

# Hyperbaric Oxygen Therapy for Cyclophosphamide-induced Intractable Refractory Hemorrhagic Cystitis in a Systemic Lupus Erythematosus Patient

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Hemorrhagic cystitis is a complication of systemic lupus erythematosus and is also a common side effect after cyclophosphamide therapy. Intractable hemorrhagic cystitis is not unusual and may be a life-threatening condition; it has no effective noninvasive treatment at present. We report a case of hemorrhagic cystitis with intractable refractory bleeding that occurred in a 40-year-old woman after cyclophosphamide treatment for systemic lupus erythematosus. The hemorrhage was resistant to various therapies but resolved after hyperbaric oxygen therapy. There was no recurrent hematuria after hyperbaric oxygen therapy during 6 months of follow-up. [*J Chin Med Assoc* 2008;71(4):218–220]

**Key Words:** cyclophosphamide, hemorrhagic cystitis, hyperbaric oxygen, systemic lupus erythematosus

## Introduction

In patients with systemic lupus erythematosus (SLE), hemorrhagic cystitis may be caused by the disease itself or by the side effect of immunosuppressive agents such as cyclophosphamide.<sup>1</sup> Hemorrhagic cystitis is a common and sometimes life-threatening complication of cyclophosphamide treatment. A 75% mortality rate has been reported in patients with intractable refractory cyclophosphamide-induced hemorrhagic cystitis.<sup>2</sup> Several noninvasive methods have been used to treat cyclophosphamide-induced hemorrhagic cystitis, but none are effective enough to control intractable bleeding.<sup>3</sup> Hyperbaric oxygen therapy promotes capillary angiogenesis and the healing process in damaged tissue; it has been shown to be an effective treatment in the management of radiation-induced hemorrhagic cystitis. Here, we report our experience with the use of hyperbaric oxygen for the treatment of intractable

hemorrhagic cystitis in an SLE patient treated with cyclophosphamide.

## Case Report

A 40-year-old woman had been visiting our hospital for gross hematuria on and off over the past 2 years, with the problem being exacerbated in recent months. Tracing her medical history, she had SLE under regular treatment and follow-up at the rheumatology department of another hospital. She had been on cyclophosphamide for 4 years for the control of her lupus. Episodes of gross hematuria were noted for 2 years on and off.

Cystoscopy was performed due to blood clot tamponade, which revealed diffuse slough of urinary bladder mucosa with active bleeding (Figure 1). Evacuation of blood clots with cauterization of the bleeding points



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**Figure 1.** Cystoscopy shows ablation of bladder mucosa with active bleeding.

was done several times with poor response, and the bleeding persisted. Blood transfusion of 4–6 units every week was necessary to maintain the patient's hemoglobin level above 10 g/dL. She refused formalin instillation due to fear of its possible complications.

She was referred to the hyperbaric oxygen center and received 100% oxygen at 2.5 atmospheres chamber pressure for 120 minutes daily for 28 days. The bleeding diminished after the 28-day hyperbaric oxygen treatment. Another 28-day course of hyperbaric oxygen therapy was given. The bleeding ceased completely by the end of the second course of hyperbaric oxygen therapy. The patient tolerated the treatment well without any complications. She did not experience any recurrence of gross hematuria during the 6-month follow-up period.

## Discussion

Cyclophosphamide is a powerful immunosuppressive agent that is commonly used to treat neoplastic and inflammatory diseases affecting various sites. Aggressive immunosuppressive therapy with cyclophosphamide has been proven to improve the outcome of major organ preservation in SLE patients.<sup>4</sup> However, hemorrhagic cystitis is a common side effect of cyclophosphamide treatment. Its urothelial toxicity is due to the urinary excretion of acrolein, a cytotoxic metabolite of cyclophosphamide that causes sloughing of bladder mucosa. The urothelial damage has been associated with acute and chronic hemorrhage. Hemorrhage usually occurs during or immediately after cyclophosphamide treatment, while delayed hemorrhage may occur in patients on long-term therapy.<sup>5</sup>

The best way to treat cyclophosphamide cystitis is prevention. Hydration and the use of mesna (2-mercaptoethane sulfonate) have shown good results for prevention. Hydration with vigorous diuresis may dilute and wash out the urothelial-toxic metabolite to minimize its damage. Mesna combines with acrolein in the urine, so minimizing the side effects of acrolein without compromising the efficacy of cyclophosphamide.<sup>3</sup> Although mesna provides effective protection to the urothelium, hemorrhagic cystitis still occurs in 10–40% of mesna-treated patients.<sup>6</sup> Several therapeutic options have been reported for the treatment of cyclophosphamide-induced hemorrhagic cystitis. Blood clot evacuation with electrocauterization of bleeding points, intravesical instillation with alum, phenol and prostaglandins have been used to control hemorrhage, but these therapies often fail.<sup>7</sup> Intravesical instillation of formalin is an effective treatment modality to control severe hemorrhagic cystitis. Formalin may occlude and fix the telangiectatic tissue and small capillaries to control bladder hemorrhage. However, formalin instillation has significant risk of complications secondary to its fixative properties. It may cause ureteral stenosis by vesicoureteral reflux and bladder contracture due to fibrosis of the bladder wall. Its potential damage to the urinary tract means that it should be reserved as the last therapeutic option when all other nonsurgical attempts have failed.<sup>1</sup>

Hyperbaric oxygen increases the oxygen gradient between the damaged urothelium and the surrounding tissue. It induces the healing of tissue damage, decreases edema and promotes capillary angiogenesis by increasing tissue oxygen levels 10- to 15-fold. Hyperbaric oxygen has been reported to be an effective treatment modality for patients with intractable radiation-induced hemorrhagic cystitis.<sup>8,9</sup> Neheman et al reported that 82% of patients treated with hyperbaric oxygen experienced an improvement or resolution of hematuria.<sup>10</sup> Hyperbaric oxygen has been shown to be useful for the prophylaxis and treatment of experimental cyclophosphamide-induced hemorrhagic cystitis.<sup>3,11</sup> There are also several case reports concerning the successful use of hyperbaric oxygen for intractable hemorrhagic cystitis in patients undergoing cyclophosphamide treatment for malignant disease.<sup>7,12</sup>

In SLE patients, hemorrhagic cystitis may be caused by the disease itself or be the side effect of immunosuppressive agents such as cyclophosphamide. In our case, hyperbaric oxygen for the treatment of refractory hemorrhagic cystitis led to an excellent result without any complications. To our knowledge, this is the first case report on the use of hyperbaric oxygen therapy for the treatment of cyclophosphamide-induced hemorrhagic cystitis in an SLE patient.

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