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Original Article: Clinical Investigation

Hyperbaric oxygen therapy for refractory radiation-induced hemorrhagic cystitis

Tiago M Ribeiro de Oliveira,[1,2] António J Carmelo Romão,[2] Francisco M Gamito Guerreiro[1] and Tomé M Matos Lopes[2]

[1]Underwater and Hyperbaric Medicine Center, Portuguese Navy, and [2]Department of Urology, Hospital de Santa Maria, Lisbon, Portugal

Abbreviations & Acronyms
HBO = hyperbaric oxygen
RIHC = radiation-induced hemorrhagic cystitis
RT = radiotherapy

Correspondence: Tiago M Ribeiro de Oliveira M.D., Rua Quinta da Formiga n°5, 3°esquerdo, 1495-170 Algés, Portugal. Email: tiagoribeirooliveira@sapo.pt

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Objectives: To analyze the efficacy of hyperbaric oxygen for the treatment of radiation-induced hemorrhagic cystitis and to identify factors associated with successful treatment.

Methods: Clinical records from 176 patients with refractory radiation-induced hemorrhagic cystitis treated at the Portuguese Navy Center for Underwater and Hyperbaric Medicine, during a 15-year period, were retrospectively analyzed. Evolution of macroscopic hematuria was used to analyze treatment efficacy and correlated with other external variables.

Results: From a total of 176 treated patients, 23.9% evidenced other radiation-induced soft tissue lesions. After an average on 37 sessions, 89.8% of patients showed resolution of hematuria, with only 1.7% of adverse events. In our sample, hematuria resolution after treatment with hyperbaric oxygen was statistically associated to the need for transfusion therapy ($P = 0.026$) and the number of sessions of hyperbaric oxygen ($P = 0.042$). No relationship was found with the remaining variables.

Conclusions: Refractory radiation-induced hemorrhagic cystitis can be successfully and safely treated with hyperbaric oxygen. Treatment effectiveness seems to be correlated with the need for transfusion therapy and the number of sessions performed.

Key words: cystitis, hematuria, hyperbaric oxygenation, proctitis, radiation injuries.

Introduction

RT is often used in the treatment of pelvic malignancies.[1–7] Despite the latest technological advances, collateral soft tissue lesions are still relatively frequent.[8–10] Because of its high morbidity and mortality, hemorrhagic cystitis is one of the most important late adverse effects of pelvic irradiation.[11,12] Ionizing radiation limits cellular growth and is associated with progressive obliterating endarteritis, and hypocelullar, hypovascular and hypoxic transformation of the vesical mucosa, with edema, ulceration, decreased regeneration and fibrosis, which are responsible for the symptoms of cystitis.[10,13,14] Although conservative techniques are considered the first-line treatment for RIHC, because of their low long-term effectiveness, most patients ultimately depend on more aggressive surgical procedures to control hematuria.[12,15–17]

Through the increase of tissue oxygenation, HBO is able to stimulate angiogenesis, leukocyte activity, fibroblastic proliferation and collagen formation, and has therefore been effectively used to treat hypoxic tissues, with a significant increase in tissue regeneration.[10,13,18–22] Despite growing evidence in favor of HBO use as a treatment modality for RIHC, due to reduced patient samples, its global effectiveness and the influence of external variables have not yet been properly analyzed.[21–27]

We aimed to analyze the effectiveness of HBO in the treatment of RIHC and to verify the influence of a number of external variables.

Methods

Study population

Clinical records from patients treated at the Portuguese Navy Center for Underwater and Hyperbaric Medicine, from August 1994 to September 2009, were retrospectively analyzed, in accordance with the ethics committee's regulations. This study was a case–control analytic

observational study, with a non-randomized convenience sample of patients treated with HBO for RIHC.

Patients were referenced for routine treatment in our center, from urology departments of several hospitals nationwide, with confirmed diagnosis of RIHC, after at least one adequate conservative treatment modality proved ineffective. Every patient underwent a previous tympanogram, followed by a global medical assessment consultation to exclude conditions contraindicated for hyperbaric chamber treatment.

Intervention and follow up

Patients were exposed to 100% oxygen at 2.5 atm, in a multiplace first class hyperbaric chamber, for 90-min periods, once daily, five times per week. During the initial consultation, 20 sessions were prescribed, after which the patient attended a decision consultation, in which the need for further treatment was assessed (10 or 20 sessions).

At the end of treatment, patients were evaluated at our center and referenced back to their original hospital, where further follow-up consultations were carried out (usually with a quarterly clinical evaluation during the first year). Patients showing recurrence of symptoms were referenced back to our center for further evaluation. For patients with severe symptoms showing no improvement with HBO, more aggressive treatment modalities were considered, namely embolization or surgery. As patients treated at our center came from different regions of the country, for some patients it was not possible to obtain the full follow-up data.

Covariates and end-points

Analyzed variables included patient sex, age (years), type of malignancy, total radiation dose (Gy), concomitant radiation-induced soft tissue lesions (proctitis or enteritis), time between RT and hematuria (months), need for transfusion therapy, time between RT and HBO (months), time between hematuria and HBO (months), number of HBO sessions, HBO side-effects, symptom recurrence and follow-up period (months).

The primary clinical outcome measure after HBO was evolution of macroscopic hematuria, categorized as "resolution," which included complete resolution (absence of macroscopic hematuria) and partial resolution (reduction of frequency or severity of macroscopic hematuria), or as "no resolution," which included absence of variation (same frequency and severity of macroscopic hematuria) and aggravation (increase of frequency or severity of macroscopic hematuria).

Statistical analysis

Clinical data was analyzed using Statistical Package for Social Sciences, version 16.0 (SPSS, Chicago, IL, USA). Descriptive statistics (frequencies and proportions for categorical variables and mean, median and percentiles for continuous variables) and the χ^2-test (two-sided Pearson χ^2-test with two degrees of freedom) were used. Statistical significance was considered for P-values <0.05.

Results

Sample characterization

Tables 1 and 2 describe the baseline characteristics of our sample, which included a total of 176 patients, 111 women and 65 men, aged 15–85 years. The most frequent indications for pelvic irradiation were uterine cervix cancer and prostate cancer (50.6% and 31.8%, respectively).

With a mean total radiation dose of 56 Gy, 23.9% of patients developed additional radiation-induced soft tissue lesions (radiation-induced proctitis or enteritis). Regarding the severity of macroscopic hematuria, 19.3% of patients required transfusion support. A mean 13.69-month period between the onset of hematuria and HBO institution was found.

Table 1 Baseline sample characterization (categorical variables), including patient sex, type of malignancy, presence of concomitant radiation-induced soft tissue lesions, need for transfusion therapy and presence of HBO side-effects

	% (*n*)
Sex	
Female	63.1 (111)
Male	36.9 (65)
Type of malignancy	
Uterine cervix	50.6 (89)
Prostate	31.8 (56)
Endometrial	9.7 (17)
Bladder	4 (7)
Rectum	1.7 (3)
Ewing's sarcoma	1.1 (2)
Ovarian	0.6 (1)
Vulva	0.6 (1)
Concomitant radiation-induced soft tissue lesions	
Yes	23.9 (42)
No	76.1 (134)
Need for transfusion therapy	
Yes	19.3 (34)
No	80.7 (142)
HBO side-effects	
Yes	1.7 (3)
No	98.3 (173)

Table 2 Baseline sample characterization (continuous variables), including patient age, total radiation dose, time between radiotherapy and hematuria, time between hematuria and HBO, time between radiotherapy and HBO, number of HBO sessions, and follow-up period

	Mean (range)
Age (years)	61.91 (15–85)
Total radiation dose (Gy)	56.27 (40–71)
Time between RT and hematuria (months)	55.72 (0–313)
Time between hematuria and HBO (months)	13.69 (0–168)
Time between RT and HBO (months)	69.41 (5–326)
No. HBO sessions	36.53 (7–179)
Follow-up period (months)	12 (0–108)

With an average of 37 HBO sessions delivered, adverse events developed in only 1.7% of patients, namely three patients with mild middle ear barotrauma. The mean follow-up period after hyperbaric oxygen therapy conclusion was 12 months.

Hyperbaric oxygen therapy effectiveness

The evolution of macroscopic hematuria, the main therapeutic outcome, is characterized in Table 3. After HBO conclusion, 89.8% of patients showed resolution of hematuria (67% complete resolution of hematuria and 22.7% partial resolution of hematuria), with just 10.2% of patients with no resolution of hematuria (9.1% absence of variation of hematuria and 1.1% aggravation of hematuria). A total of 24 patients (15.2%) had recurrence of hematuria in the available follow-up period.

Relationship of hematuria resolution rates with the remaining variables

Table 4 represents the pattern of hematuria resolution rates according to the distribution of seven different variables. In order to allow a more comprehensive analysis of the available data, the four considered continuous variables were categorized into clinically relevant categories (representing at least 20% of the total sample), as described further on.

When patient sex was considered, there was no significant difference between the group of patients with hematuria resolution and the group of patients without hematuria resolution after HBO ($P = 0.738$).

Regarding the indication for pelvic irradiation, given the reduced number of patients with some types of malignancies (endometrium, bladder, rectum, Ewing's sarcoma, ovarian or vulva), only the two most frequent malignancies (namely uterine cervix cancer and prostate cancer) were statistically analyzed. There was no significant difference between the group of patients with hematuria resolution and the group of patients without hematuria resolution after HBO when the type of malignancy was considered ($P = 0.228$).

There was a statistically significant difference in the distribution of patients according to the need for transfusion support in the group with hematuria resolution and the group without hematuria resolution after HBO ($P = 0.026$), with the group with hematuria resolution having 82.9% of patients without previous need for transfusions, versus 61.1% in the group without hematuria resolution.

Time from RT to hematuria onset and time from RT to HBO institution were categorized in three periods: up to 2 years (≤24 months), from 2 to 4 years (25–48 months) or more than 4 years (>48 months). Time from hematuria onset to HBO institution was categorized in three periods: up to 1 month (≤1 month), from 2 to 6 months (2–6 months) or more than 6 months (>6 months). The distribution of patients with resolution and without resolution of hematuria after HBO according to the time from RT and hematuria onset, time from hematuria onset and HBO or time from RT and HBO did not show a statistical association between either of the considered variables and hematuria resolution after HBO ($P = 0.236$, 0.199 and 0.44, respectively).

The number of HBO sessions was categorized into three groups: up to 20 sessions (≤20 sessions), from 21 to 40

Table 3 HBO effectiveness, including the evolution of macroscopic hematuria and symptom recurrence

	% (*n*)
Hematuria	
Complete resolution	67 (118)
Partial resolution	22.7 (40)
Absence of variation	9.1 (16)
Aggravation	1.1 (2)
Hematuria	
Resolution	89.8 (158)
No resolution	10.2 (18)
Recurrence	
Yes	13.6 (24)
No	86.4 (152)

Table 4 Analyzing hematuria resolution rates according to the distribution of the considered categorical and continuous variables (after categorization)

	Hematuria, % (*n*)		
	Resolution	No resolution	*P*-value
Sex			
Female (*n* = 111)	62.7 (99)	66.7 (12)	0.738
Male (*n* = 65)	37.3 (59)	33.3 (6)	
Type of malignancy			
Uterine cervix (*n* = 89)	59.8 (79)	76.9 (10)	0.228
Prostate (*n* = 56)	40.2 (53)	23.1 (3)	
Endometrial (*n* = 17)	16	1	
Bladder (*n* = 7)	5	2	
Rectum (*n* = 3)	3	0	
Ewing's sarcoma (*n* = 2)	1	1	
Ovarian (*n* = 1)	1	0	
Vulva (*n* = 1)	0	1	
Need for transfusion therapy			
Yes (*n* = 34)	17.1 (27)	38.9 (7)	0.026
No (*n* = 142)	82.9 (131)	61.1 (11)	
Time between RT and hematuria			
≤24 months (*n* = 66)	35.4 (56)	55.6 (10)	0.236
25–48 months (*n* = 48)	28.5 (45)	16.7 (3)	
>48 months (*n* = 62)	36.1 (57)	27.8 (5)	
Time between hematuria and HBO			
≤1 month (*n* = 36)	22.2 (35)	5.6 (1)	0.199
2–6 months (*n* = 68)	38.6 (61)	38.9 (7)	
>6 months (*n* = 72)	39.2 (62)	55.6 (10)	
Time between RT and HBO			
≤24 months (*n* = 38)	20.3 (32)	33.3 (6)	0.44
25–48 months (*n* = 48)	27.8 (44)	22.2 (4)	
>48 months (*n* = 90)	51.9 (82)	44.4 (8)	
No. HBO sessions			
≤20 sessions (*n* = 70)	39.9 (63)	38.9 (7)	0.042
21–40 sessions (*n* = 57)	34.8 (55)	11.1 (2)	
>40 sessions (*n* = 49)	25.3 (40)	50 (9)	

P-values were obtained with the χ^2-test. Regarding the type of malignancy requiring radiotherapy, only the two most frequent malignancies were considered (uterine cervix and prostate).

sessions (21 to 40 sessions) or more than 40 sessions (>40 sessions). There was a statistically significant difference in the distribution of patients between each of the considered categories in the group with hematuria resolution and the group without hematuria resolution after HBO ($P = 0.042$).

Discussion

Ionizing radiation causes hypoxia and tissue fibrosis through the limitation of cellular and vascular proliferation, and has therefore been extensively used in the therapeutic management of different types of cancer. Consequently, short- and long-term soft tissue lesions on collateral tissues have become relatively common.[8,10,13] Through the increase of tissue oxygenation, angiogenesis and fibroblastic proliferation, hyperbaric oxygen therapy has been shown to be effective in the treatment of radiation-induced soft tissue lesions.[13,20]

Hemorrhagic cystitis is one of the most important long-term side-effects of pelvic radiotherapy.[11] Although several conservative techniques have been used to treat RIHC, their long-term effectiveness has proven to be limited.[12] Reflecting the good results shown in some studies with HBO for the treatment of RIHC,[23–27] the Undersea and Hyperbaric Medicine Society considers RIHC an indication for HBO.[13]

According to a systematic review by Feldmeier and Hampson, in 2002 a total of 17 published case–control studies were available worldwide regarding the use of HBO for RIHC.[28] From a total of 190 patients treated, 145 (76.3%) showed resolution of macroscopic hematuria after hyperbaric oxygen therapy. Nevertheless, and considering that apart from a more recent study by Chong *et al.* (with a sample of 60 patients)[24] all published studies have relatively small samples, it is still not possible to obtain significant conclusions regarding the global effectiveness of HBO and the influence of external variables.

With a total of 176 patients with RIHC treated with HBO, the present study almost doubles the number of cases described in the literature.[28] In our sample, almost 90% of patients treated with HBO showed complete or partial resolution of macroscopic hematuria. These data are particularly relevant considering that our sample consists of patients referenced to our center after at least one adequate conservative technique proved ineffective. The hematuria resolution rate was slightly higher in our series when compared with other studies, which is probably because of differences between samples.[27,28]

For an average of 12 months follow up for each patient treated, the hematuria recurrence rate was relatively low (15.2%), which is in line with the available literature.[29] However, as the majority of patients treated in our center were referenced from hospitals nationwide, an adequate follow-up period was not always possible. For that reason, we chose not to test if the recurrence rate was statistically related to other variables analyzed.

Considering that a considerable proportion of our sample consisted of female patients, most indications for pelvic RT were primary malignancies of the female genital system. The second most frequent indication for pelvic irradiation was prostate cancer. In our sample, patient sex and type of malignancy were not statistically related to the hematuria resolution rate, which suggests that these parameters might not be relevant in the prediction of the response rate of HBO.

In addition to hemorrhagic cystitis, 23.9% of patients developed other radiation-induced soft tissue lesions, namely proctitis and enteritis. As HBO has been proven to be effective for the treatment of other radiation-induced soft tissue lesions, we believe that HBO should be considered as a first-line therapy for patients with concomitant radiation-induced lesions.[13,21]

The severity of macroscopic hematuria was analyzed through the need for transfusion support. A total of 19.3% of patients required transfusions before HBO was instituted. In our sample, there was a statistically significant association between the need for previous transfusion therapy and the response to HBO ($P = 0.026$), which might be related to more severe cases of RIHC. According to these results, we consider that the need for transfusion therapy can be a good parameter to predict the response rate to hyperbaric oxygen therapy. Nevertheless, as other conservative techniques have shown limited results, and given that even in these patients high hematuria resolution rates were achieved after HBO, we consider that the need for transfusion support must not be a motive to exclude HBO treatment in patients with RIHC.[12]

Although some studies advocate that the time from the onset of macroscopic hematuria to the institution of HBO seems to influence its therapeutic effectiveness,[24] in our sample no statistical relationship was found between the hematuria resolution rate and the time from RT to the onset of hematuria, the time from RT to HBO or the time from hematuria onset to HBO, which suggests that these variables do not seem to be important in the prediction of the response rate to HBO. Nevertheless, it is important to mention that the group of patients with hematuria resolution had 22.2% of patients with ≤1 month and 39.2% of patients with >6 months from hematuria onset to HBO institution versus 5.6% and 55.6%, respectively, in the group without hematuria resolution after HBO, which could indicate a tendency to achieve better treatment responses with the early institution of HBO.

The number of HBO sessions required to treat RIHC has been a controversial issue.[23,27] In our series, there was a statistical relationship between hematuria resolution and the number of sessions of HBO ($P = 0.042$), with the group of patients with hematuria resolution having 39.9% of patients with ≤20 sessions and 25.3% of patients with >40 sessions, versus 38.9% and 50%, respectively, for the group without hematuria resolution after HBO. Although these results could reflect the presence of more severe and refractory cases of RIHC, they can provide new information regarding the adequate number of HBO sessions for patients with refractory RIHC.

From a total of 176 patients, three suffered adverse events as a result of treatment in a hyperbaric chamber, all mild and without long-term consequences. Therefore, when compared with other therapeutic modalities for RIHC, and after an adequate selection of patients, HBO can be considered a relatively safe technique, that bares a small number of mild, well-known and easily manageable risks.[12]

For some patients, it was not possible to obtain detailed information regarding malignancy histology, total radiation dose, prior diagnostic exams and therapeutic modalities before HBO, number of transfusions, and number and severity of each hematuria episode. This lack of thorough clinical information for some patients, as well as the lack of adequate follow-up information, are the main limitations of our study and derive from the fact that patients treated in our center are referred from different hospitals nationwide.

In conclusion, this is, at the present time, the largest study regarding the use of HBO for RIHC. There was a high prevalence of concomitant radiation-induced soft tissue lesions, which grants hyperbaric oxygen a major role in the treatment of these patients. The present results can also help to define the adequate number of HBO sessions, namely for patients with more severe and refractory symptoms.

With vast therapeutic effectiveness and reduced adverse event potential, HBO proved to be the best conservative technique available for the treatment of RIHC, especially in patients with refractory symptoms and concomitant radiation-induced soft tissue lesions.

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Conflict of interest

None declared.

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