

# The Use of Hyperbaric Oxygen Therapy in Radiation-Induced Haemorrhagic Cystitis

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## Abstract

Haemorrhagic cystitis is a diffuse inflammatory condition of the bladder leading to bleeding from the bladder mucosa. Severe haemorrhagic cystitis can be caused by radiotherapy, chemotherapy or infection. We report the case of a 58 year old male, who developed haemorrhagic cystitis secondary to previous salvage radiotherapy for prostate cancer. After failing all conservative measures including bladder irrigation, tranexamic acid, and cystoscopic cauterisation, he underwent 48 sessions of hyperbaric oxygen therapy. This proved efficacious in managing this difficult condition. At 3 month follow up post final hyperbaric treatment, he has had no further episodes of bleeding. Further, we provide a review of current treatment options for hemorrhagic cystitis.

## INTRODUCTION

Haemorrhagic cystitis is a diffuse inflammatory condition of the bladder leading to bleeding from the bladder mucosa. Severe haemorrhagic cystitis may arise after radiotherapy, chemotherapy or infection. It is a challenging urological problem and can cause substantial morbidity. Various modalities of treatment have been described for the management of haemorrhagic cystitis.

## CASE SUMMARY

A 58 year-old man presented with a two month history of recurrent haematuria and intermittent urinary retention. The patient has previously undergone a Radical Retropubic Prostatectomy (RRP) for Gleason 3+3=6 prostate cancer in 2002. Pathological analysis revealed a positive surgical margin at the right apex. Post operative PSA nadir was <0.1. In 2004 his PSA had risen to 0.4 and consequently he underwent salvage radiotherapy. Since this time his PSA has been undetectable.

Following radiotherapy the patient developed lower urinary tract symptoms (LUTS) including frequency, urgency and urge incontinence. In 2008 a cystoscopy was performed which demonstrated an anastomotic stricture at the bladder neck. Subsequently the patient underwent a bladder neck incision. Despite a wide open anastomosis the patient's LUTS continued. In 2011 the patient presented to our tertiary referral centre with intractable haematuria requiring continuous bladder irrigation and blood transfusion.

The patient was stabilised and evaluated for a reversible source of bleeding. Clotting profile, INR and APTT were normal. Urinary tract infection was excluded and there was no cytological evidence of urothelial malignancy. CT urogram, did not demonstrate any evidence of upper tract pathology. At cystoscopic examination diffuse tissue fragility and numerous bleeding vessels were encountered in the bladder and urethra. This was suggestive of radiation cystitis. As the patient was requiring continuous bladder irrigation, oral therapy with tranexamic acid was commenced.

This complex case was discussed at an uro-oncology multidisciplinary meeting where various modalities of management were considered. Due to the patients' severe and intractable LUTS intravesical therapies were not favoured as they may worsen his symptoms. Consequently, hyperbaric oxygen therapy was deemed a suitable option of therapy.

Subsequently the patient was scheduled for 48 sessions of hyperbaric oxygen therapy over 10 weeks, with each session lasting 2 hours. The haematuria improved so that continuous bladder irrigation was no longer required and the hyperbaric oxygen therapy could be managed as an outpatient. During the first 30 sessions the patient had to re-present to the emergency department on several occasions for a bladder washout and irrigation. After the 30<sup>th</sup> session the haematuria was significantly reduced and no further presentations to the emergency department were required. The haematuria had

completely resolved by the 44<sup>th</sup> session and the patient completed all 48 session. Unfortunately, the patients LUTS have not altered throughout his treatment despite maximal treatment with anticholinergic agents. At 3 month follow up post final hyperbaric treatment, he has had no further episodes of bleeding.

### **TREATMENT OF RADIATION INDUCED HAEMORRHAGIC CYSTITIS**

Haemorrhagic cystitis may occur as a complication of pelvic radiotherapy. The radiotherapy induces a microscopic obliterative endarteritis that leads to mucosal ischemia. The ischemic bladder mucosa can ulcerate and bleed. Furthermore, this ischemic change can induce neovascularity which is also fragile and subject to bleeding. These pathological changes can occur from 3 months to 10 years post treatment [1].

All patients with haemorrhagic cystitis should undergo a thorough evaluation to determine the cause of haematuria. Once stabilised, clotting and coagulation profiles must be checked, as well as urine culture, urine cytology, upper tract imaging and cystoscopy. The patient's medications must be evaluated and anticoagulants ceased. Other causes of drug induced haemorrhagic cystitis such as cyclophosphamide must be sought and ceased.

A 3 way urethral catheter, evacuation of clots, and commencement of continuous bladder irrigation may be all that is required. At cystoscopy, the bladder should be carefully evaluated for malignancy and for sources of bleeding. Suspicious lesions are biopsied and bleeding points fulgurated at this time.

For patients who do not respond to the above simple manoeuvres, other medical management may be required. Tranexamic acid inhibits the binding of plasminogen and plasmin to fibrin, thus preventing the breakdown of clots on the bleeding surface. However, this agent increases the risk of thrombotic adverse events [2]. Conjugated estrogens have had success rates of 60 – 85% in hemorrhagic cystitis, and are thought to act by stabilizing the microvasculature [3]. However, estrogens increase the risk of venous thromboembolism and cerebrovascular accidents [2]. Sodium pentosanpolysulphate restores the bladder glycosaminoglycan layer. As it may take several weeks to work it is only suitable for patients with chronic slow blood loss [4].

There are numerous intravesical agents that have been

described for hemorrhagic cystitis. Aminocaproic acid can be given orally, parenterally or intravesically. Aminocaproic acid is an antifibrinolytic agent that inhibits plasminogen activation [5]. The main disadvantage of this treatment is the formation of hard clots that are difficult to flush from the bladder. Patients should be clot free and have no upper tract bleeding prior to commencing treatment.

Prostaglandin E1, E2, and F2 have demonstrated clinical efficacy in hemorrhagic cystitis [6]. The postulated mechanism of action is smooth muscle contraction in the mucosa and submucosa of blood vessels. Haemostasis is also achieved by platelet aggregation. Silver nitrate may also be used as a bladder instillation. This agent causes an eschar to be formed at the bleeding sites. Vesicoureteric reflux should be excluded prior to treatment as this agent may precipitate and obstruction the ureters.

Intravesical alum triggers protein precipitation, vasoconstriction and decreased capillary permeability [7]. Intravesical alum is delivered as a continuous irrigation. It may take many days for the haematuria to resolve and retreatment is common. The precipitated blood products may cause the catheter to block, and regular manual washout may be required. Systemic absorption of alum is low, however if long periods of irrigation are required aluminium toxicity may occur. Aluminium toxicity may cause a microcytic hypochromic anaemia, osteomalacia, dementia, encephalopathy, metabolic acidosis and coagulopathy [7].

Formalin (40% formaldehyde) is the most effective intravesical haemostatic agent [5]. Formalin achieves haemostasis by causing fixation of the bladder. Thus further necrosis and blood loss are prevented. Fixation occurs through a process of protein cross linking. As this fixation will occur in any tissue that the formalin is exposed to, it is important to exclude vesicoureteric reflux prior to treatment. This is a painful procedure which requires general anaesthetic.

Hyperbaric Oxygen Therapy (HBO) is a safe and highly effective therapy for hemorrhagic cystitis secondary to pelvic radiation [8]. The proposed mechanism of action is through elevating the tissue oxygen to supraphysiological levels. The increased tissue oxygenation is thought to stimulate angiogenesis, fibroblast proliferation and collagen formation [7]. HBO is generally well tolerated and can be considered a first line alternative in difficult cases.

Selective angio-embolisation can be a useful adjunct to

intravesical therapies. Unfortunately, it is often not possible to identify a single source of bleeding and thus the coils may be deployed in either the superior vesical artery or the internal iliac artery. Further, as the arterial supply to the bladder is bilateral with large anastomoses, the bleeding may continue despite complete occlusion of the ipsilateral internal iliac artery. If the internal iliac artery is occluded there is an increased risk of vascular erectile dysfunction, and gluteal claudication. Should angio-embolisation not be available then surgical ligation of the internal iliac artery may be necessary. Cystectomy is reserved for intractable cases as a treatment of last resort, or life threatening emergencies.

### **References**

1. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) Int J Radiat Oncol Biol Phys. 1995;31:1341–6.
2. www.amh.net.au
3. Heath JA, Mishra S, Mitchell S, Waters KD, Tiedemann K. Estrogen as treatment of haemorrhagic cystitis in children and adolescents undergoing bone marrow transplantation. Bone Marrow Transplant. 2006;37:523–6.
4. Hampson S, Woodhouse C. Sodium pentosanpolysulphate in the management of haemorrhagic cystitis: Experience with 14 patients. Eur Urol. 1994;25:40–2.
5. Lakhani A, Raptis A, Frame D, Simpson D, Berkahn L, Mellon-Reppen S, Klingemann H. Intravesicular instillation of E-aminocaproic acid for patients with adenovirus-induced hemorrhagic cystitis. Bone Marrow Transplant. 1999 Dec;24(11):1259-60.
6. Levine LA, Krane DM. Evaluation of carboprost tromethamine in the treatment of cyclophosphamide-induced haemorrhagic cystitis. Cancer. 1990;66:242–5.
7. R. Manikandan, Santosh Kumar, and Lalgudi N. Dorairajan. Hemorrhagic cystitis: A challenge to the urologist. Indian J Urol. 2010 Apr-Jun; 26(2): 159–166.
8. Parra C, Gómez R, Marchetti P, Rubio G, Felmer A, Castillo OA. [Management of hemorrhagic radiation cystitis with hyperbaric oxygen therapy]. Actas Urol Esp. 2011 Mar;35(3):175-9. Epub 2011 Feb 18.

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