



CASUISTRY

Management of hemorrhagic radiation cystitis with hyperbaric oxygen therapy

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Received August 31, 2010; accepted September 18, 2010

KEYWORDS

Radiation Therapy;
Radiation-induced
cystitis;
Bladder hemorrhage;
Hyperbaric oxygen
therapy

Abstract

Introduction and objectives: Hemorrhagic cystitis (HC) after pelvic radiotherapy occurs in 2–8% of patients. A variety of treatments have been described, most of them with uncertain results. We assessed the efficacy of hyperbaric oxygen therapy (HBOT) in HC cases.

Patients and methods: Retrospective analysis of patients with HC after pelvic radiotherapy receiving HBOT at our center between January 2002 and January 2010. Our protocol included 40 sessions of HBOT in a multiplace hyperbaric chamber with 90 minutes of 100% oxygen breathing at 2.2 atm. Success was evaluated in terms of total or partial stop of bladder bleeding. Telephone follow-up was updated at the time of submission in all cases.

Results: Twenty-five patients were treated (21 male, 4 female); the mean age was 66.7 years. Twenty men were irradiated for prostate cancer and one for bladder cancer. Three women had cervix cancer and one endometrial cancer. In all cases previous conservative treatment had failed and HBOT was considered only after other measures failed. All the patients responded to HBOT and none recurred after end of treatment at a mean follow-up of 21.2 months. There were no serious complications.

Conclusion: HBOT is a highly effective and safe, non-invasive therapy for HC secondary to pelvic radiation; it should be considered as a first-line alternative in these difficult cases.

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PALABRAS CLAVE

Radioterapia;
Cistitis actínica;
Hemorragia vesical;
Oxigenoterapia
hiperbárica

Tratamiento de la cistitis actínica hemorrágica mediante oxigenoterapia hiperbárica**Resumen**

Introducción y objetivo: La cistitis actínica (AHC) secundaria a la radioterapia pélvica ocurre en 2-8% de los pacientes. Se han descrito múltiples tratamientos con resultados variables, habitualmente frustrantes. Nuestro objetivo fue evaluar la eficacia de la oxigenoterapia hiperbárica (OHB) como tratamiento de la AHC.

Material y métodos: Análisis retrospectivo de los pacientes con AHC secundaria a radioterapia pélvica que recibieron OHB entre enero de 2002 y enero de 2010. Los pacientes recibieron 40 sesiones de OHB en una cámara hiperbárica multiplaza, respirando 90 minutos de oxígeno al 100% a 2,2 atm. Se evaluó la respuesta con relación al cese total o parcial de la hemorragia.

Resultados: Veinticinco pacientes fueron tratados (21 varones y 4 mujeres), con edad promedio de 66,7 años. Veinte hombres fueron irradiados por cáncer de próstata y uno por cáncer de vejiga. Tres mujeres tenían cáncer de cuello uterino y una cáncer de endometrio. En todos los pacientes habían fracasado los tratamientos conservadores previos y la OHB fue considerada sólo tras fallar otras medidas. Todos los pacientes respondieron al tratamiento con OHB y ninguno ha presentado recidiva después de terminar el tratamiento en un período de seguimiento promedio de 21,2 meses. No hubo complicaciones graves.

Conclusión: La OHB es un tratamiento no-invasivo, altamente eficaz y seguro para el tratamiento de la AHC secundaria a radioterapia pélvica, por lo que debe considerarse como alternativa de primera elección en estos complejos casos.

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Introduction

One of the recognized complications of pelvic radiation is hemorrhagic cystitis (HC). Its etiology is related to chronic damage of the bladder mucosa secondary to radiation therapy, which produces atrophy of the mucosa, hypovascularity, hypoxia and ischemia of the tissue, mucosal ulceration and subsequent bleeding.¹ Radiation therapy may also alter the tissue's regenerative capacity, so that lesions tend to not heal. Damage due to radiation may vary in extent depending on each individual case, on the dosage administered and on the area affected by the radiation. Clinically, HC may be asymptomatic or can be very disabling, manifested itself by irritant bladder symptoms, urinary urgency and frequency, bladder pain, hematuria, and bleeding to different extents. This bleeding may occur intermittently or be acute and massive, in which situation we would talk about radiation-induced hemorrhagic cystitis (AHC). The incidence of AHC ranges from 2% to 8%; it may appear from 2 months to 10 years after irradiation^{2,3} and may represent a urologic emergency that requires transfusions and different hemostatic procedures.

Multiple treatments have been tried to control the bleeding, whether systemic, such as the administration of tranexamic acid, or local therapies such as bladder irrigation and irrigation with saline solution usually associated with instillation of formalin or aluminum or silver nitrate solutions. Invasive procedures are also often required, such as endoscopic coagulation of the bleeding points with various methods of hemostasis, and even extreme measures such as ligation or embolization of the hypogastric vessels or, finally, cystectomy. All these procedures have their own

morbidity and overall results are disappointing or transient. A percentage of these patients require complex bypass surgery, as demonstrated by Kaplan and Wolf in a series of 33 patients with AHC, of which up to 39% required more than one procedure of cystoscopy with bladder lavage and 12% underwent cystectomy and urinary diversion with ileal conduit.⁴

Hyperbaric oxygen therapy (HBOT) emerged during the 80's as a treatment alternative proposed by several working groups, based on the correction of the causal mechanism of the bladder lesion, as hyperbaric oxygen enhances angiogenesis, tissue regeneration and improves healing. This therapy was initially tested in cases in which other management alternatives had failed, and the results were favorable, both regarding efficacy and safety,^{5,6} which is why it is today normally proposed as part of primary treatment.⁷ We present our experience with the use of HBOT in the management of radiation-induced hemorrhagic cystitis.

Patients and methods

We performed a retrospective analysis of medical records of patients diagnosed with AHC who were subjected to HBOT at the Department of Baromedicine of the Hospital del Trabajador in Santiago, between January 2002 and January 2010. Hemorrhagic cystitis was confirmed by cystoscopy and when necessary, a biopsy was performed to rule out malignancy. Diagnoses were recorded by which pelvic radiotherapy was performed and the time between the latter and the beginning of the AHC, as well as the time between

the AHC and the initiation of treatment with hyperbaric oxygen therapy. Our protocol includes 40 sessions of HBOT in a multiplace hyperbaric chamber, 90 minutes breathing 100% oxygen at 2.2 atm. Complications were described in the medical records or reported directly by patients. Response was evaluated in relation to the total or partial cessation of bleeding. Patient follow-up was based on data from the clinical records and by telephone control.

Results

During the period under review, we treated 25 patients, 21 males and 4 females. The average age was 66.7 years (range 42-80). Twenty males were irradiated for prostate cancer (17 of them adjuvant to radical prostatectomy and 3 as primary treatment). Three women were irradiated for cervical cancer and endometrial cancer. All patients had previously undergone one or more bladder lavage procedures with elimination of clots and/or cauterization under anesthesia. One patient received irrigation with aluminum. HBOT was considered only after the failure of these initial measures. The mean follow up was 21.2 (range 3-66) months. The average interval between radiotherapy and AHC was 31 (range 1-106) months, and the occurrence of AHC and the beginning of HBOT therapy was 4.7 (range 1-12) months. Mean HBOT was 40 sessions (range 15-44).

All patients responded to HBOT with progressive and complete disappearance of macroscopic bleeding. Only one patient had an intra-treatment hemorrhage in session 29, which required KTP laser coagulation before completing the 40 sessions, who later evolved favorably. To date no patient has required invasive treatment or hospitalization due to bleeding after completion of treatment. In our series, success was not related to the time between the occurrence of AHC and the initiation of HBOT.

As regards complications, there were two cases of barotraumatic otitis. In one of the patients it was resolved by means of myringotomy, subsequently achieving complete treatment with oxygen therapy. In the other patient, the symptoms appeared in session 30 and it was treated with analgesics, anti-inflammatories and decongestants, with good response. No other complications were observed.

Discussion

Radiation-induced damage to tissues has been associated with hypoxia and obliteration of blood vessels, chronic hypoxia and ischemic damage. This condition may become manifest from weeks to several years after radiation. These phenomena cause ischemia, ulceration and tissue breakdown, which tend to persist due to poor reparative inflammatory response mediated by the weak capacity to replace lost collagen and cells in the irradiated tissues.⁷ The persistence of these alterations is responsible for the long-term effects of radiation therapy. There is evidence that microvascular endothelial damage is a major effector of radiation-induced tissue damage.⁸

The presentation of AHC is varied, ranging from mild hematuria, intermittent and transient, to heavy bleeding

that requires transfusions and fluid replacement. The current management of AHC includes bladder lavages, saline irrigation and intravesical instillations of aluminum or silver nitrate solutions. Additionally, it is often necessary to perform endoscopic coagulation of bleeding lesions, sometimes to clear arterial embolization and even cystectomy and urinary diversion in the most extreme cases. None of these conservative treatments is able to stop or reverse tissue damage secondary to radiation therapy, therefore their results are often transient and relapses are the norm. On its part, hyperbaric oxygen therapy has consistently proven to be successful in the treatment of radiation-induced lesions in various tissues,⁹ and also in the healing of chronic wounds in different areas.¹⁰ Hyperoxygenation enhances angiogenesis, fibroblast proliferation, increased aerobic metabolism and secondary vasoconstriction resulting in the reduction of the chronic edema. These mechanisms boost tissue repair. It has been proven that HBOT increases the vascular density of irradiated tissue by 8 to 9 times in comparison with control tissues in normobaric oxygen conditions.¹¹ This angiogenesis occurs as a consequence of HBOT and continues with time. This has been proven with transcutaneous tissue oxygen measurements in a follow-up of up to 4 years.¹²

Due to the limited availability of hyperbaric chambers and the low application rate of this therapy, until now, this treatment has been applied in only the most serious cases in which one or more previous treatment alternatives have failed. In 1995, Bevers et al. presented the first prospective series of 40 patients with significant hemorrhagic cystitis, with a mean follow-up of 23 months, in whom at least one previous treatment had been unsuccessful. These authors obtained complete remission of bleeding in 75%, 12.5% partial response and 12.5% failure of treatment.⁶

Neheman et al. had an experience with 7 patients in whom they achieved complete short-term remission in all the cases and recurrence in two patients (27%).⁷ The series presented by Del Pizzo et al. shows less encouraging results, since it ultimately achieved remission of bleeding in 3 of 11 patients (27%).¹³ Five cases of this series had recurrent bleeding up until the fifth month and in 3 there was no response. All the patients included had undergone previous failed treatments.

Of a total of 57 evaluable patients, Corman et al. reported an 86% complete response with an average of 33 sessions.¹⁴ Chong et al. achieved complete or partial response in 80% of 60 cases. Furthermore, they demonstrated statistically significant efficacy independent of prior therapy and better results when oxygen is applied within the first six months of onset of bleeding.¹⁵

Mathews et al. obtained a complete response in 11 of 17 patients that had previous unsuccessful therapies (64%).¹⁶ Additionally, they were able to demonstrate a statistically significant benefit in those who received oxygen therapy earlier, i.e., within the first two weeks of onset of bleeding. In our series, there was no significant difference in response according to the time of evolution of the AHC prior to the initiation of HBOT.

Table 1 presents a comparative analysis of the different series published in literature.^{5-7,13-19} If we combine our

Table 1 Principal series of patients with radiation-induced hemorrhagic cystitis treated with hyperbaric oxygen therapy

Author, year	Citation	no.	Mean follow-up (months)	Sessions	No. of patients with total and partial response (%)
Weiss et al, 1994	5	13	30	51	12 (92%)
Beyers et al, 1995	6	40	23.1	20	37 (92%)
Norkool et al, 1993	17	14	23.2	28	10 (71%)
Del Rizzo et al, 1998	13	11	30	40	8 (73%)
Mathews et al, 1999	16	17	21	14	11 (64%)
Corman et al, 2003	14	57	10-120	33	49 (86%)
Neheman et al, 2005	7	7	24	30	7 (100%)
Chong et al, 2005	15	60	12	33	48 (80%)
Yoshida et al, 2008	18	8	15.5	19	6 (75%)
Mohamad Al-Ali et al, 2010	19	14 (10)*	18	30	2 (20%)
Current series		25	21.2	37.7	25 (100%)
Total		237	25.2	30.5	215 (90.7%)

*Of the 14 patients, only 10 received treatment.

experience with the series shown in this compilation, a combined response rate can be observed, considering a cumulative total and partial response of 90.7% in a case series of 237 patients treated. There was no morbidity associated with the procedure in any of the series, and there were only anecdotal cases of claustrophobia and reversible otic problems.¹⁴

The work of Mohamad Al-Ali et al. is interesting. It is a retrospective study that compares two groups of AHC, in which 10 patients received HBOT and 4 did not.¹⁹ In the group treated, only two patients recovered, which was less than the spontaneous resolution observed in the control group without HBOT. This low response is noticeable, as it contrasts with reports from all the other authors. Several factors may have influenced these results, such as patient age, smoking, radiation dosage and different comorbidity. Our success rate of 100% at almost two years of follow-up is also surprising, which we must take with caution. It is possible that in future some of our patients may relapse and this rate may thus decrease. However, a recurrence of the bleeding would not prevent retreatment, considering that it is a non-invasive therapy that is virtually devoid of complications. However, there is no serious experience in the field of recurrence therapy.

In summary, hyperbaric oxygen therapy is a noninvasive treatment that involves administering 100% oxygen at a pressure higher than atmospheric pressure. It seems to be a highly effective and safe treatment for AHC secondary to pelvic radiation and therefore, in our opinion, it should be considered as an alternative choice in these complex cases. Although the evidence generated is based on retrospective series and is from the same institution, the experience reflected in the literature with this treatment seems satisfactory. In this regard, an important, multicenter, double-blind and randomized study is being conducted to definitively evaluate the efficacy of HBOT in the treatment of radiation cystitis.²⁰ Its findings will no doubt be welcome.

Conflict of interest

The authors declare that they have no conflict of interest.

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