Hyperbaric oxygen: an important treatment modality in severe hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation

Hiperbarik oksijen: Allojeneik hematopoietik kök hücre nakli sonrası gelişen ağır hemorajik sistit olgularında önemli bir tedavi seçeneği

Mustafa Nuri Yenerel, Sevgi Kalayoğlu-Beşışık, Oktay Perdeci, Nuray Gürses, Murat Tunç, Deniz Sargın

İstanbul University, İstanbul Faculty of Medicine, Department of Internal Medicine, Division of Hematology, İstanbul, Turkey

Abstract

Objective: Hemorrhagic cystitis (HC) is a generally self-limited complication of hematopoietic stem cell transplantation (HSCT). It may occur in the early or late posttransplant period and can promote sometimes severe morbidity. We analyzed our data regarding HC in allogeneic HSCT patients in order to establish the efficacy of hyperbaric oxygen (HBO) therapy in severe HC and to document the main problems during its use.

Material and Methods: Between March 1993 and August 2006, 161 patients received allogeneic HSCT. Mesna, hyperhydration and forced diuresis were used as early HC prophylaxis of cyclophosphamide-induced HC. However, HC was diagnosed in 49 of the 161 recipients and 17 of them were considered as severe HC. We analyzed their data retrospectively.

Results: Forced diuresis with hyperhydration (up to 8 L/day) and transfusion support to maintain a platelet count above $30x10^9$/L were sufficient in 10 of the 17 patients with severe HC. Alternative therapies used included intravesical irrigation with formalin and prostaglandin (PG)F2 alpha and HBO, and HBO appeared to be the most useful among them.

Conclusion: We conclude that HBO offers a noninvasive therapeutic alternative in the management of intractable HC in the HSCT setting. *(Turk J Hematol 2009; 26: 176-80)*

Key words: Hyperbaric oxygen, hemorrhagic cystitis, stem cell transplantation

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Özet

Amaç: Hemorajik sistit, hematopoetik kök hücre naklinin genellikle kendiliğinden düzelen bir yan etkisidir. Nakil sonrası erken ve geç dönemlerde gelişebilen bu komplikasyon bazen oldukça ağır geçebilmektedir. Biz allojeneik hematopoetik kök hücre nakli sonrası hemorajik sistit gelişen olgularımızı, özellikle hiperbarik oksijen tedavisinin bu olgulardaki etkinliğini ve kullanımda dikkat edilmesi gereken özellikler açısından değerlendirdik.

Address for Correspondence: Assoc.Prof. Mustafa Nuri Yenerel, İstanbul University, İstanbul Medical Faculty, Department of Internal Medicine, Hematology Field, Çapa, İstanbul, Turkey
Phone: +90 212 414 20 00-31613 E-mail: mnyenerel@gmail.com

Yöntem ve Gereçler: Mart 1993 ve Ağustos 2006 yılları arasında 161 hastaya allojeneik hematopoetik kök hücre nakli uygulandı. Siklofosfamide bağlı hemorajik sistit gelişimi engelleyebilmek amacıyla profilaktik olarak Mesna, hiperhidrasyon ve zorlu diürez uygulandı. Buna rağmen 161 olgunun 17'si ağır olmak üzere 49'unda hemorajik sistit gelişti. Tedavi yaklaşımı ve bulgular geriye dönük olarak değerlendirildi.

Bulgular: Zorlu diürez ve günde 8 litreye varan hiperhidrasyon tedavisi ile trombosit sayısını 30.000/mm^3 üzerinde tutacak şekilde trombosit transfüzyonları ağır hemorajik sistit olan olguların 10'unda yeterli oldu. Alternatif tedavi yaklaşımları olarak mesane içinin formalin ve prostaglandin F2 alpha ile yıkanması ile hiperbarik oksijen tedavisi kullanıldı. Bu tedavilerden en yararlısının hiperbarik oksijen olduğu gözlendi.

Sonuç: Bu nedenle özellikle hematopoetik kök hücre nakilleri sonrası gelişen inatçı hemorajik sistit olgularının tedavisinde hiperbarik oksijen uygulamasının önemli bir tedavi yaklaşımı olduğunu düşünüyoruz. *(Turk J Hematol 2009; 2009; 26: 176-80)*

Anahtar kelimeler: Hiperbarik oksijen, hemorajik sistit, kök hücre nakli

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Introduction

Hemorrhagic cystitis (HC) is a frequent complication of hematopoietic stem cell transplantation (HSCT). The reported frequency changes mainly with the definition (according to inclusion or exclusion of microscopic hematuria) and preventive manipulations. It may occur in the early or late posttransplant period and can promote sometimes severe morbidity. Several risk factors are reported to date, which include drugs, chemical toxins, infection, and pelvic irradiation [1,2]. It is mostly self-limited, and supportive treatment with hyperhydration and increased transfusion can be sufficient [3]. To facilitate the urinary flow, placement of urinary catheter is sometimes needed for intermittent or continuous bladder irrigation. Instillation of agents such as alum, silver nitrate, prostaglandin (PG) or formalin is the therapeutic intervention used to halt hemorrhage in severe HC [4-7].

Such agents are cumbersome for both patients and physicians and are seldom selected. Hyperbaric oxygen (HBO) therapy is a relatively new treatment modality for HC. The role of HBO therapy in HC was reported firstly in radiation-induced cystitis, but in recent years HBO has also been used in cyclophosphamide (CY)-induced HC [8-13]. It decreases tissue edema and ensures the necessary oxygen gradients required to stimulate continued angiogenesis, fibroblast proliferation, collagen formation, and leukocyte activation, which are required for tissue healing and repair [9]. We analyzed our data regarding HC in allogeneic (allo)HSCT patients in order to establish the efficacy of HBO therapy in severe HC and to document the main problems occurring during its use.

Materials and Methods

Between March 1993 and August 2006, 161 patients underwent alloHSCT (bone marrow transplantation (BMT): n=91; peripheral blood (PB) stem cell transplantation: n=70). All of the patients had hematological malignancies except three (aplastic anemia: n=2; paroxysmal nocturnal hemoglobinuria: n=1). The donors were all HLA-matched siblings. One hundred fifty-three of the patients received CY (60 mg/kg per day-2) as part of the conditioning regimen combined with busulfan (in 136 patients) (4 mg/kg per day divided in 4 doses-4) or total body irradiation (TBI) (in 17 patients) (1200 cGy). Mesna (6 mercapto-ethane sodium sulphonate, a sulfhydryl-containing compound) (1/2 of the CY total dose x 6), hyperhydration (3 L/m^2/day) and forced diuresis were used as early HC prophylaxis of CY-induced HC. The first dose of Mesna was given 30 minutes before CY infusion, and was followed by subsequent infusions every four hours until the day following the last dose of CY. Cyclosporine (CsA, 12.5 mg/kg per day divided in 2 doses) and a short-course of methotrexate (15 mg/m^2 per day on day-1 and 10 mg/m^2 per day on days-3,-6 and-11) were given as graft-versus-host disease (GVHD) prophylaxis. Written informed consent was obtained from all patients.

Heme dipstick testing was used as a method for hematuria investigation and was performed on a daily basis beginning with conditioning regimen until the end of hospitalization. When heme was found to be positive, the urine specimen was sent for microscopic analysis and culture. Diagnosis of HC was based on the appearance of microscopic hematuria with negative bacterial and fungal culture. HC was graded according to the following criteria: grade I, microscopic hematuria; grade II, macroscopic hematuria without clots; grade III, macroscopic hematuria with clots; and grade IV, gross hematuria and clinical complications secondary to urinary outflow obstruction. Patients with grade III and grade IV were accepted as having severe HC. Urine culture for adenovirus could be performed in only five patients. Cytomegalovirus (CMV) antigen was screened in both PB and urine samples in all the patients with HC. We did not have the opportunity to screen the urine for BK virus in our patients with HC.

When severe HC is diagnosed in our HSCT unit, forced diuresis with hyperhydration (3 L/m^2 up to 8 L/day) and transfusion support to maintain a platelet count above 30x10^9/L are the first-line treatment methods employed. Pelvic ultrasonographic examination is also performed in those patients to determine any obstruction in the vesicle and, if present, continuous bladder irrigation at 6-7 L/day through a tri-lumen irrigation catheter is also started. If severe HC is refractory to the first-line management, we choose alternative therapies such as intravesical instillation of PG (200 micrograms in 50cc isotonic sodium chloride solution), formalin and/or HBO therapy. We could not perform alum irrigation in our patients.

HBO therapy: Patients were referred to the HBO center. All patients received HBO therapy in a single room. They received 100% oxygen at 2.5 atmospheres chamber pressure for 120 minutes daily at least one month but continued until the symptoms subsided and bleeding completely disappeared. All calculations were performed using the SPSS software package, version 14 (SPSS Inc, Chicago, IL, USA)

Results

Hemorrhagic cystitis was diagnosed in 49 of 161 (30%) HSCT recipients at a median +39 days (range: from -2 to +241 days). HC occurred in 25 of the 70 alloPBSCT group (36%) and in 24 of the 91 BMT group (26%), and the difference was not statistically significant (p=0.228).

Seventeen of the 49 HC cases (8 BMT, 9 PBSCT) were described as severe HC (>grade II). Although most of our patients with HC responded to the first-line therapies, HC affected the morbidity in a median of 12 days (range: 4- 90 days). Nine of the patients died before resolution of HC with complications of severe GVHD.

Four of the HC cases (8.1%) developed in the first week of the transplantation and preparative regimens in these cases included CY and busulfan. Urine culture for adenovirus was found to be positive in one case. CMV antigenemia was also observed in six of the patients with HC.

The results of all patients with HC: Forced diuresis with hyperhydration up to 8 L/day and transfusion support to maintain a platelet count above $30x10^9$/L were sufficient in all the patients with mild HC and in eight of the 17 patients with severe HC. Cystoscopy was needed in 14 of the patients and evacuations of the hematoma were performed before increasing the irrigation solutions up to 30-40 L/day. Vesical sarcoma was diagnosed in one case with cystoscopy and the patient underwent radical cystectomy. Alternative therapies were applied in eight of the patients. The first patient was successfully treated with intravesical formalin irrigation therapy. The next patient did not respond to formalin and then intravesical PGF2 alpha irrigation and was successfully treated with HBO 2.4 atmospheres absolute (30 minutes 3 times daily for 8 days).

The results of HBO therapy: We performed HBO as a first-choice alternative therapy in another six patients. All results for these seven cases are summarized in Table 1. We found HBO therapy quite useful in our first four cases. We followed our patients with weekly CMV antigenemia and noted CMV reactivation in our fifth patient after three days of HBO and stopped the therapy. This patient died with multiorgan failure after three months follow-up and HC never resolved. We only used three and four days of HBO therapy, respectively, in our last two patients and they also died with severe GVHD and severe HC in a short period of two weeks.

Discussion

Hemorrhagic cystitis can occur at any time after HSCT and may affect the morbidity of the procedure. The incidence of HC varies considerably according to the preparative regimen, the preventative measures employed and perhaps the incidence of GVHD. HC occurring during or shortly after the conditioning regimen of high-dose chemotherapy or chemoradiotherapy is referred to as early-onset [14]. Oxazaphosphorine drugs such as CY or ifosfamide have been widely used as preparative regimen agents. The acrolein formed as a urinary byproduct of the metabolism of these drugs is thought to be responsible for

Table 1. Clinical findings and therapy results of 7 patients with intractable hemorrhagic cystitis (HC)

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age, sex	42, Male	32, Female	22, Male	20, Female	26, Male	23, Female	21, Female
Disease	CML	CML	CML	CML	T-ALL	B-ALL	CML
Stem cell source	PBSC	PBSC	BMT	PBSC	BM	BM	BM
Preparative regimen	Bu/CY	Bu/CY	Bu/CY	Bu/CY	Bu/CY	Bu/CY	Bu/CY
GVHD grade		2	-	-	22	2	
HC grade and time	III, day +69	II, day +32	III, day +27	III, day +60	IV, day +45	IV, day +60	IV, day +32
Alternative therapies	Intravesical formalin, PGF2	-	-	-	-	-	
Duration	3 weeks	21 days	5 weeks	21 days	3 months	?	?
HBO response (Until asymptomatic)	in 8 days	in 10 days	in 14 days	in 9 days	-	-	
HBO duration	35 days	40 days	60 days	40 days	3 days	3 days	4 days
HBO complication	none	none	none	none	CMV reactivation??	none	none
Last visit	Exitus	Alive	Alive	Alive	Exitus	Exitus	Exitus

CML: Chronic Myelogenous Leukemia ALL: Acute Lymphoblastic Leukemia PBSC: Peripheral Blood Stem Cell BM: Bone Marrow

the urothelial toxicity [1]. We use Mesna and hyperhydration protocol for the prevention of CY-induced HC in our Unit. In our study, since only four out of 49 HC cases (8.1%) developed in the first week of the transplantation, we consider this to be quite effective in preventing early-onset HC. Preparative regimens of these cases were also composed of busulfan, which may have been an additional risk factor for early HC in these patients [15]. We observed an incidence of HC of 30% in our study, which is comparable with the other reports (1,16). We analyzed our patients to see if stem cell source had any effect on this complication, but were unable to determine any statistically significant difference with respect to incidence or severity of the HC (p=0.228 and p=0.445, respectively).

Hemorrhagic cystitis cases occurring weeks to months after HSCT are referred to as late-onset HC. Early HC is one of the recognized risk factors for late HC, but significant proportions of the late HC cases are reported to be associated with viruria and/or GVHD. The viruses most frequently implicated in HC are BK polyomavirus and adenovirus type 11 [16-18]. HC is generally self-limited and usually resolves in a few days to weeks without any sequelae. Occasionally, intermittent or persistent hematuria may be severe enough to require frequent transfusions. In more severe cases, cystoscopy should be performed to determine any problems with the vesical mucosa and to remove blood clots, followed by continuous bladder irrigation [19]. We diagnosed vesical sarcoma in one of our patients who required cystoscopy. Eight of the severe HC cases in our study failed to respond to standard management. Formalin and PGF2a were chosen for intravesical instillation in addition to bladder irrigation and platelet transfusions in two patients, respectively. Formalin was effective in controlling bleeding but PGF2 was not, which was likely due to insufficient doses because of the limited supply of this drug in our country [20]. Our first patient became asymptomatic in eight days with HBO therapy. We used this treatment modality in all seven cases with intractable HC. We used HBO therapy without any other alternative therapies in our other three responding patients, who became asymptomatic in 10, 14 and 9 days of HBO, respectively. We used HBO until microscopic hematuria disappeared in those patients. We followed our patients with weekly CMV antigenemia and determined CMV reactivation in our fifth patient after three days of HBO therapy. Although it might have been a coincidental finding in such a patient with severe GVHD, we thought HBO therapy might have facilitated the reactivation of GVHD and stopped the therapy despite persistent HC in that patient. We were unable to use HBO effectively in our last two patients because of severe CMV infection and graft failure symptoms and death was anticipated. We did not want to accept these cases as HBO- unresponsive because of the very short duration of the therapy.

Clinical and experimental studies suggest that HBO could be useful in preventing chemotherapy-induced HC [21-23]. HBO is considered as an adjunctive treatment to medical and surgical care. HBO induces the healing of tissue damage, decreases edema and promotes capillary angiogenesis by increasing tissue oxygen levels. Plafki et al. [24] reviewed complications and side effects in 782 patients treated for various indications, with a total of 11,376 HBO therapy sessions, and summarized that the predominant complication is related with pressure equalization problems within the middle ear. We did not observe any complication directly related with HBO therapy. We did observe CMV reactivation coincidentally during HBO therapy, and even though we could not determine any deleterious effect such as viral reactivation, we stopped the therapy. There are some reports speculating that HBO therapy has an antiviral effect in hepatitis B and human immunodeficiency virus infection [25,26]. We conclude that moder ately severe HC can be treated conservatively in most patients. When hyperhydration, transfusion support and intravesical irrigation fail to treat HC, addition of HBO therapy may be beneficial, and HBO treatment should be considered without further delay.

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