HYPERBARIC OXYGEN THERAPY FOR THE MANAGEMENT OF HEMORRHAGIC RADIO-INDUCED CYSTITIS

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Summary.- OBJECTIVES: Radio-induced cystitis (RADC) is an inflammatory bladder disease that presents as anemic-hematuria in its most serious form. Classic treatments can not control the disease in the mid-to-long term because they don’t treat the pathogenesis of the disease. Thus, we evaluated the effectiveness of hyperbaric oxygen (HBO) therapy as a potential treatment for patients with RADC.

METHODS: This prospective study included 38 patients, 21 men and 17 women, mean age of 66.5 years (46-75), who had been subjected to pelvic radiotherapy (RT), with the diagnosis of RADC with or without radio-induced proctitis (RADP), gross hematuria and lower urinary tract symptoms. HBO treatment was applied in a multi-place chamber; patients breathed pure oxygen (100%) at 2-2.5 atmospheres of pressure (ATAs). Patients received an average of 31.2 sessions (10-48 sessions) and the median follow-up period was 56 months (4-72 months).

RESULTS: Hematuria was completely resolved in 34 of the 38 patients. After HBO 6 patients required readmission, 5 for anemic hematuria and 1 for acute obstructive pyelonephritis. In general, patients tolerated treatment well; however, one patient experienced barotrauma requiring myringotomy.

CONCLUSIONS: HBO can be used to satisfactorily treat RADC, leading to clinical improvements that begin during the initial sessions in the majority of cases, and with a more than acceptable level of patient tolerance.

Keywords: Prostate adenocarcinoma. Radiotherapy. Hyperbaric oxygen therapy. Hemorrhagic cystitis.

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Resumen.- OBJETIVO: La Cistitis rádica (CRAD) es una enfermedad inflamatoria vesical que se presenta de forma más grave como hematuria anemizante. Los tratamientos clásicos no consiguen controlar la enfermedad a medio-largo plazo ya que no actúan sobre su patogénesis. Evaluamos la respuesta clínica de pacientes con cistitis radioiducida tras ser tratados mediante Oxigenoterapia Hiperbárica.

MÉTODOS: Estudio prospectivo en el que se incluyen 38 pacientes, 21 hombres y 17 mujeres, edades desde los 46 a los 75 (media de edad de 66.5 años) sometidos a radioterapia (RT) pélvica, diagnosticados...
INTRODUCTION

Currently, radiotherapy (RT) is used in the treatment of many pelvic cancers. In spite of the administration of individualized doses and the restriction of the treated areas, there are still side effects that affect healthy tissue due to DNA damage caused by ionizing energy (1-4). One of the possible and most severe urological complications of RT is radio-induced hemorrhagic cystitis (RADC).

The pathogenesis of RADC originates as a progressive obliteration of the small blood vessels of the bladder wall with consequent development of hypoxia and tissue damage. This pathology can occur long after radiation treatment has ended, from 2 months to 15 years later. Previous case studies have observed that 3-5% of RT patients develop RADC. A study by Levenback et al. reported the highest rate of RADC; in that study, 1784 women who had been administered RT due to stage Ib cervical cancer were followed over 29 years, and the rate of hemorrhagic cystitis was 6.5% (5).

Classic treatment methods, whether conservative or more aggressive, have not been very effective for the treatment of RADC in the mid-to long-term (6, 7). Because the clinical benefits of hyperbaric oxygen (HBO) therapy for the treatment of pathologies stemming from hypoxia have been described for decades (8), in this study, we aimed to evaluate the effectiveness of HBO in the management of RADC.

MATERIALS AND METHODS

This prospective study included patients with hemorrhagic radio-induced bladder injury +/- radio-induced proctitis (RADP) who were treated with HBO. We used the classification system of the Radiation Therapy Oncology Group (RTOG) to objectively establish the level of bladder disease (Table I).

Selection of patients

Patients selected for this study had undergone previous treatment with RT and had a confirmed diagnosis of RADC with or without the presence of RADP.

RADC was definitively diagnosed by the existence of diffuse, patchy ulceration with vascular ectasia of the vesical mucosa by urethrocystoscopy.

Treatments prior to the application of HBO

During this study, 14 patients received HBO treatment the first time, whereas 24 had received previous treatment with HBO. We did not consider continuous vesical irrigation to be a specific treatment for hematuria due to RADC, but rather as a containment measure.

Method of treatment application

For the HBO treatment, 100% oxygen was administered via a nasal cannula at an ambient pressure that oscillated from 2 to 2.5 atmospheres (ATAs) during 90-minute sessions. Sessions occurred 5 times per week in an IBERCO® multi-seater hyperbaric chamber that had individual seats, a capacity for 12 patients and the capability to generate an ambient pressure of up to 6 bars (Figure I). A complete treatment protocol was considered to be 20 sessions/patient.

Follow-up protocol for patients

Patient follow-up included 1 visit per month after the end of treatment, followed by a visit every 3 months during the first year after treatment and an
HYPERBARIC OXYGEN THERAPY FOR THE MANAGEMENT OF HEMORRHAGIC RADIO-INDUCED CYSTITIS

We administered a monthly telephone questionnaire to all of the patients throughout a maximum period of three years in which we inquired about the presence of hematuria, including to what degree and with what frequency hematuria occurred as well as any subjective improvements that occurred after HBO therapy.

RESULTS

We set the cut-off point for follow-up of the patients at 5 years after the beginning of the study. Demographics of patients are shown in Table II.

We included a total of 26 patients with level 3 RADC and 12 patients with level 4 RADC.

Previous to HBO, 18 patients received concentrated red blood cell transfusions; the criteria for these transfusions varied as a function of the general state of the patient and their hemoglobin levels.

The number of sessions were 20-48, and the average number of sessions per patient was 31.2.

Of the 38 patients, 6 (15.8%) required urgent readmission to the hospital, with 5 (83.3%) of the readmissions being for anemic macroscopic hematuria and 1 for acute obstructive pyelonephritis.

After an average follow-up of 36.3 months (12-60 months), hematuria was completely resolved in 36 (94.7%) patients. One patient (2.6%) had been presenting with occasional non-anemic hematurias due to a recurrence of her neoplastic illness (endometrial cancer), and another patient (2.6%) died months after completing the treatment due to complications from his malignancy.

Only 18 patients consistently participated in the telephone surveys during the 12-month follow-up period; the results of these surveys are summarized in Table III.

DISCUSSION

An increase in oxygen would, in theory, provide a clear benefit to certain pathologies in which hypoxia is the main physiopathological mechanism. However, hemoglobin does not have an “infinite” capacity for the transport of oxygen (O2), but rather becomes saturated such that each gram of 100% saturated hemoglobin is associated with 1.34ml of O2. Thus, the challenge in raising O2 levels in the body is delivering a larger quantity of O2 to hypooxygenated tissues; this delivery is achieved by increasing the quantity of oxygen dissolved in

<table>
<thead>
<tr>
<th>Grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLADDER</td>
<td>Nothing</td>
<td>Atrophic epithelium changes.</td>
<td>Frequency telangiectasy hematuria</td>
<td>High frequency and urgency gross hematuria hemorrhagic at mucosa bladder accommodation&lt;150cc</td>
<td>Necrosis at mucosa gross severe hematuria bladder accommodation&lt;100cc</td>
<td>Death</td>
</tr>
</tbody>
</table>

FIGURE 1. Hyperbaric chamber at hospital General Castellon.
the blood with HBO administration (11). There is evidence that high O2 concentrations promote neoangiogenesis, neosteogenesis, neocollagenesis and reactivation of O2-mediated polymorphonuclear neutrophil phagocytosis in level 1 RADC (12).

Clinical benefits of HBO for illnesses stemming from tissue hypoxia have been described for decades (13-15). For urological diseases, the most desirable use of HBO is for the treatment of RADC. Ionizing radiation produces a patchy and hemorrhagic inflammation of the vesical mucosa. Patients generally present with hematuria and problems with and/or pain during urination; the latter two symptoms may appear in isolation or, more frequently, in association with hematuria (16,17).

Treatment with HBO has yielded good results in the management of radio-induced hemorrhagic cystitis, as is evidenced by multiple studies that were published prior to 2010, with a total of 359 patients treated and an overall response rate of 87% (18-26). Of these studies, the study by Bevers et al. has particular significance due to its inclusion of a larger number of patients (40 patients) (18). The aim of this study was to elucidate whether a relationship existed between the severity of RADC symptoms and the response to HBO treatment. Symptoms of recurrent bleeding at the 1-year follow-up were due to tumor recurrence in the patient groups with light and moderate hematuria and to a recurrence of RADC in the group with serious hematuria. Thus, the response to HBO treatment appears to depend on the severity of the hematuria, and recurrent bleeding is generally due to tumor recurrence.

At the 1-year follow-up of our study, patients with light and moderate hematuria had a response rate of 100%, whereas those who had presented with serious hematuria had a response rate of 75%; one patient (2.6%) had recurrent bleeding due to tumor recurrence. Taken together, our global response rate (94%) is similar to the rates reported in previous studies.

There is still controversy about the number of sessions necessary for control of RADC, with the preferred number oscillating between 20 and 40 sessions/patient, although the current trend is to approach 40 sessions/patient (19). The average

### TABLE II. DEMOGRAPHICS OF PATIENTS; P: PATIENTS.

<table>
<thead>
<tr>
<th>Rt doses</th>
<th>74 Gray (64-106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRAD</td>
<td>27 p</td>
</tr>
<tr>
<td>CRAD+PRAD</td>
<td>11 p</td>
</tr>
<tr>
<td>Gross hematuria</td>
<td>38 p</td>
</tr>
<tr>
<td>Gross hematuria+anemizing</td>
<td>18 p</td>
</tr>
<tr>
<td>Lower urinary tract symptoms</td>
<td>16 p</td>
</tr>
<tr>
<td>Suprapubic pain</td>
<td>12 p</td>
</tr>
<tr>
<td>Diagnostic proves:</td>
<td></td>
</tr>
<tr>
<td>ECO</td>
<td>18 p</td>
</tr>
<tr>
<td>CITOLOGY</td>
<td>18 p</td>
</tr>
<tr>
<td>CT SCAN</td>
<td>12 p</td>
</tr>
<tr>
<td>CYSTOSCOPY</td>
<td>3 p</td>
</tr>
<tr>
<td>ANATOMICAL STUDY</td>
<td>1 p</td>
</tr>
</tbody>
</table>

### TABLE III. TREATMENTS PREVIOUS TO HBO.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caproic acid</td>
<td>8</td>
</tr>
<tr>
<td>Alum solution</td>
<td>10</td>
</tr>
<tr>
<td>Transuretral electrocoagulation</td>
<td>4</td>
</tr>
<tr>
<td>embolization</td>
<td>2</td>
</tr>
</tbody>
</table>
HYPERBARIC OXYGEN THERAPY FOR THE MANAGEMENT OF HEMORRHAGIC RADIO-INDUCED CYSTITIS

The number of sessions/patient was 31.2 in our study, and we observed that hematuria began to be controlled at session 20. Thus, our study would agree with the notion that seems most widely accepted in that early adoption of HBO more effectively controls bleeding.

Only one other study has used HBO as the primary treatment for RADC (20); that study had a successful response rate of approximately 95% with an average of 30 sessions/patient. Although only 7 patients were treated in this study, the results are quite similar to those presented in the current study, where HBO was administered as the primary treatment for RADC in 18 patients and also resulted in the achievement of early control of the illness.

With respect to the evaluation of the effectiveness of HBO, almost all studies have used hematuria as a factor for appraising the response to the treatment because the correlation between cystoscopic improvement of the vesical mucosa and diminution of hematuria is well established (21). In addition, there have been few published side effects, and those that have been reported are almost all due to changes in the ambient barometric pressure. Accordingly, in our study, 1 patient experienced an episode of barotrauma that required a myringotomy but had no additional occurrences. The rest of patients tolerated the treatment well.

CONCLUSIONS

In this study, we present a significant number of patients who were treated with HBO for RADC.

With respect to the resulting control of the illness and the tolerance of the treatment, our results were similar to those previously reported in the literature with the exception that this was a prospective study.

Based on the results of this study, it would be appropriate to begin HBO treatment in patients with RADC at an early stage, without a need for categorizing patients and establishing beforehand the number of sessions, but rather administering as many treatment sessions as are necessary for control of hematuria.

We observed that the tolerance of this treatment by the patients was good, with few side effects. Thus, in our opinion, HBO is an effective, safe and well-tolerated method that can be used for the management of RADC, and we recommend its use for treatment of this pathology.

REFERENCES AND RECOMMENDED READINGS

(*of special interest, **of outstanding interest)

3. Barbagelata López A, Ponce Díaz-Reixa JL, Romero Selas E, Gómez Veiga F, Fernández Rosado E, González Martín M. External beam radiotherapy on locally advanced prostate carcinoma follo-

<table>
<thead>
<tr>
<th>QUESTION</th>
<th>PREVIOUS HBO</th>
<th>AFTER HBO (12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>How are you worried about the disease?</td>
<td>38 p Very much</td>
<td>0 p Very much</td>
</tr>
<tr>
<td></td>
<td>0 p much</td>
<td>8 p much</td>
</tr>
<tr>
<td></td>
<td>0 p A little</td>
<td>4 p A little</td>
</tr>
<tr>
<td></td>
<td>0 p nothing</td>
<td>0 p nothing</td>
</tr>
<tr>
<td>Do you feel better than pre HBO?</td>
<td>10 p Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>2 p No difference</td>
<td></td>
</tr>
<tr>
<td>How often is the hematuria?</td>
<td>0 p 1/week</td>
<td>0 p 1/week</td>
</tr>
<tr>
<td></td>
<td>0 p 2/week</td>
<td>2 p 2/week</td>
</tr>
<tr>
<td></td>
<td>38 p More than 2/week</td>
<td>0 p More than 2/week</td>
</tr>
</tbody>
</table>
wing iliac staging lymphadenectomy. Actas Urol Esp. 2006 Oct;30(9):856-65