

# Hyperbaric oxygen—A new horizon in treating cyclophosphamide-induced hemorrhagic cystitis

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## ABSTRACT

Hemorrhagic cystitis consists of acute or insidious diffuse bleeding from the bladder mucosa. It can be caused by radiation, drugs, autoimmune diseases, viral and bacterial infections, etc. Hemorrhagic cystitis is a well-recognized complication of cyclophosphamide therapy and it can be potentially fatal. We discuss two cases of cyclophosphamide-induced hemorrhagic cystitis where outcome of conventional management was not satisfactory and a novel therapy using hyperbaric oxygen was used. Hyperbaric oxygen therapy (HBOT) reduces inflammation, stimulates neoangiogenesis, maintains tissue oxygenation and heals tissue hypoxia and radio necrosis. Patients received 100% oxygen in a hyperbaric chamber at 2.5 atmosphere absolute (ATA) for 90 minutes, 5 days a week. One patient was given 36 sessions and the other was given 19 sessions of HBOT. HBOT resulted in complete cessation of bleeding; no side effect was noted during the course of therapy. There was no relapse after 12 months of cessation of treatment. In future, this form of therapy can offer a safe alternative in the treatment of cyclophosphamide-induced hemorrhagic cystitis.

**Key words:** Cyclophosphamide, haemorrhagic cystitis, hyperbaric oxygen

## INTRODUCTION

Hemorrhagic cystitis is a pathological condition which is characterized by recurrent hematuria, urinary urgency and supra pubic pain. The etiology includes radiation, chemotherapeutic drugs, viral and bacterial infections. Radiation-induced cystitis generally occurs as an adverse effect of therapeutic radiation administered to the pelvis for various malignancies, mostly of prostate, urinary bladder and cervix. The incidence of radiation cystitis in patients undergoing radiotherapy has been determined to be between 5.7 and 11.5%.<sup>[1]</sup>

The basic pathology of radiation tissue damage is cytotoxicity, causing sub-lethal cellular damage, progressive obliterative endarteritis, tissue ischemia,

loss of collagen and fibrosis. Hypovascularity causes tissue hypoxia and under such conditions, damaged fibroblasts fail to produce collagen along with superadded infection. Bladder biopsy shows mucosal edema, vascular telangiectasis, sub-mucosal hemorrhages, obliterative endarteritis and smooth muscle fibrosis.<sup>[2]</sup> Conventional treatments include intravascular instillation of formalin, alum and silver nitrate, systemic use of steroids and aminocaproic acid, antibiotics, cauterization of bleeding vessels, prostaglandin infusion and bilateral ligation of hypogastric arteries.<sup>[2]</sup>

## CASE HISTORY

We treated two cases of drug-induced hemorrhagic cystitis with hyperbaric oxygen therapy (HBOT). In both the cases, there was prompt remission of hematuria and other symptoms. Both the patients tolerated the treatment well without any complications and there was no relapse reported during 12 month follow-up period. A brief description of the two cases is given below.

## CASE REPORTS

### Case 1

A 36-year-old lady received allogenic bone marrow transplant for acute myeloid leukemia. She was on cyclophosphamide and mesna but still, developed hemorrhagic cystitis. Urine microscopy revealed several RBCs and ultrasound scan

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revealed a hematoma within the urinary bladder. Coagulation parameters were normal. Patient was treated with bladder irrigation, hydration and packed cell transfusion but hematuria did not subside. She was given HBOT [2.5 atmosphere absolute (ATA) for 90 minutes, 5 days a week] for a total of 36 sessions. After 18 sessions of HBOT, patient was reviewed and her condition improved symptomatically. After 36 sessions, microscopic hematuria completely resolved. Cystoscopic examination was normal. No relapse was reported during follow-up period of 12 months.

### Case 2

A 40-year-old lady who underwent allogenic bone marrow transplant for chronic myeloid leukemia was treated with busulphan, cyclophosphamide, cytosine arabinoside and methotrexate along with mesna. She developed gross hematuria. Standard conservative modalities like hydration and bladder irrigation did not lead to any improvement. She was subjected to HBOT (a profile of 2.5 ATA for 90 minutes, 5 days a week), for a total of 19 sessions. Her symptoms improved, post-HBOT urine microscopy was within normal limits. The HBOT profile followed in both the cases was in adherence to international standards [2]

## DISCUSSION

### HBOT in hemorrhagic cystitis

HBOT has variously been tried in radiation-induced hemorrhagic cystitis. Hart and Strauss in 1986, reported relief of symptoms of tenesmus and hematuria in 15 patients of radiation cystitis, treated with a combination of HBOT and surgery.[2] Rijkmans *et al*, in 1989 used HBOT to treat 10 patients with radiation cystitis using a profile of 3 ATA for 90 minutes, for an average of 20 sessions. Hematuria stopped completely with better resolution of tumor.[2] Weisse and Neville treated eight patients with radiation cystitis with a series of 60 HBOT sessions (2 ATA, 2 hours daily). There was symptomatic relief and significant reversal of tissue injury in the patients, monitored by using cystoscopy.[2] Shoenrock and Ciani, Velu and Myers, Nakad *et al* and Shameem *et al*. have also reported improvement of hemorrhagic cystitis with HBOT. [2] Neheman *et al* in 2005 studied the effects of giving HBOT to seven patients with radiation cystitis. They were given an average of 30 HBO treatments and followed up for an average of 24 months. The hematuria resolved completely in all seven patients shortly after treatment; two had recurrence of gross hematuria. They were re-treated with HBO until the hematuria resolved. HBOT appears to give good short-term and medium-term results. It is currently reserved for cases refractory to the standard treatments for radiation cystitis.[3]

The pathology of hemorrhagic cystitis induced by both radiation and cytotoxic drugs seems to be similar. Cyclophosphamide-induced hemorrhagic cystitis is due to acrolen, a metabolite of cyclophosphamide. The early lesion of drug-induced hemorrhagic cystitis is characterized by

oedema, ulceration and hemorrhage. Acute radiation cystitis leads to edema, inflammation of mucosa and lamina propria. Mucosal ischemia due to endarteritis causes hypoxic surface damage, ulceration and bleeding. Both these conditions finally lead to diffuse telangiectasia, mucosal fibrosis and chronic inflammatory cell infiltrates.[4,5] HBOT has not been tried that extensively in cystitis caused by drugs like cyclophosphamide. Nevertheless, the few studies which employed HBOT for the treatment of drug-induced hemorrhagic cystitis have reported a favorable outcome. Yazawa *et al*. in 1995 reported a case of cyclophosphamide-induced hemorrhagic cystitis for which HBOT (2 ATA for 60 minutes a day for 30 days) was administered. After treatment the symptoms subsided and haematuria disappeared. Cystoscopic findings also demonstrated marked improvement.[6] Hughes *et al*. in 1998 reported another case of hemorrhagic cystitis treated with HBOT successfully.[7] HBOT reduces inflammation, stimulates neoangiogenesis and maintains tissue oxygenation there by heals tissue hypoxia and radio necrosis. The hemorrhage which was refractory to multiple conventional treatments resolved after a course of hyperbaric oxygen.[3-7]

## CONCLUSIONS

Our experience is in concurrence with the results described in literature. Cases with drug-induced hemorrhagic cystitis share a common histopathology with radiation-induced cystitis and both seems to be respond to HBOT. HBOT is an efficacious and safe treatment modality for patients with radiation/drug-induced hemorrhagic cystitis in whom conventional modalities of management have failed.

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