Narrative review of hyperbaric oxygen therapy for radiation induced hemorrhagic cystitis

Robert Dieu[1], Kevin Heinsimer[2]^

[1]Morsani College of Medicine, University of South Florida, Tampa, FL, USA; [2]Department of Urology, University of South Florida, Tampa, FL, USA

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Correspondence to: Kevin Heinsimer, MD. University of South Florida, 2 Tampa General Circle, STC Floor 6, Tampa, FL 33606, USA.
Email: kheinsimer@usf.edu.

Abstract: To evaluate the benefits of hyperbaric oxygen in the treatment of radiation-induced hemorrhagic cystitis (HC). Hyperbaric oxygen has been shown to be an effective long-term treatment for early and late radiation- and chemotherapy-induced HC. It has been proven safe for adult and pediatric patients. Treatment typically required 10–40 "dives" for 60–120 min, making it very time intensive for patients. Complete response has been reported in up to 87% of patients with recurrence ranging from 0–35% in most studies. It works both as an initial treatment and after less time-intensive therapies have failed. Better responses have been seen with initiation within 6-month of presentation. Additional risk factors for treatment failure include: higher radiation doses, more severe hematuria, incomplete treatment, and blood thinner use. In addition to being effective for hematuria, it has also been shown to improve the lower urinary tract symptoms associated with radiation cystitis. Repeat treatments are effective for some patients, but if hematuria fails to resolve after hyperbaric oxygen therapy (HBOT), patients must be reassessed for malignancy as a source of their hematuria. The overall complication rate is low, and these tend to be self-limited with the most common adverse effects being blurred vision and ear pain which resolve after treatment. While expensive and time intensive, it may prove to be cheaper in the long run and offer a better alternative to patients otherwise facing bladder embolization or cystectomy.

Keywords: Radiation cystitis; hemorrhagic cystitis (HC); hyperbaric oxygen; hematuria; pelvic radiation

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Introduction

Hemorrhagic cystitis (HC) is characterized by diffuse inflammation and bleeding from the bladder mucosa often arising in the setting of pelvic radiotherapy for pelvic malignancy (e.g., prostate, bladder, rectal, or gynecologic) or chemotherapy (e.g., ifosfamide, cyclophosphamide).

Radiation cystitis has a reported incidence of 6.5% following radiation therapy for pelvic malignancy. Late radiation tissue injury to the bladder may develop from 6 months to 20 years following radiation treatment, with a mean of 35.5 months following completion of pelvic radiotherapy (1). In addition to hematuria, presenting symptoms may include urgency, frequency, nocturia, and dysuria.

Severity of radiation toxicity may be graded using criteria

^ ORCID: 0000-0002-4400-0294.

defined by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), the Radiation Therapy Oncology Group (RTOG), or the European Organization for Research and Treatment of Cancer (EORTC) (2,3).

Initial workup of HC includes urinalysis, urine culture to exclude infectious etiology, as well as cytology, cystoscopy, and upper urinary tract imaging in order to evaluate for primary and secondary malignancy.

First-line treatment of HC includes conservative management with bladder irrigation with clot-evacuation, IV hydration and transfusion as necessary. Should conservative management fail, second-line treatments consist of intravesical instillation of astringents such as alum, aminocaproic acid, or silver nitrate. Systemic therapy with sodium pentosan polysulfate, conjugated estrogen, and tetrachlorodecaoxide (WF10) have also been described (4). In addition to intravesical and systemic therapies, cystoscopy and fulguration of bleeding vessels using electrocautery or laser may be used (5). If these measures fail, more invasive or time intensive options include hyperbaric oxygen therapy (HBOT), arterial embolization, or urinary diversion with or without cystectomy.

HC represents a continued clinical challenge following pelvic radiotherapy. Should conservative management fail, more aggressive interventions such as formalin instillation and urinary diversion are associated with relatively increased morbidity, thus HBOT represents a low-risk alternative. Clear consensus regarding the systematic management of radiation-induced HC has yet to be established. The goal of this review is to summarize key findings regarding the use of HBOT for HC, including response rate, risk factors for treatment failure, adverse effects, and cost. We present the following article in accordance with the Narrative Review reporting checklist (available at https://amj.amegroups.com/article/view/10.21037/amj-20-178/rc).

Methods

Literature search was performed using the electronic MEDLINE (PubMed) and Cochrane Library databases. Search was performed using of the following keywords either individually or in combination: “hemorrhagic cystitis”, “pelvic radiation”, “refractory hematuria”, “hyperbaric oxygen”, and “radiation cystitis”. Articles were screened via abstract and full-text reading. Manual search of the references of selected articles was also performed as needed. Only titles and abstracts in English were included. We did not limit articles reviewed by date of publication.

Discussion

Mechanism of action

Hyperbaric oxygen is defined by the Undersea and Hyperbaric Medical Society as inhaling near-100% oxygen in a hyperbaric chamber pressurized to 1.4 atmosphere absolute (ATA) or greater (6). HBOT chambers may be single-occupancy (monoplace) or multiple-occupancy (multiplace). Typically, a complete course of treatment includes 20–40 once-daily sessions or “dives” at 2–2.5 ATA, each lasting 60–120 min.

Under hyperbaric conditions breathing 100% oxygen at 3 ATA, combined oxygen content in whole blood may increase by 42% from baseline owing to an increase in gaseous oxygen dissolved within plasma (7). HBOT is unique in the setting of radiation-induced HC as it is thought to cure radiation-induced cystitis by way of reversing the pathophysiology of radiation injury, whereas other treatments such as intravesical instillation provide solely therapeutic benefit (8). HBOT is thought to reverse radiation injury by increasing oxygen delivery to damaged tissue, restoring function to macrophages, fibroblasts, and granulocytes during wound healing as well as directly promoting neovascularization of ischemic tissue (9). This angiogenesis appears permanent, as normalization of tissue oxygen persists for years after HBOT (10). The aforementioned effects (tissue hyperoxia, leukocyte activation, and stimulation of angiogenesis) have also been shown to have benefit in chemotherapy-induced HC. It has been demonstrated that rats treated with HBOT both before and after intravesical acrolein instillation had significantly increased intact urothelium compared to those untreated. In addition, rats which received HBOT exhibited urothelial hyperplasia earlier than those which were untreated. These results suggest that HBOT limits urothelial injury and enhances urothelial regeneration in the setting of chemotherapy-induced HC (11).

HBOT outcomes for HC

The first publication of HBOT for refractory hematuria was by Weiss *et al*. in 1985. The authors showed resolution of hematuria in 3 patients with HC secondary to pelvic radiotherapy without recurrence for up to 14 months. Symptomatic improvement was accompanied by cystoscopic

Table 1 Outcomes of studies for HBOT for radiation-induced HC

Author	Year	Number of patients	Mean duration of follow up in months [range]	Complete response rate, N [%]	Partial response rate, N [%]	Patients with recurrence of hematuria, N [%]	Treatment failures, N [%]	Mean radiation dose in Gray [range]
Bevers *et al.*	1995	40	13 [1–74]	30 [75]	7 [17.5]	7 [17.5]	3 [7.5]	N/A
Del Pizzo *et al.*	1998	11	61.2 [38.4–102]	3 [27]	N/A	5 [45]	8 [73]	75 [60–96]
Corman *et al.*	2003	62	48 [10–120]	21 [34]	28 [45]	N/A	8 [13]	N/A
Oliai *et al.*	2012	11	39 [7–70]	9 [81]	2 [18]	4 [36]	0 [0]	[50–75.6]
Shao *et al.*	2011	20	18	9 [45]	15 [75]	N/A	N/A	[45–70]
Nakada *et al.*	2012	38	139.2 [88.8–230.4]	26 [81]	N/A	10 [26]	2 [5.3]	67 [46–96]
Liss *et al.*	2013	22	26.4 [4.2–163.2]	11 [50]	N/A	N/A	5 [23]	70
Ribeiro de Oliveira *et al.*	2015	176	12 [0–108]	118 [67]	40 [22.7]	24 [13.6]	18 [10.2]	56.27 [40–71]
Mougin *et al.*	2016	71	15 [1–132]	37 [52.1]	9 [12.7]	19 [26.8]	25 [35.2]	66 [45–138]
Dellis *et al.*	2017	38	29.3 [3–94]	33 [86.8]	5 [13.2]	3 [7.9]	2 [5.3]	63.8 [32–80]

HBOT, hyperbaric oxygen therapy; HC, hemorrhagic cystitis.

evidence of reversal of tissue injury following HBOT (8). Several retrospective studies have continued to report success with HBOT in the setting of both radiotherapy-induced and chemotherapy-induced HC, summarized in *Table 1*.

There is significant variability between HBOT protocols. The systematic review performed by Villers *et al.* report as few sessions as one and as many sessions as 179, although typically protocols specified anywhere from 10 to 40 sessions. Pressures ranged from 1.8 to 2.5 ATA, and sessions lasted from 60–120 min (12). In the study conducted by Dellis *et al.*, all patients were assigned up to 45 sessions of HBOT (1.8 ATA for 90 minutes per day, five days per week) with cessation of HBOT should complete response be reached. If no benefit was observed after 45 sessions, significant complications occurred, or the patient declined further HBOT, conservative or surgical management was then pursued. In this study, the average number of sessions was 32 (range, 27 to 44) (13).

Although most reports have focused on adult patients, there has been some investigation into the efficacy of HBOT in the pediatric setting. In a 1995 case series, HBOT was demonstrated to be efficacious and well-tolerated as therapy for osteoradionecrosis in 3 patients, age 3.5 to 11 years old. Authors report complete resolution of osteonecrosis following treatment, with no major side effects (14). HBOT has also been successfully used to treat refractory HC in a pediatric setting, Furness *et al.* first report resolution of HC following HBOT in an 18-month-old girl with HC secondary to cyclophosphamide and radiation therapy for bladder embryonal rhabdomyosarcoma (15). In 2004, Bratsas *et al.* reported successful treatment of refractory HC in a 15-year-old boy caused by cyclophosphamide for acute B-cell lymphoblastic leukemia, with no further hematuria 2 years later (16). However, there is little literature which directly discusses isolated radiation-induced HC in the pediatric population. The majority of investigations address pediatric HC in the setting of bone marrow transplant, where the etiology of HC is multifactorial and has been associated with primarily with chemotherapy conditioning regimens and reactivation of BK virus and adenovirus (17).

Meta-analysis by Cardinal *et al.* demonstrated an overall response rate (partial or complete resolution) of 84%, with the complete response rate ranging from 20% to 100% (18). On study, Del Pizzo *et al.* reported a complete response rate at 73% at a median follow up of 2.5 years; however, at median follow up of 5 years only 27% (3 of 11) experienced complete and durable resolution of symptoms. The remaining 8 patients ultimately required urinary diversion. The authors note that their cohort received high initial doses of radiation (mean 75 Gy) and underwent HBOT only after failing previous treatment; factors which may have contributed to

their observed rate of treatment failure (19).

While HBOT is typically used following failure of more conventional treatment, it has been demonstrated effective as the primary treatment of HC. A prospective study performed by Dellis *et al*. in 2017 report an 86.8% complete response rate and 13.2% partial response rate using HBOT as primary therapy for severe HC requiring transfusion (20). These reports further suggest that HBOT may be considered prior to intravesical instillations, which may exacerbate bladder fibrosis and reduce compliance (13).

Recurrence rate of HC after initially successful treatment with HBOT is approximately 14% (18). For patients who show a positive response to a first course of HBOT but subsequently recur, retreatment with HBOT appears to be effective. Corman *et al*. report a durable response in 66% (4 of 6) of patients who underwent re-treatment with HBOT for recurrence of hematuria at a mean of 18 months after completion the first course of therapy (10). Mougin *et al*. report that retreatment with HBOT was effective in 89% (8 of 9) patients who underwent re-treatment with HBOT, supporting retreatment in patients with an initial good response (21).

HBOT outcomes for lower urinary tract symptoms

The efficacy of HBOT with regards to improving lower urinary tract symptoms associated with HC has also been investigated. In 2013, Oscarsson *et al*. investigated the effect of HBOT on symptoms of radiation-induced cystitis. Urinary symptoms were measured by the urinary domain of the Expanded Prostate Cancer Index Composite (EPIC). Originally designed for prostate cancer, the EPIC urinary domain evaluates urinary symptoms including urgency, frequency, nocturia, hematuria and incontinence (22). A good quality of life was defined as an EPIC score ≥80 and clinically significant improvement is an increase of 10 points. In Oscarsson's cohort of 29 patients undergoing HBOT, 76% experienced improvement in EPIC urinary total score with 31% achieving EPIC urinary total score ≥80 (22). In 2019, a phase 2–3 trial, Radiation-Induced Cystitis treated with Hyperbaric oxygen—A Randomized controlled Trial (RICH-ART), compared the effect of HBOT *vs*. standard care on quality of life outcomes including EPIC urinary total score. Ultimately, RICH-ART found a 17.8-point improvement in EPIC urinary total score in the HBOT arm compared to a 7.7-point improvement in the standard care arm (P=0.013). On further analysis, 40% of patients in the HBOT arm scored ≥80 on the EPIC urinary total score, versus 9% of patients in the standard care group (23). These results are corroborated by Nakada *et al*., who demonstrate improvement in dysuria, frequency, and bladder irritability in 88%, 78%, and 78% of patients, respectively, following HBOT at a mean of 11.6 years follow up (24). These findings demonstrate that HBOT is effective in alleviating the lower urinary tract symptoms associated with HC and thus represents an important therapeutic option for improving patient quality of life.

Risk factors for treatment failure

Clinical factors at have shown to be associated with effectiveness of the HBOT include timing of HBOT, previous radiation dose, previous number of transfusions, and use of anticoagulation.

Compliance is an important factor to consider when assessing the efficacy of HBOT, as patients may be unable to complete the prescribed number of sessions. However, data is limited regarding the minimum effective number of HBOT sessions. There has been no statistical analysis of patients who fail to complete the full course of HBOT, and studies vary on how completion of treatment is defined. A retrospective series by Corman *et al*. found that of 57 patients, 8 showed no resolution of hematuria, of those 8 who did not improve, authors noted that 3 received fewer than 30 sessions of HBOT (10). In contrast, Degener *et al*. describe seven patients who completed fewer than 30 sessions, of these, six patients (85.7%) experienced resolution of hematuria (9). Ribeiro de Oliveira *et al*. categorized the number of HBOT sessions into three groups, finding that 20 or fewer sessions, 21–40 sessions, and more than 40 sessions was associated with 38.9%, 11.1%, and 50% of patients with continued hematuria, respectively (P=0.042) (25). These results demonstrate the difficulty of separating the effect of number of HBOT treatments from the severity of HC.

In the studies assessed, age was not found to be a statistically significant risk factor for poorer response to HBOT. In the retrospective study performed by Chong *et al*., there did appear to be improved outcomes in younger patients—patients with complete resolution, partial resolution, no change, and worsened hematuria had mean ages of 69, 70, 75, and 80 years old, respectively. However, the authors caution that these results are inconclusive as they did not control for concomitant comorbidities and risk factors such as diabetes, smoking, or atherosclerosis (26).

Dellis *et al*. report when comparing patients with

complete response *vs*. partial response, there was a statistically significant difference in time-to-HBOT after onset of hematuria (4.9 *vs*. 22 months, P<0.001), with all patients with complete response having received HBOT within 6 months of hematuria (20). Similarly, Chong *et al*. found that patients who had HBOT initiated within 6 months of onset of hematuria had a better response rate to treatment compared to those who were started later than 6 months (96% *vs*. 66% respectively, P=0.003). They also found that response rate was independent of previous intravesical therapy (26). Nakada *et al*. also found that patients who had HBOT initiated later were more likely to have recurrent hematuria compared to those who had it initiated earlier (24). These results suggest that early initiation of HBOT, potentially within 6 months of onset of hematuria, may confer a better response.

Higher doses of radiation have been associated with worse response to HBOT. Nakada *et al*. found that patients who experienced recurrence of hematuria received an 18% higher (72 *vs*. 62 Gy, P<0.001) radiation dose compared to those who did not recur (24).

Response to HBOT has also been correlated to the initial severity of hematuria. Mougin *et al*. demonstrate that using the CTCAE grading criteria, hematuria grade <3 (defined as hematuria with clots or warranting hospital admission) was associated with a successful therapeutic outcome (HR 4.4, P=0.01) (21). Taking the need for transfusion support as a measure of disease severity, Ribeiro de Oliveira *et al*. showed that patients with resolution of hematuria were less likely to have to have required transfusion support (17.1% versus 38.9% in the group without resolution, P=0.026) (25).

It is unsurprising that HC is also more challenging in patients in which cessation of anticoagulation is not possible. For patients on anticoagulation, Bouaziz *et al*. and Mougin *et al*. both showed use of anticoagulation during HC was a predictor of treatment failure (21,27). In the analysis by Mougin *et al*., antiplatelet and anticoagulant therapies were stopped as soon as possible according to evaluation by a cardiologist and an anesthesiologist.

Lastly, failure to respond to HBOT may be an indication of underlying malignancy, and while HC work up includes evaluation for bladder cancer as a source of the hematuria, failure to respond to treatments without other risk factors may warrant a high suspicion for malignancy. Bevers *et al*. had a total of 9 patients with continued hematuria following HBOT. Of these 9 patients, 7 were found to have cancer which was previously masked by HC. In these patients, assessment of bladder pathology at the time of cystoscopy was limited by bleeding, edema and inflammation (28). In a cohort studied by Norkool *et al*., three patients demonstrated presence of cancer on cystectomy following recurrence of hematuria after HBOT. All three had negative biopsies prior to HBOT, but experienced initial improvement followed by recurrence of hematuria requiring cystectomy (29). Similarly, Dellis *et al*. describes a patient with refractory HC after HBOT. The patient ultimately underwent cystectomy and urinary diversion, with final pathology revealing muscle-invasive bladder cancer (20). With this in mind, malignancy should remain a consideration following recurrence of hematuria after complete or partial response to HBOT, especially if assessment of malignancy during pre-treatment cystoscopy is limited by the symptoms of HC or symptoms are refractory to conservative management.

Adverse effects

A major benefit regarding the use of HBOT is its low incidence of major adverse effects. Systematic review by Villeirs *et al*. reveals a pooled adverse event rate of 9.6% with a range of 0% to 33.3% (12). A Cochrane systematic review of HBOT for late radiation tissue injury reports the most common adverse effects associated with HBOT as temporary myopia and middle-ear barotrauma resulting directly from compression, with myringotomy being required in up to 5% of cases (9,30). Ear pain is also common, occurring in up to 33.3% of patients (31). These side effects typically resolve after cessation of treatment. More severe side effects of HBOT include central nervous system toxicity leading to seizure, pulmonary O_2 toxicity, and pneumothorax, although these have not been reported in the setting of treatment for HC. Due to the risk of previously mentioned side effects, relative contraindications for HBOT include underlying seizure disorder, severe emphysema or COPD, and history of spontaneous pneumothorax (32).

Another concern of HBOT is that it may lead to proliferation of underlying malignancy due to angiogenesis; however Chong *et al*. found that HBOT did not appear to accelerate the growth of human prostate cancer cells injected into severe combined-immunodeficient mice (33). Although there have been reports which support the possibility of a stimulatory effect of HBOT on underlying malignancy, the majority of literature reports a neutral of inhibitory effect. Feldmeier *et al*. compiled results of 15 clinical reports in which patients were exposed to

HBOT. finding that 72 patients were involved in studies where HBOT exposure was associated with recurrence or progression of cancer, compared to more than 3,000 patients in studies which report a neutral or inhibitory effect of HBOT. Furthermore, they indicate that hypoxic tumor cells have been demonstrated to release angiogenic growth factors, behave more aggressively, and exhibit increased drug resistance (34). Similarly, Daruwalla *et al*. reiterate that reoxygenation of hypoxic tumor cells has been shown to induce degradation of angiogenic growth factors (35). Ultimately Feldmeier *et al*. and Daruwalla *et al*. conclude that the majority of evidence suggests that HBOT does not directly contribute to increased tumor growth or recurrence.

Cost

Radiation-induced HC is associated with significant economic costs to the patient and the healthcare system. Radiation cystitis has been found to have a median cost $7,151 per hospitalization per patient (36). HBOT costs anywhere from $200 to $500 per dive, with >20 dives, the total costs can be $8,700 to $20,000 for a complete course of treatment (10,29,37). Comparing these two, HBOT may provide significant cost savings in the setting of HC when initiated early in the protocol to prevent re-admissions and repeated intravesical treatments. In Australia, Smart *et al*. conducted a cost-analysis case study comparing costs associated with radiation cystitis prior to and after treatment with HBOT. In the 2.5 year following HBOT, healthcare costs were $231.09/day prior to HBOT compared to $19.08/day after treatment with HBOT (38). While expensive, HBOT decreases the need for additional admissions and treatments, and may provide the health care system with an overall savings.

Conclusions

HBOT is an effective treatment for HC associated with high success rates and few adverse effects. Data supports better outcomes when used earlier in patients with HC suggesting it should be considered as a first-line treatment. Alternative treatments for HC are invasive in nature may damage bladder tissue whereas HBOT is non-invasive and treats both bleeding and lower urinary tract symptoms associated with radiation cystitis. Current barriers to widespread adoption include high upfront cost, limited availability, and intensive time requirement for treatment. While HBOT will not work for every patient, if the alternative is urinary diversion with cystectomy, HBOT offers a lower risk, highly effective treatment to be implemented for these patients.

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