be explored in this field to improve the morbidity in the patients and to confirm the superiority of one treatment over other.

INTRODUCTION

Radiation proctitis or proctopathy is the radiation induced rectal mucosal injury, with an incidence rate varying from 5%–20% [1]. It is seen following radiation treatment to the pelvic organs [2]. Radiation therapy leads to tissue changes including changes like loss of mucosa, endothelial swelling in the arterioles and subsequent fibrosis of connective tissue and arteriolar endarteritis [3,4]. The management of radiation proctitis is extremely challenging as no recommended treatment guidelines are available. Treatment options include medical measures like anti-inflammatory agents (sulphasalazine, balsalazide, mesalazine), antioxidants, sucralfate, formalin, steroid enemas, sodium butyrate enemas, hyperbaric oxygen therapy, pentoxifylline, rebamipide enema therapy, oestrogen/ progesterone, sodium pentosan polysulphate and misoprostol [5-37].

Now-a-days, endoscopic therapies form the mainstay of treatment. They include contact methods, like bipolar electrocautery and heater probe, and non-contact methods, such as argon plasma coagulation, laser therapy (neodymium:yttrium-aluminium-garnet (Nd:YAG) laser, potassium titanyl phosphate (KTP) laser, cryotherapy and radiofrequency ablation [38-54]. The varied response is seen in the symptomatic control of bleeding and other factors with the different modalities. Surgery is considered in the resistant or refractory cases [1]. As there is no established protocol for treating radiation proctitis, so one of the objective of this article is the in-depth review of current treatment options, and to see the role of each treatment modality in the management of radiation proctitis.

MATERIALS AND METHODS

This literature review was performed by conducting a systematic search of PUBMED, MEDLINE, PMC, GOOGLE SEARCH including all articles up to February 2015. Keywords used for the search included 'radiation proctitis', 'radiation proctopathy', 'management

Keywords: Endoscopic, Medical, Proctopathy, Steroids, Surgery

of radiation proctitis', or 'radiotherapy complications of pelvic malignancies'.

RESULTS

Details are given in [Table/Fig-1].

Results derived from search (n= 349) Duplicate results excluded (n=168)
Studies screened by title or abstract (n= 181) Irrelevant studies excluded (n=73)
Full text studies included for further evaluation (n=108) Studies excluded (n=54) (full text not retrieved = 29) (ineligible studies = 25)
Included studies (n= 54)

[Table/Fig-1]: Table representing the selection of the studies.

DISCUSSION

Radiation proctitis is a common complication following radiation therapy of pelvic malignancies, like malignancies of prostate, cervix, uterus, bladder, testicles, rectum and lymphomas [2]. Acute radiation proctitis occurs during or within three months of the radiotherapy treatment and are usually self limiting [1]. It is usually seen in about 13% of patients receiving radiotherapy, while 5-10% of patients develop chronic radiation proctitis [5]. Chronic Radiation Proctitis (CRP) either continues from the acute phase or begins after a latent period of at least 90 days. Chronic proctitis occurs generally in patients with severe acute proctitis and in those with predisposing conditions of diabetes mellitus, inflammatory bowel disease, hypertension, peripheral vascular disease, or even chemotherapy [1].

Pathology and Clinical Course

Tissue changes can occur early in the course of radiation therapy. The initial microscopic changes include mucosal cell loss and distortion of the vascular endothelial cells. Acute inflammation

in the lamina propria, endothelial swelling in the arterioles and eosinophilic crypt abscess formation, are seen as the injury progresses [1,2]. Other changes include neovascularisation and dilatation of small vessels. Severely affected portions develop progressive fibrosis of connective tissue, arteriolar endarteritis and tissue ischaemia, leading to eventual mucosal friability, ulcers, strictures and fistulation [3,4].

The most common presenting symptoms are bleeding per rectum and intestinal obstruction from strictures and sepsis [1]. The rectum is commonly affected organ and the common site of injury following radiotherapy of the pelvic and perineal organs due to its relatively fixed central position in the pelvis. Acute radiation proctitis may present with mild diarrhoea, urgency, tenesmus, generally without rectal bleeding [2]. Chronic lesions are irreversible and progressive, and can lead to arteritis obliterans and interstitial fibrosis of the entire rectal wall [6]. The prognosis of radiation proctitis remains unclear. Though rarely life-threatening, radiation proctitis may eventually progress to become chronic with morbid sequelae including persistent bleeding, strictures and fistulae and rarely, carcinomatous change [7].

Treatment

Management of patients with symptomatic radiation proctitis remains essentially empirical and is suitably individualized. There are a few randomized trials and no consistent guidelines for the treatment of radiation proctitis which have been put forward. In general, non-surgical interventions usually form the first line of treatment and surgery is reserved for the advanced or refractory cases [1,2].

A. MEDICAL MEASURES

Anti-Inflammatory Agents

Sulphasalazine, balsalazide and mesalazine are some of the anti-inflammatory drugs which have been tried in the treatment of radiation proctitis. The active component in these drugs is 5-Aminosalicylic acid (5-ASA) which probably decreases the severity of acute intestinal inflammation. The anti-inflammatory action is exhibited by varied mechanisms, which includes scavenging of oxygen radicals, inhibition of biosynthesis of prostaglandins, and alteration of bacterial flora [8]. In a case series of four patients, sulphasalazine showed improvement in symptoms [9]. The use of balsalazide in patients undergoing prostate cancer radiotherapy has shown to prevent the radiation proctitis and improve the toxicity grades. Balsalazide was administered as 2250 mg of dose, twice daily beginning 5 days before RT and continuing for 2 weeks after completion of the treatment [10]. Seo et al., treated 23 patients of radiation proctitis with oral and topical mesalazine combination therapy. There were improvements in the mean telangiectasia score and the bleeding score with the mesalazine [11]. Overall, the clinical evidence on the role of 5-ASA in the treatment of radiation proctitis is not sufficient to recommend the routine use in radiation injury [12].

Antioxidants

Antioxidants are supposed to have cytoprotective effects to the intestinal tissue by reducing the cellular oxidative stress following radiation. Kennedy et al., has found a sustained therapeutic benefit with vitamin E and C in patients of chronic radiation proctitis [13]. In another trial by Ehrenpries et al., retinol palmitate significantly reduced rectal symptoms of radiation proctopathy [14]. Though, benefits seem to occur, more studies are required to establish its role in the current practice [12].

Sucralfate

Sucralfate (aluminium sucrose octasulfate) is a sulphonated polysaccharide which adheres and thus, protects the mucosal

cells. Other mechanisms responsible for its cytoprotective effects are stimulation of prostaglandin synthesis, increased local blood flow and more local production of epidermal growth factor [15]. It is administered either by the oral route or as suspension enema. Sasai et al., has observed benefits with oral administration of sucralfate in the treatment of chronic radiation proctopathy [16]. Patients with refractory proctopathy were given oral sucralfate and after two months of the treatment, all three patients improved endoscopically and clinically. During a mean follow-up period of 3 years, none of them developed significant recurrent haemorrhage [16]. Sucralfate enemas are safe and well tolerated. Sucralfate enemas have been evaluated by Kochhar et al., in 26 patients. All were treated with 20 mL of 10% rectal sucralfate enemas [17]. Positive response was achieved in 20 patients at 4 weeks, 22 patients at 8 weeks and 24 patients (92.3%) at 16 weeks. No treatment-related complications were noted [17]. Sucralfate paste enemas have shown clinical improvement in 23 patients of chronic radiation proctitis, when given twice daily for two weeks [18]. Additional use of metronidazole may enhance this effect of sucralfate [19]. The use of sucralfate is not recommended in patients with acute proctitis as prophylactic treatment [20].

Steroid Enemas

They have anti-inflammatory action and exert their effect by inhibiting the arachidonic acid cascade, inhibiting cytokine production, blocking histamine release and stabilizing cell membranes [2]. Sanguineti et al., conducted a study to find that hydrocortisone enema is not superior to sucralfate in preventing acute rectal toxicity [21]. At present, it is anticipated that corticosteroid enemas have limited effects on chronic radiation proctopathy.

Formalin Therapy

Formalin therapy is effective in about 48% of patients of chronic radiation proctitis [22,23]. Local instillation of formalin has shown good results in the management of haemorrhagic radiation proctitis [24]. In radiation proctitis, formalin helps to sclerose and seal the fragile neovasculature and has been widely used. Its success relies on the accurate localisation and application at all the affected areas [1]. Pironi et al., stated that the application of 4% formalin solution is an effective, safe, and well-tolerated treatment for chronic radiation-induced haemorrhagic proctitis with minimal discomfort and no severe complications [25].

Sodium butyrate enemas

Sodium butyrate enemas were found to alleviate acute symptoms in the cases with radiation proctitis, though there seems to be no effect on the incidence and severity of late proctitis [26]. In a recent study, Vernia et al., observed that on administering sodium butyrate enemas at a dose of 80ml/24h, remission in clinical symptoms of radiation proctitis can be achieved [27].

Hyperbaric Oxygen Therapy (HBOT)

Hyperbaric oxygen is postulated to exert its therapeutic role in the treatment of CRP. This therapy reverses tissue hypoxia by inducing neovascularisation [28]. It also stimulates collagen formation and re-epithelialization [28]. HBOT successfully alleviated the symptoms in 89% of the patients with radiation proctitis. There were only trivial symptoms after HBOT in 22% of the patients. No severe side effects were observed and treatment compliance remained high [29].

Treatment with hyperbaric oxygen in chronic radiation proctitis has also shown promising results in a large randomized trial done on 120 patients. It has significantly improved the healing responses with better bowel-specific quality of life in patients with refractory radiation proctitis [30].

Pentoxifylline

Treatment of radiation proctitis with pentoxifylline might have modest benefit when given for longer duration. Venkitaraman et al., have done a prospective randomised controlled study on 40 patients and could not show a statistically significant advantage with 6 months of pentoxifylline compared with standard measures for late radiation-induced rectal bleeding [31].

Rebamipide Enema Therapy

Rebamipide enema therapy for radiation proctitis is a safe and effective treatment when first treatment or other conservative management has failed. Kim et al., administer enemas containing 150 mg rebamipide per dosing after morning bowel movement, and always prior to bedtime, twice daily for 4 weeks. The mean improvement in bleeding point scores, friable mucosa scores and telangiectasia scores were all statistically significant and also no side effects were noted in any of the patients [32].

Vitamin A

Retinol palmitate significantly reduces rectal symptoms of radiation proctopathy, most probably because of wound-healing effects. A study comparing retinol palmitate (10,000 IU per oral for three months) to placebo revealed that oral administration of retinol palmitate (vitamin A) is able to reduce radiation proctitis symptoms [33].

Short Chain Fatty Acid Enemas

Pinto et al., conducted a prospective, randomized trial in which short chain fatty acid enemas were compared with placebo in 19 patients of chronic radiation proctopathy [34]. Patients were given daily enemas for five weeks and were subsequently followed up for 6 months. No statistically significant difference was noticed between the placebo and the treated group after six months of follow-up [2].

Oestrogen/ Progesterone

In a study, two patients of radiation proctopathy were treated for the complaint of bleeding with a combination of oestrogen/ progesterone. Complete cessation of bleeding was seen in both the patients but they developed worsening cardiovascular disease [35].

Sodium Pentosan Polysulphate

In a study on sodium pentosan polysulphate, 13 patients of chronic radiation proctitis were taken and evaluated. Complete response was seen in nine patients (82%). Maculopapular rash during therapy was noticed in one patient [36].

Misoprostol

Misoprostol promotes mucosal blood flow and acts as a cytoprotective agent. Khan et al., performed a prospective, randomized study to evaluate the role of misoprostol rectal suppositories in the prevention of radiation proctopathy. Misoprostol suppositories (made from two 200µg tablets) were given to the patients and symptom scores were found to be significantly lower than those in the placebo group [37].

B. ENDOSCOPIC THERAPIES

Endoscopic therapies are considered as the treatment of choice in patients of chronic radiation proctitis with troublesome bleeding. These may also be used along with medical therapies in treating the patients [12]. The goal of endoscopic therapy, is the obliteration of telangiectasias, regardless of methodology [2]. Options include contact methods, like the heater probe and bipolar electrocautery, and non-contact methods, such as laser therapy, argon plasma coagulation, radiofrequency ablation and cryotherapy [28].

It appears, however, that non-contact methods are better in comparison to thermal contact methods of endoscopic treatment. The methods like heater probe and bipolar electrocautery have reported higher incidence of bleeding as a side effect of the treatment and they also require significantly longer sessions of the endoscopic treatment.

Contact Probe Therapy

The heater probe and bipolar electrocautery probe are the contact probes, and deliver the therapy directly to the site of active bleed [28]. The common disadvantage includes the formation of char on the tip of the probe which leads to decrease efficiency of the treatment and require repeated cleaning [28]. Eight patients were treated by Fuentes et al., with the heater probe for rectal bleeding. One to four treatment sessions were required for the symptomatic improvement in bleeding [38]. Jensen et al., treated 21 patients either by a bipolar electrocautery probe or a heater probe. Episodes of severe bleeding were significantly lesser with the heater probe (67% vs 11%) and bipolar probe (75% vs 33%) in comparison to the medical therapy [39].

Laser Therapy

The importance and use of endoscopic laser therapy in the treatment of chronic radiation proctitis was first described in 1982. The lasers are in common use and are effective in the treatment of chronic radiation proctopathy [2].

Nd:YAG Laser

Nd:YAG laser was among the first endoscopic laser modality used [28]. Nd:YAG laser is ideal for deeper vessel coagulation as it is well absorbed by tissue protein [40]. The wavelength used for the treatment is 1064nm and it penetrates to a depth of up to 5mm [28]. Complication rates are around 5-15% [2]. Stricture formation, transmural necrosis and recto-vaginal fistula are some of the complications seen [28]. Successful treatment of rectal bleeding was seen by Leuchter et al., in a patient after four applications [41]. The use of this laser for chronic radiation proctitis has declined due to its cost, the possibility of severe endoscopic damage and the need to aim directly and accurately at telangiectasias [28].

KTP laser

The beam from the Nd:YAG laser is passed through a KTP crystal and is then used as KTP laser. The wavelength of this laser is reduced by half (532 nm). The energy is absorbed at this wavelength by haemoglobin and thus, the depth of penetration is shallow (1-2 mm). Therefore, it is useful for treating superficial vascular lesions [28]. Twenty six patients of chronic radiation proctitis were treated with KTP laser and evaluated by Taylor et al. The treatment was given using 4-10 W and a median of two sessions. Symptomatic improvement was observed in 65% patients, while 30% of the patients have shown no response. No complications like fistula or perforations were reported [42].

Argon laser

The argon laser and KTP laser are functionally similar and have similar wavelength. The depth of tissue penetration is about 1-2 mm. Hence, it is also useful in blood vessel photocoagulation for superficial lesions [28]. The argon beam laser appears to be safer with less transmural inflammation, fibrosis, stricture formation [2]. O'Conner treated five patients and cessation of bleeding was seen after two to four sessions of the treatment. Argon laser at 1.5 W was used in the study. Each treatment session consisted of approximately 50 pulse where each pulse was applied to the telangiectatic lesions with direct circumferential contact [43]. Taylor et al., reported symptomatic control in 14 patients after a

median of three sessions. Maintenance therapy was required in ten patients (71%) for recurrent bleeding approximately every 7 months [44].

Argon Plasma Coagulation

Argon Plasma Coagulation (APC) uses inert argon gas as a conducting medium and bipolar diathermy current is delivered. Limited depth of coagulation (0.5-3mm), uniform and predictable application are some of the advantages seen with its use. The risks of perforation, stenosis and fistulisation are reduced. Another benefit is that, it can also be applied radially and axially, thus, allowing tangential coagulation of lesions [28]. In addition, as APC treatment is being delivered using the colonoscope, it can reach more proximally affected parts of the rectum [1]. Now-a-days, APC has rapidly become the preferred and first-line endoscopic therapy for haemorrhagic CRP [28].

It has been found that APC has the potential to complement topical formalin application and can be used in combination to treat the proximal and distal rectum concurrently. This series has also found that all the patients failed initial conservative management for per rectal bleeding, and should thus be either offered empirical treatment at the time of diagnosis with formalin or APC, or at least be followed up closely following a course of stool softeners and antibiotics such as metronidazole [1].

Most studies have shown benefit on using APC for the management of chronic radiation proctitis. Improvement in rectal symptoms like tenesmus, diarrhoea has been noticed in 60%-75% of the cases. APC also alleviates rectal bleeding in 80%-90% of the cases [28]. Multiple treatment sessions are required in the diffuse lesions, usually ranging from one to five sessions [28].

Hortelano et al., have recently analysed the response of APC in 30 patients of chronic radiation proctitis. Out of all, 77% patients demonstrated complete response while 16% patients revealed partial response. Transfusion was not required in any of the patients following therapy. Long-term (>6 weeks) grade 2 rectal ulceration and grade 2 rectal incontinence were seen in two patients [45].

Overall, the varied complication rates have been observed with the use of APC. Overall morbidity was reported in 47%, post-treatment pain in 20% and severe complications (severe bleeding, extensive necrosis and perforation) in 10% of the patients [28]. The commonest procedure-related complication observed is rectal or anal pain and it usually resolves spontaneously [28]. Rectal ulcers are common following APC treatment. Therefore, recommendation is to give brief pulse treatment to the lesions [46]. Occurrence of ulcers may be affected by the various factors, including the method of application, the time interval between the sessions of the treatment and the flow rate of the argon gas [47]. Rare complications reported include urinary retention, necrosis and arteriovenous fistula [28]. The occurrence of strictures is less common and varies among different studies, from 2%-13.3% [28].

Radiofrequency Ablation

Radiofrequency Ablation (RFA) is a possible treatment of radiation proctitis though the data confirming its role is scarce. RFA restricts the treatment to the superficial mucosa and the deep tissue injury is avoided especially in relatively ischemic mucosa and thus, the lesser risk of post-treatment ulceration and structuring. In comparison to the point-by-point approach as required with APC, heater or bipolar probes, RFA allows simultaneous treatment of much broader areas of tissue. It also leads to squamous re-epithelialization and thus prevents the rebleeding [28].

Zhou et al., have used RFA for treating three patients suffering from CRP. In all cases, the BARRx Halo90 system was used for the delivery of treatment and the procedure was tolerated well.

Haemostasis was achieved effectively after one or two sessions of RFA. No ulceration or stricturing was seen after 19 months of follow-up after the treatment [48]. The BARRx unit was mobile. A consistent amount of energy was delivered to the surface by BARRx unit which minimizes the possibility of over-treatment that may lead to ulcerations or perforations [28].

In another study, RFA was used to treat another case with extensive proctitis that continued to bleed despite giving treatment with APC. Post first treatment session, no significant bleeding was reported. Also, the patient remained free of symptoms for a period of 6 months during follow-up [49].

Some recent studies have suggested that RFA may prove to be an effective alternative to other endoscopic therapies, especially APC. Its effect was reported in the two cases of chronic radiation proctitis, one of whom was transfusion-dependent and was successfully treated with focal RFA. Subsequent to treatment, haematochezia was decreased significantly. In total, three to four sessions were required to eradicate the neovascular lesions [50]. Similarly, Dray et al., reported that with use of RFA, clinical symptoms were decreased significantly and haemoglobin concentration was increased, thus reducing the need for transfusions. After RFA, the concentration of haemoglobin was increased in all 17 patients during the follow-up period of 6 months [51].

Cryoablation

Cryoablation is a procedure in which tissue destruction is done via application of extreme cold temperatures to the target. It has the advantage of uniform treatment of larger surface areas. The first case of successful use of low-pressure cryoablation in resolving the symptoms of radiation proctitis was reported by Shaib et al. Cryoablation therapy was administered using a liquid nitrogen spray which is injected through the cryoablation catheter. Each area of proctitis was treated by a total of four applications with each of 10s duration. No adverse effects after cryoablation were seen [52]. Battish et al., have shown similar results in a case series of two patients who underwent cryoablation using liquid nitrogen for the radiation proctitis. Each patient underwent 4 applications of 10 s each and complete resolution of mucosal bleeding and telangiectasias was noticed on the subsequent endoscopy [53].

Hou et al., have observed the benefit of using cryoablation therapy in a prospective study of 10 patients with haemorrhagic radiation proctitis. Mean follow-up in the study was 3.3months. All of the patients received a single session of cryotherapy. Each session consists of three applications of 5s each to each area of involved mucosa. There was a 37% decrease in the rectal telangiectasia density. Though, symptomatic improvement was observed in 80% of patients, endoscopic improvement was seen in 70% of the patients. Severe complication of cecal perforation was seen in one patient secondary to over-insufflations. One case (10%) of rectal ulcer was also observed [54].

Only a few studies have been reported using cryoablation in CRP and there has been no prospective study confirming and comparing the utility of cryoablation with other treatment modalities [28]. [Table/Fig-2,3] outlines the different modalities used for the treatment of radiation proctitis.

C. Mesenchymal Stem Cell Therapy

Mesenchymal Stem Cells (MSCs) are isolated from bone marrow. They are the pluripotent progenitor cells and play an important role in the maintenance and regeneration of various connective tissues [5]. MSC therapy is supposed to have role in extracellular matrix remodelling, proangiogenesis and inflammatory modulation. In a recent study by Linard et al., on pigs, autologous MSCs (2 × 10⁶ MSCs per kilogram in sterile phosphate-buffered saline (PBS)) were given in the ear vein once a week on days 27, 34, and 41 postirradiation to assess the response in the radiation induced

Sr. No.	Drugs	Authors	Year of Study
1.	Anti-inflammatory drugs		
	Sulphasalazine	Goldstein et al., [9]	1976
	Mesalazine	Seo et al., [11]	2011
	Basalazide	Jahraus et al., [10]	2005
2.	Antioxidants		
	Vitamin E	Kennedy et al., [13]	2001
	Vitamin C	Kennedy et al., [13]	2001
3.	Sucrafate		
	Oral	Sasai et al., [16]	1999
	Enemas	Kochhar et al., [17]	1999
	Paste enemas	Mc Elvanna et al., [18]	2014
4.	Steroid		
	Hydrocortisone enema	Sanguineti et al., [21]	2003
5.	Others		
	Formalin	Pironi et al., [25]	2013
	Sodium butyrate enema	Vernia et al., [27]	2000
	Hyperbaric oxygen therapy	Oscarsson et al., [29]	2013
	Pentoxifylline	Venkitaraman et al., [31]	2008
	Rebamipide enema	Kim et al., [32]	2008
	Vitamin A	Ehrenpreis et al., [33]	2005
	Short chain fatty acid enema	Pinto et al., [34]	1999
	Oestrogen/Progesterone	Niv et al., [35]	1995
	Sodium pentosan polysulphate	Grirsby et al., [36]	1990
Misoprostol suppository	Khan et al., [37]	2000	

[Table/Fig-2]: Pharmacologic interventions for radiation proctitis.

Sr. No.	Technique	Authors	Year of Study
1.	Contact probe therapy		
	Heater probe	Fuentes et al., [38]	1993
	Bipolar electrocautery probe	Jensen et al., [39]	1997
2.	Laser therapy		
	Nd:YAG laser	Leuchter et al., [41]	1982
	KTP laser	Taylor et al., [42]	2000
	Argon laser	Taylor et al., [44]	1993
3.	Argon plasma coagulation	Hortelano et al., [45]	2014
4.	Radiofrequency ablation	Zhou et al., [48]	2009
5.	Cryoablation	Hou et al., [54]	2011

[Table/Fig-3]: Endoscopic interventions for radiation proctitis.

proctitis. In a pig model, repeated injections of MSCs have shown improvement in radiation induced fibrosis and inflammation. This therapy may be a light of hope to the patients suffering from severe proctitis and refractory to the nonsurgical interventions [5].

D. Surgery

Fortunately, surgery is often a last resort to be used when severe complications occur, such as refractory bleeding, strictures leading to intestinal obstruction or sepsis. Surgery can range from a simple proximal diversion to a formal resection with or without an anastomosis [1]. It is noteworthy that all the patients who underwent an anterior resection with proximal diversions ultimately had their stomas reversed and there were no leaks thereafter. Thus, when appropriately indicated, surgery can offer an effective solution [1].

CONCLUSION

Many therapeutic agents ranging from oral drugs to the surgical interventions have been tried to control or alleviate the symptoms. Most of the studies pertaining to the treatment of chronic radiation proctitis are case studies or case series with a few randomized trials comparing the different modalities of the treatment. Non

surgical interventions form the first line of treatment, especially endoscopic therapies. Now-a-days, APC has rapidly become the preferred and first-line endoscopic therapy. Surgery is reserved for the intractable symptoms or severe complications of radiation proctitis. Treatment with mesenchymal stem cell injections may prove beneficial in future. Though, different options are available, exact utility and superiority of one line of treatment over other is yet to be found.

REFERENCES

- Wong MTC, Lim JF, Ho KS, Ooi BS, Tang CL, Eu KW. Radiation proctitis: a decade's experience. *Singapore Med J.* 2010;51(4):315-19.
- Hong JJ, Park W, Ehrenpreis ED. Review article: current therapeutic options for radiation proctopathy. *Aliment Pharmacol Ther.* 2001;15(9):1253-52.
- Radiation-induced proctosigmoiditis (editorial). *Lancet.* 1983;1:1082-83.
- Anselme PF, Lavery IC, Fazio VW, Jagelman DG, Weakley FL. Radiation injury of the rectum: evaluation of surgical treatment. *Ann Surg.* 1981;194:716-14.
- Linard C, Busson E, Holler V, Strup-Perrot C, Lacave-Lapalun JV, Lhomme B, et al. Repeated autologous bone marrow derived mesenchymal stem cell injections improve radiation-induced proctitis in pigs. *Stem Cells. Transl Med.* 2013;2(11):916-27.
- Sharma B, Pandey D, Chauhan V, Gupta D, Mokta J, Thakur SS. Radiation proctitis. *Journal Indian Academy of Clinical Medicine.* 2005;6(2):146-51.
- Quan SH. Factitial proctitis due to irradiation for cancer of the cervix uteri. *Surg Gynecol Obstet.* 1968;126:70-74.
- Bondesen S, Rasmussen SN, Rask-Madsen J, Nielsen OH, Lauritsen K, Binder V, et al. 5-Aminosalicylic acid in the treatment of inflammatory bowel disease. *Acta Med Scand.* 1987;221:227-42.
- Goldstein F, Khoury J, Thornton JJ. Treatment of chronic radiation enteritis and colitis with salicylazosulfapyridine and systemic corticosteroids. A pilot study. *Am J Gastroenterol.* 1976;65:201-08.
- Jahraus CD, Bettenhausen D, Malik U, Sellitti M, St Clair WH. Prevention of acute radiation-induced proctosigmoiditis by balsalazide: a randomized, double-blind, placebo controlled trial in prostate cancer patients. *Int J Radiat Oncol Biol Phys.* 2005;63(5):1483-87.
- Seo EH, Kim TO, Kim TG, Joo HR, Park J, Park SH, et al. The efficacy of the combination therapy with oral and topical mesalazine for patients with the first episode of radiation proctitis. *Dig Dis Sci.* 2011;56(9):2672-77.
- Shadad AK, Sullivan FJ, Martin JD, Egan LJ. Gastrointestinal radiation injury: Prevention and treatment. *World J Gastroenterol.* 2013;19(2):199-98.
- Kennedy M, Bruninga K, Mutlu EA, Losurdo J, Choudhary S, Keshavarzian A. Successful and sustained treatment of chronic radiation proctitis with antioxidant vitamins E and C. *Am J Gastroenterol.* 2001;96(4):1080-84.
- Ehrenpreis ED, Jani A, Levitsky J, Ahn J, Hong J. A prospective, randomized, double-blind, placebo-controlled trial of retinol palmitate (vitamin A) for symptomatic chronic radiation proctopathy. *Dis Colon Rectum.* 2005;48(1):1-8.
- O'Brien PC, Franklin CI, Dear KB, Hamilton CC, Poulsen M, Joseph DJ, et al. A phase III double-blind randomised study of rectal sucralfate suspension in the prevention of acute radiation proctitis. *Radiation Oncol.* 1997;45(2):117-13.
- Sasai T, Hiraishi H, Suzuki Y, Masuyama H, Ishida M, Terano A. Treatment of chronic post-radiation proctopathy with oral administration of sucralfate. *Dis Colon Rectum.* 1999;42(10):1357.
- Kochhar R, Sriram PVJ, Sharma SC, Goel RC, Patel F. Natural history of late radiation proctosigmoiditis treated with topical sucralfate suspension. *Dig Dis Sci.* 1999;44(5):973-78.
- McElvanna K, Wilson A, Irwin T. Sucralfate paste enema: a new method of topical treatment for haemorrhagic radiation proctitis. *Colorectal Dis.* 2014;16(4):281-84.
- Cavci J, Turci J, Martinac P, Jelinci Z, Zupanci B, Panijan-Pezzerovi R, et al. Metronidazole in the treatment of chronic radiation proctitis: clinical trial. *Croat Med J.* 2000;41:314-18.
- Hovdenak N, Sorbye H, Dahl O. Sucralfate does not ameliorate acute radiation proctitis: randomised study and metaanalysis. *Clin Oncol (R Coll Radiol).* 2005;17:485-91.
- Sanguineti G, Franzese P, Marcenaro M, Foppiano F, Vitale V. Sucralfate versus mesalazine versus hydrocortisone in the prevention of acute radiation proctitis during conformal radiotherapy for prostate carcinoma. A randomized study. *Strahlenther Onkol.* 2003;179(7):464-70.
- Raman RR. Two percent formalin retention enemas for haemorrhagic radiation proctitis: a preliminary report. *Dis Colon Rectum.* 2007;50:1032-39.
- Alfadhli AA, Alazmi WM, Ponich T, Howard JM, Prokopiw I, Alqaeeel A, et al. Efficacy of argon plasma coagulation compared to topical formalin application for chronic radiation proctopathy. *Can J Gastroenterol.* 2008;22:129-32.
- Chattopadhyay G, Ray D, Chakravarty S, Mandal S. Formalin instillation for uncontrolled radiation induced haemorrhagic proctitis. *Trop Gastroenterol.* 2010;31:291-94.
- Pironi D, Panarese A, Vendettuoli M, Pontone S, Candioli S, Manigrasso A, et al. Chronic radiation-induced proctitis: the 4% formalin application as non-surgical treatment. *Int J Colorectal Dis.* 2013;28(2):261-66.
- Hille A, Herrmann MK, Kertesz T, Christiansen H, Herrmann RM, Pradier O, et al. Sodium butyrate enemas in the treatment of acute radiation-induced proctitis in patients with prostate cancer and the impact on late proctitis. A prospective evaluation. *Strahlenther Onkol.* 2008;184:686-82.

- [27] Vernia P, Fracasso PL, Casale V, Villotti G, Marcheggiano A, Stigliano V, et al. Topical butyrate for acute radiation proctitis: randomized crossover trial. *Lancet*. 2000;356(9237):1232-35.
- [28] Rustagi T, Mashimo H. Endoscopic management of chronic radiation proctitis. *World J Gastroenterol*. 2011;17(41):4554-62.
- [29] Oscarsson N, Arnell P, Lodding P, Ricksten SE, Seeman-Lodding H. Hyperbaric oxygen treatment in radiation-induced cystitis and proctitis: a prospective cohort study on patient-perceived quality of recovery. *Int J Radiat Oncol Biol Phys*. 2013;87(4):670-75.
- [30] Clarke RE, Tenorio LM, Hussey JR, Toklu AS, Cone DL, Hinojosa JG, et al. Hyperbaric oxygen treatment of chronic refractory radiation proctitis: a randomized and controlled double-blind crossover trial with long-term follow-up. *Int J Radiat Oncol Biol Phys*. 2008;72:134-43.
- [31] Venkitaraman R, Price A, Coffey J, Norman AR, James FV, Huddart RA, et al. Pentoxifylline to treat radiation-induced cystitis and proctitis: a prospective randomised trial. *Clin Oncol (R Coll Radiol)*. 2008;20(4):288-82.
- [32] Kim TO, Song GA, Lee SM, Kim GH, Heo J, Kang DH, et al. Rebamipide enema therapy as a treatment for patients with chronic radiation proctitis: initial treatment or when other methods of conservative management have failed. *Int J Colorectal Dis*. 2008;23(6):629-33.
- [33] Ehrenpreis ED, Jani A, Levitsky J, Ahn J, Hong J. A prospective, randomized, double-blind, placebo-controlled trial of retinol palmitate (vitamin A) for symptomatic chronic radiation proctopathy. *Dis Colon Rectum*. 2005;48(1):1-8.
- [34] Pinto A, Fidalgo P, Cravo M, Midões J, Chaves P, Rosa J, et al. Short chain fatty acids are effective in short-term treatment of chronic radiation proctopathy: randomized, double-blind, controlled trial. *Dis Colon Rectum*. 1999;42(6):788-85.
- [35] Niv Y, Henkin Y. Estrogen-progestin therapy and coronary heart disease in radiation-induced rectal telangiectases. *J Clin Gastroenterol*. 1995;21(4):295-97.
- [36] Grigsby PW, Pilepick MV, Parsons CL. Preliminary results of a phase I/II study of sodium pentasaupolysulfate in the treatment of chronic radiation-induced proctopathy. *Am J Clin Oncol*. 1990;13:28-31.
- [37] Khan AM, Birk JW, Anderson JC, Georgsson M, Park TL, Smith CJ, et al. A prospective randomized placebo-controlled double-blinded pilot study of misoprostol rectal suppositories in the prevention of acute and chronic radiation proctopathy symptoms in prostate cancer patients. *Am J Gastroenterol*. 2000;95(8):1961-66.
- [38] Fuentes D, Monserat R, Isern AM, Salazar J, Bronstein M, Gumina C, et al. Colitis due to radiation: endoscopic management with heat probe. *GEN*. 1993;47:165-67.
- [39] Jensen DM, Machicado GA, Cheng S, Jensen ME, Jutabha R. A randomized prospective study of endoscopic bipolar electrocoagulation and heater probe treatment of chronic rectal bleeding from radiation telangiectasia. *Gastrointest Endosc*. 1997;45(1):20-25.
- [40] Wilson LC, Gilling PJ. Lasers for prostate surgery: an update. *Business Briefing, Eur Kidney Urol Dis*. 2006:1-5.
- [41] Leuchter RS, Petrilli ES, Dwyer RM, Hacker NF, Castaldo TW, Lagasse LD. Nd: YAG laser therapy of rectosigmoid bleeding due to radiation injury. *Obstet Gynecol*. 1982;59: 65S-67S.
- [42] Taylor JG, Disario JA, Bjorkman DJ. KTP laser therapy for bleeding from chronic radiation proctopathy. *Gastrointest Endosc*. 2000;52:353-57.
- [43] O'Connor JJ. Argon laser treatment of radiation proctitis. *Arch Surg*. 1989;124:749.
- [44] Taylor JG, DiSario JA, Buchi KN. Argon laser therapy for haemorrhagic radiation proctitis: long-term results. *Gastrointest Endosc*. 1993;39:641-44.
- [45] Hortelano E, Gómez-Iturriaga A, Ortiz-de-Zárate R, Zaballa M, Barturen Á, Casquero F, et al. Is argon plasma coagulation an effective and safe treatment option for patients with chronic radiation proctitis after high doses of radiotherapy? *Rev Esp Enferm Dig*. 2014;106(3):165-70.
- [46] Villavicencio RT, Rex DK, Rahmani E. Efficacy and complications of argon plasma coagulation for hematochezia related to radiation proctopathy. *Gastrointest Endosc*. 2002;55:70-74.
- [47] Ravizza D, Fiori G, Trovato C, Crosta C. Frequency and outcomes of rectal ulcers during argon plasma coagulation for chronic radiation-induced proctopathy. *Gastrointest Endosc*. 2003;57:519-25.
- [48] Zhou C, Adler DC, Becker L, Chen Y, Tsai TH, Figueiredo M, et al. Effective treatment of chronic radiation proctitis using radiofrequency ablation. *Therap Adv Gastroenterol*. 2009;2:149-56.
- [49] Nikfarjam M, Faulx A, Laughinghouse M, Marks JM. Feasibility of radiofrequency ablation for the treatment of chronic radiation proctitis. *Surg Innov*. 2010;17:92-94.
- [50] Huegle U, Müller-Gerbes D, Dormann AJ. Radiofrequency ablation effectively treats chronic radiation proctitis. *Z Gastroenterol*. 2013;51(9):1092-95.
- [51] Dray X, Battaglia G, Wengrower D, Gonzalez P, Carlino A, Camus M, et al. Radiofrequency ablation for the treatment of radiation proctitis. *Endoscopy*. 2014;46(11):970-76.
- [52] Shaib Y, Hou J. Complete endoscopic healing of radiation proctitis with low pressure cryoablation. *Am J Gastroenterol*. 2008;103Suppl 1:S230.
- [53] Battish R, Shah H, Bashir R. Short-term follow-up of Cryoablation treatment for radiation proctitis. *Am J Gastroenterol*. 2009;104:S390.
- [54] Hou JK, Abudayyeh S, Shaib Y. Treatment of chronic radiation proctitis with cryoablation. *Gastrointest Endosc*. 2011;73:383-89.

PARTICULARS OF CONTRIBUTORS:

1. Senior Resident, Department of Radiotherapy, Pt. B.D. Sharma PGIMS, Rohtak, India.
2. Senior Resident, Department of Radiotherapy, Pt. B.D. Sharma PGIMS, Rohtak, India.
3. Associate Professor, Department of Radiotherapy, Pt. B.D. Sharma PGIMS, Rohtak, India.
4. Senior Professor, Department of Radiotherapy, Pt. B.D. Sharma PGIMS, Rohtak, India.
5. Senior Professor, Department of Radiotherapy, Pt. B.D. Sharma PGIMS, Rohtak, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Nupur Bansal,
 KU -152, Pitam Pura, Delhi-110088, India.
 E-mail: drnupurbansal@gmail.com

Date of Submission: **Oct 26, 2015**

Date of Peer Review: **Jan 04, 2016**

Date of Acceptance: **Feb 24, 2016**

Date of Publishing: **Jun 01, 2016**

FINANCIAL OR OTHER COMPETING INTERESTS: None.