MINI-REVIEW

Radiation Induced Cystitis and Proctitis - Prediction, Assessment and Management

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Abstract

Cystitis and proctitis are defined as inflammation of bladder and rectum respectively. Haemorrhagic cystitis is the most severe clinical manifestation of radiation and chemical cystitis. Radiation proctitis and cystitis are major complications following radiotherapy. Prevention of radiation-induced haemorrhagic cystitis has been investigated using various oral agents with minimal benefit. Bladder irrigation remains the most frequently adopted modality followed by intra-vesical instillation of alum or formalin. In intractable cases, surgical intervention is required in the form of diversion ureterostomy or cystectomy. Proctitis is more common in even low dose ranges but is self-limiting and improves on treatment interruption. However, treatment of radiation proctitis is broadly non-invasive or invasive. Non-invasive treatment consists of non-steroid anti-inflammatory drugs (NSAIDs), anti-oxidants, sucralfate, short chain fatty acids and hyperbaric oxygen. Invasive treatment consists of ablative procedures like formalin application, endoscopic YAG laser coagulation or argon plasma coagulation and surgery as a last resort.

Keywords: Cystitis - proctitis - radiation-induced - assessment - management

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Introduction

Cystitis and proctitis are defined as inflammation of bladder and rectum respectively. Etiologies of cystitis can be infective and non-infective (sterile). Cause of sterile cystitis can be radiation, chemical, mechanical and interstitial. Non-infective cystitis is usually more severe and can cause intense pain, irritative voiding symptoms and hematuria. Haemorrhagic cystitis is the most severe clinical manifestation of radiation and chemical cystitis. Radiotherapy is one of the most common treatment modality used for treatment of carcinoma cervix, rectum and prostate. Radiation proctitis and cystitis are major complications following radiotherapy. Montana GS et al evaluated 527 patients of carcinoma cervix treated with radiotherapy and found a dose response relationship between bladder dose and cystitis and rectal dose and proctitis (Montana et al., 1989). The risk of cystitis increased as a function of mean bladder dose ranging from 3% for patients receiving less than or equal to 5000 cGy to the bladder to 12% for patients receiving greater than or equal to 8001 cGy to the bladder. A similar correlation was also found for rectal dose and proctitis. The risk of proctitis increased as a function of mean rectal dose ranging from 2% for patients receiving less than or equal to 5000 cGy to the rectum to 18% for patients receiving greater than or equal to 8001 cGy to the rectum. There is no time-frame for the risk of radiation cystitis or proctitis and patient can develop the symptoms from days to years after radiation. Patients typically present with hematuria, anaemia, urinary frequency, dysuria and incontinence or retention secondary to blood clots obstructing the urethra. The potential risk factors of patients with cervical carcinoma for the incidence of radiation proctitis and radiation cystitis after receiving radiotherapy have not yet been fully determined. In a study by Yang et al. (2012), 1518 women who received radiotherapy for the treatment of cervical carcinoma were retrospectively reviewed (Yang et al., 2012). Among the 1518 patients, 10.61% and 6.20% patients were diagnosed with radiation proctitis and radiation cystitis respectively.

Grading

Based on the severity of the symptoms, radiation cystitis and proctitis has been classified into a graded system from grade 0-4 by RTOG (Radiation Therapy Oncology Group) and EORTC (European Organisation for Research and Treatment of Cancer) where grade 0 stands for no change from baseline while grade 4 is the most severe grade or fatal complication (Herrmann et al., 1987). Radiation induced haemorrhagic cystitis is a potentially life threatening complication with an estimated incidence of 2-3% (Maier et al., 1997).

Risk Factors:

In a study by Kim et al. (2008), 54 patients of carcinoma cervix who received definitive radiotherapy were reviewed (2008). External beam radiotherapy was

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delivered in 1.8 Gy daily fractions to a whole pelvis dose of 50.4 Gy followed by intracavitary irradiation at total point A doses ranging from 75 Gy to 85 Gy. Grade 3 rectal and bladder morbidity by Radiation Therapy Oncology Group (RTOG) criteria developed in 4 patients (7.4%) and 1 (1.9%), respectively. An age of >60 years (P=0.01) and a total dose to the rectal reference point of > or=80 Gy (P=0.03) were found to be correlated with a higher rate of rectal morbidity. Total dose (> or =80 Gy), dose rate (> or=0.75 Gy/h), and biologically effective doses (> or=135 Gy3) at the bladder reference point were found to be significant factors for the development of late bladder morbidity. By multivariate analysis, age was identified as the only significant factor of late rectal complications, and biologically effective doses at the bladder reference point was the only significant factor of late bladder complications. Kapp et al evaluated rate of various complications in patients of stage IB-IVB cervical carcinoma (Kapp et al., 1997). They found that several pre-treatment factors influenced the likelihood of complications, including age, marked obesity, previous surgery, history of inflammatory disease and stage. The study demonstrated that only the stage of cervical carcinoma was closely associated with the incidence and severity of radiation proctitis and radiation cystitis by univariate and multivariate analysis. It was stated that limited, moderate or severe radiation proctitis and radiation cystitis in patients with early tumor stage with favourable anatomy permitted optimal site-directed radiation, thus sparing normal tissue.

Newer techniques of radiotherapy like intensity modulated radiotherapy (IMRT) and Image guided radiotherapy (IGRT) allows dose painting optimize beam placement to meet predefined dose limit and reduce setup error with reduced planning target volume (PTV) margin which can improve dose distribution and decrease the toxicity.

Pathogenesis of Cystitis

Most common cause of cystitis is infection. Bacterial infection is the commonest cause. Uropathogenic E. Coli (UPEC) is the commonest organism responsible for cystitis. Radiation causes single and double stranded DNA breaks which leads to activation of DNA damage gene repair gene and apoptosis. Additionally DNA penetrates the deeper muscle of urinary bladder causing endarteritis and compromised blood supply and inadequate supply of nutrients to bladder tissue. These damaged blood vessels can survive from months to years after damage which makes it difficult to predict when radiation cystitis will develop.

Treatment

There is no preventive modality to decrease the incidence of radiation-induced hemorrhagic cystitis except dose modification. Prevention of radiation-induced hemorrhagic cystitis has been investigated using various oral agents (steroids, vitamin E, trypsin and Orgotein), but efficacy has not been clearly demonstrated.

Assessment

Before starting the treatment, other causes of hematuria such as urinary calculi, tumors, infections, Bleeding anomalies (medications and coagulopathies) and other non-bladder sources of bleeding (renal, ureter and prostate urethra) need to be ruled out by the urine and serum studies, cystoscopy and imaging. Treatment modalities of hemorrhagic cystitis include continuous bladder irrigation by three way catheter with evacuation of clots, instillation of alum or formalin, fulguration with electro-cautery, hyperbaric oxygen therapy, internal iliac embolization, intra-vesical hydrostatic pressure therapy and in extreme cases, cystectomy with urinary diversion. Discontinuation of any systemic anti-coagulant is advised. These methods of treatment can cause significant damage of bladder tissue and thus may result in deterioration of bladder function. Serial haemoglobin level should be checked during the treatment and blood transfusion should be provided if required.

Bladder irrigation

Continuous bladder irrigation and clot removal are the basis of initial treatment. Bladder irrigation should be monitored as perforation can occur if clots obstruct the catheter. Urokinase is an anti-coagulant secreted by kidneys in bladder. Continuous bladder irrigation with saline stops bleeding by removing urokinase. Various other agents like aluminium potassium sulphate (alum), silver nitrate, formalin or phenol can also be used for bladder irrigation. These agents cause chemical corrosion of the bladder urothelium and coagulate the bladder tissue to stop bleeding (Haldar et al., 2014).

Formalin

Intra-vesical formalin instillation to control hematuria was first used by Brown in 1969. It is an effective method of controlling hematuria with a success rate of 80-90% (Kumar et al 1975). It precipitates cellular proteins of bladder mucosa and has occluding and fixative action on telangiectatic tissue and on small capillaries (McGuire et al., 1974). This leads to oedema, inflammation and necrosis of all layers of urinary bladder. Formalin instillation is done under general or spinal anaesthesia. Various concentrations have been used (1-10%). Higher complication rates (75%) have been reported when using 10 % formalin while no significant complications were reported when using 1-2% concentration (Fair et al., 1974). A contact period of 3-30 minutes has been used in various studies by clamping the catheter. Serious complications which can be encountered during the procedure include a small contracted bladder, urinary incontinence, VUR, ureteric strictures, vesico-ureteric junction obstruction with hydro-ureteronephrosis, acute tubular necrosis with anuria, vesico-vaginal fistula, vesico-ileal fistula, a toxic effect on myocardium, and rupture of the bladder (Godec et al., 1983). Deaths have been reported in extreme cases.

Alum irrigation

Alum Irrigation is in use since 1982 when six patients

with massive bladder haemorrhage due to radiation cystitis were successfully treated with 1% solution of Alum (Ostroff et al., 1982). It acts as an astringent at the site of bleeding, causing a protein precipitation at the urothelial surface which leads to decreased capillary permeability, contraction of intercellular space, vasoconstriction and reduction in oedema and inflammation. It can result in formation of precipitant which may further block the catheter and can be avoided by increasing the flow rate (Choong et al., 2000). Kennedy et al prepared 1% solution of alum by dissolving 400 grams of potash of alum (McCarthy's) in 4 L of hot sterile water and 300 ml of this solution was added to 3 L of sterile normal saline through a sterilising filter to form irrigating alum solution (Kennedy et al., 1984). Eight patients with uncontrolled vesicle bleeding were treated with this solution. This method usually does not require any anaesthesia. Bladder was irrigated with up to 30 L of this solution in 24 hrs. All patients stopped bleeding within 4 days of starting bladder irrigation and tolerated the procedure well. Two patients developed suprapubic discomfort, 2 had mild fever (<38oC) and two developed ileus. Goel et al has used 1% alum in 9 patients with massive bladder haemorrhage, persisted after clot evacuation and continuous bladder irrigation after 24 hours (Goel et al., 1985). All patients responded to the treatment although 3 patients had transient response. There were no delayed urinary symptoms at 6 months follow up. The 1 % solution of alum in sterile water has a concentration of 1.05 g/L and a PH of 4.5 which may account for its side effects like suprapubic pain and spasm. Pathological accumulation of aluminium may occur as a result of renal insufficiency or cumulative absorption. The toxicity of aluminium causes neurofibrillary degeneration in the CNS which manifests as encephalopathy, malaise, speech disorder, dementia, convulsions and vomiting. Kavoussi LR has reported sever renal impairment, encephalopathy, metabolic acidosis and coagulopathy while receiving continuous intra-vesical alum irrigation for severe urinary haemorrhage (Kavoussi et al., 1986). Death has also been reported in extreme cases after continuous intra-vesical alum irrigation (Choong et al., 2000). Although alum irrigation is a safe, easy and low cost procedure, severe aluminium toxicity may occur in patients with renal impairment. Procedure should be abandoned in patients who develop lethargy, confusion or metabolic acidosis.

Amino-caproic acid

Amino caproic acid has been used in the past which can be given orally, intravenously or intra-vesically via bladder irrigation (Singh et al., 1992). It is plasminogen activator inhibitor and counteracts the effect of urokinase. Major disadvantage of amino-caproic acid is that it results in the formation of hard clots which makes further clot evacuation difficult. Hyperbaric oxygen has been used to treat refractory haemorrhagic cystitis (Ajith et al., 2011).

Other agents

Activated recombinant human factor VII has been also used for the treatment of haemorrhagic cystitis. There are many other oral agents available with variable efficacy including: WF-10 or tetrachlorodecaoxide, pentoxifylline, sodium pentosan sulfate, conjugated oestrogen etc. Sub-mucosal Botulinum toxin-A injection in the bladder has been shown to be effective. Besides alum and formalin, prostaglandin, silver nitrate and placental extract has also been used intra-vesically for haemorrhagic cystitis.

Hyperbaric oxygen

Irradiation of the bladder causes a progressive obliterative endarteritis of the small blood vessels, resulting in cellular hypoxia. Conventional treatments reduce hematuria but not the radiation cystitis itself. Hyperbaric oxygen reverses the pathophysiology of the radiation cystitis and reduces bleeding by causing neovascularisation, enhancing angiogenesis and granulation tissue formation, and lastly by optimizing immune functions at the cellular level. In a prospective study of radiation cystitis, 40 patients were treated with hyperbaric oxygen (HBO) (Bevers et al., 1995). Twenty sessions of 100% oxygen inhalation were given in 3-bar pressure for 90 minutes in a multi-place hyperbaric chamber. Treatment was given on daily basis with 5-6 sessions in a week. In 4 patients, 40 sessions were required because of persistent hematuria. Overall 30 patients (75%) had no hematuria for at least 3 months, 7 patients (17%) had occasional slight hematuria and 3 (7.5%) patients did not respond to treatment. Recurrence of severe hematuria was seen in 4 patients leading to cystectomy. Overall rate of recurrence was 0.12/year. In a recent prospective study to define primary role of hyperbaric oxygen in radiation cystitis, 11 patients were treated with HBO (Dellis et al., 2014). Nine patients (81.8 %) and 3 patients (18.2%) had complete and partial response respectively. Mean number of required sessions was 32.8 (range 27-44). Better response was seen in those patients in whom HBO was given early after the onset of hematuria. So the author concluded that early use of HBO is an effective and safe method for the treatment of radiation cystitis. Similar trials reported encouraging results with HBO in the treatment of radiation cystitis (Oliai et al., 2012; Oscarsson et al., 2013). NCT01659723 is an ongoing trial to demonstrate efficacy of hyperbaric oxygen and to see its effect on bladder mucosa.

Surgical Options

Surgical options for refractory haemorrhagic cystitis include cystoscopy and fulguration with electro-cautery and cystectomy with urinary diversion as a last resort

Laser Coagulation

Endoscopic laser coagulation with neodymium:yttrium-aluminum-garnet (Nd:YAG) has been used for treatment of haemorrhagic cystitis (Kaushik et al., 2012). This results in thermal coagulation of bleeding mucosa which allows coagulated tissue to slough results in mucosal ulceration and mucosal re-epithelisation. Damage to bladder tissue may eventually lead to fibrosis, scar formation and bladder

perforation in extreme cases. Recently, endoscopic laser application of potassium titanyl phosphate (KTP) has been considered safe and efficacious in the management of radiation induced hemorrhagic cystitis (Zhu et al., 2013; Talab et al., 2014). In a retrospective review of 20 patients with radiation induced hemorrhagic cystitis who underwent endoscopic laser application of KTP between October 2005 to January 2013, it was observed that the procedure was able to stop bleeding 92% of the time and the average hematuria-free interval after ablation was 11.8 months, with a range of 1-37 months (Talab et al., 2014).

Embolization

Internal iliac artery embolization is used in those patients who do not respond to conservative approach. Therapeutic embolization of one or both internal iliac arteries can be achieved by blood clot, Gelfoam or Histoacryl. A more selective approach can be to identify the bleeding points and then embolise the particular branch of the artery (Olliff S et al., 1990). Most common complication of the embolization is gluteal pain. Gangrene of the bladder and in rare case neurological deficit of one or both lower limbs can occur (Carmignani et al., 1980).

Urinary Diversion and Cystectomy

TIn refractory cases urinary diversion remains the only treatment option. The available urinary diversion techniques are percutaneous nephrostomy, cutaneous ureterostomy or bowel conduit (transverse colon or non-irradiated ileal conduit). In extreme cases cystectomy and urinary diversion is the treatment option. Banerji et al recently reported cost effectiveness in of early urinary diversion with ileal conduit and vesicovaginostomy for the treatment of severe haemorrhagic cystitis (Banerji et al., 2014).

Proctitis

Risk factors

Pathophysiology of radiation proctitis is same as radiation cystitis. But it develops at a lower radiation dose as compared to radiation cystitis. Incidence of radiation proctitis varies from 2-39% depending of radiotherapy dose and technique. Use of IMRT has reduced the incidence of radiation proctitis from 1-9% (Zelefsky et al., 2008). Incidence of radiation proctitis in patients treated with brachytherapy alone is 8% to 13% and up to 21% when brachytherapy is combined with EBRT. Radiation proctitis has been divided into acute and chronic based the duration between radiation exposure and presenting symptoms. Acute radiation proctitis is defined as development of symptoms immediately after initiation of treatment or within 3 months of treatment completion Denton et al., 2002. Up to 20% patients require treatment interruption (Cotti et al., 2003).

Treatment

Usually it is self-limiting and improves on treatment interruption. In these cases only supportive treatment like anti-inflammatory, anti-diarrhoeal, hydration and steroid or 5-aminisalicylic acid enema is required. Chronic proctitis may not become apparent for months to years after cessation of treatment (median time 8-12 months) and the diagnosis is made only after exclusion of co-existing diseases (Denton et al., 2002). Incidence of chronic radiation proctitis ranges from 2-20% (Tagkalidis et al., 2001). Patients with inflammatory bowel disease are at increased risk of developing radiation proctitis. In a retrospective analysis of 28 patients with inflammatory bowel disease who received external beam abdominal or pelvic radiotherapy, it was observed that incidence of severe proctitis was 46 % (13/28) (Willett et al., 2000). Six (21%) patients had severe acute toxicity that required treatment interruption while 8 (29%) patients had severe late toxicity. One patient developed both acute and late rectal toxicity. Rate of late toxicity at 5 years was 73 % in patients treated with conventional radiotherapy as compared to 23 % in patients who were treated with specialized techniques (p-0.02). It was suggested that patients with IBD need special attention while planning for radiotherapy. There are reports suggesting that AIDS patients are more likely to have radiation proctitis probably because of systemic glutathione deficiency which leads to decrease radio-protective thioles and increased oxidative stress. There are no established preventive measures for development of radiation proctitis.

Treatment of Chronic Proctitis

Management of chronic proctitis can be divided into non-invasive or invasive. Non-invasive treatment consists of NSAIDs, Anti-oxidants, Sucralfate, short chain fatty acids and hyperbaric oxygen. Invasive treatment consists of ablative procedures like formalin application, endoscopic YAG laser coagulation or argon plasma coagulation and surgery as a last resort.

Formalin instillation

Mechanism of action of formalin instillation is same as in the treatment of radiation cystitis. It was first used in 1986. Two preparations have been used, 4% and 10% (Denton et al., 2002). Topical formalin is generally applied through proctoscope and a contact period of 2-3 minutes is allowed. Perianal skin needs to be protected to prevent stricture and skin damage. Formalin instillation is generally safe but bleeding, perforation and fistulas have been reported in few studies. In a study of 100 patients, 93 % patients had cessation of bleeding after a median 3.5 applications at 2-4 week interval (Haas et al., 2007). Eight patients required re-treatment at a mean duration of 2 years. Complication rate of 1.1 % was noted, 3 patients complained of perianal pain and 1 patient has dizziness after the procedure.

Hyperbaric oxygen

Hoggan et al conducted a systematic review to find the effectiveness of HBO in the treatment of radiation induced soft tissue reaction and proctitis (Hoggan et al., 2014). The authors reported favourable result for patients with proctitis treated with HBO.

Table 1. Treatment Algorithm in Haemorrhagic Cystitits

Patient presenting with features of haemorrhagic Cystitis
↓
CBC, LFT, KFT, USG Pelvis, Cystoscopy, CECT/CEMRI Pelvis to find any evidence of tumor/calculi/Infection/bleeding anomalies
↓
Stabilize patient/Blood trnsfusion/IV fluid
↓
Continuous bladder irrigation with 1.5% Glycine/Normal Saline
↓
Oral Pentosane Sulfate/ iv WF10 (Not used routinely)
↓
Intravesical instillation of Formalin 1-2% (contact period 30 mins), Alum 1%
↓
Cystoscopy and fulguration
↓
Hyperbaric Oxygen therapy/Endoscopic laser coagulation
↓
Internal Iliac artery Embolization/ Urinary diversion/Cystectomy

Laser coagulation

YAG laser coagulation and argon plasma laser coagulation is also an attractive option for management of radiation proctitis although available studies are retrospective. Single or multiple sessions (usually 2-3) can be used. Almost all the studies have shown improvement in bleeding and haemoglobin level. In a retrospective analysis of 30 patients, treated with argon plasma coagulation for radiation cystitis, 23 patients had complete response, 5 had partial response and 2 patients had no response (Hortelano et al., 2014). Median time for development of radiation proctitis was 13 months and a total of 94 therapeutic sessions were performed. Two patients developed grade 2 rectal incontinence and rectal ulceration. Most of the reported complications are mild cramps, mucus discharge and stricture; however large ulcers, perorations and fistulas have been also reported. Less than 10 % patients may require surgery (Jao SW et al., 1986).

Surgical treatment

Faecal diversion with either colostomy or ileostomy is the commonest procedure. These procedures will improve symptoms but symptoms may recur after reversal of the procedure if additional interventions are not performed. Excision of fistula with reconstruction is another option. In complicated fistulous disease especially if associated with pain and incontinence, proctectomy or pelvic exenteration is recommended. This treatment is associated with significant morbidity including anastomotic leak, incontinence and perianal wound complication.

Conclusion

Radiation cystitis and proctitis are well known accompaniments of radiation treatment. Detection and early treatment can minimize the effect of these side effects on quality of life. The presently available non-invasive techniques are effective in reducing the intensity of these complications to significant extent. However, surgical intervention is warranted for refractory complications. Newer drugs, laser therapy are expected to be more effective treatment. However, sophisticated radiation technique will definitely reduce the incidence of such complications.

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