Hyperbaric oxygen therapy (HBOT) in case of hemorrhagic cystitis after radiotherapy

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KEY WORDS

bladder cancer ◗ hematuria ◗ hemorrhagic cystitis ◗ hyperbaric oxygen therapy ◗ radiotherapy

ABSTRACT

Introduction. We present the effect of hyperbaric oxygen therapy (HBOT) after radiotherapy for cancer in the pelvic cavity resulting in hematuria. Increasing the pressure of oxygen (PO2) in ischemic tissues favors the formation of new blood vessels and increases the secretion of collagen.

Material and methods. We evaluated 10 patients who were treated with HBOT from October 2006 to December 2010 due to persistent radiation damage to the lining of the bladder leading to recurrent hematuria. The study group was comprised of seven men and three women. In the case of cervical and endometrial cancers, 30 Gy of brachytherapy with 45-50 Gy of teleradiotherapy were used. In prostate cancer (PCa), we applied 50 Gy of teleradiotherapy with an additional dose of 20-24 Gy, and in the case of bladder cancer (BCa), 50 Gy of teleradiotherapy was applied with an additional dose of 16 Gy. HBOT consisted of 60 HBO2 treatments, in which patients were administered 100% oxygen at a pressure of 2.5 atm.

Results. The group effect of total or partial resolution was observed in six patients. In one case, treatment was discontinued due to an increase in hematuria and the consequent suspicion of bladder tumor recurrence. While in and additional three cases, the treatment did not produce the desired result.

Conclusions. Treatment of hemorrhagic cystitis is a difficult therapeutic challenge. One possible method is the implementation of HBOT. In very difficult cases, HBO2 treatment appears to be effective in giving more than half of patients a chance of getting better.

INTRODUCTION

Hemorrhagic cystitis (HC) is a diffuse inflammatory state of the urinary bladder that can occur as a complication of radiotherapy, chemotherapy, or infection. It may result in hemorrhage of the bladder mucosa, which is observed clinically as hematuria. The focus of this article will be on radiation-induced HC, a relatively uncommon but serious complication of radiation therapy. Levenback et al. report a 6.5% risk of developing radiation-induced HC in patients treated with radiotherapy due to cervical cancer [1]. Radiation-damage of the bladder does not become clinically evident until six months after initiation of the radiotherapy [2]. Irradiated tissue sustains damage that results in microscopic obliterative endarteritis and progressive arteriopathy leaving the affected tissue hypocellular, hypovascular, and ischemic. Collagen and cells are replaced during the healing process, but complete restoration is unlikely to occur [3, 4]. Primarily, the ischemic bladder mucosa may cause mucosal ulceration and bleeding. Bleeding may also occur as a consequence of the formation of structurally weak and brittle vessels that easily rupture [5]. The use of hyperbaric oxygen treatment (HBOT) in the treatment of tissue damaged by radiation was pioneered by Marx et al. who suggested that HBOT enhances healing of tissues subjected to radiation therapy [5]. They were the first to describe the therapeutic effects of HBOT in humans – on patients having undergone protracted radiation therapy of the head and neck. In an animal study predating the human study, the authors showed that animals subjected 100% O_2 in a hyperbaric environment had an 8-9 times higher vascular density in irradiated tissue compared to both a normobaric group and an air-breathing control group [6]. A four-year follow-up study showed that the angiogenic effect was long lasting. Oxygen in hyperbaric conditions leads to an increase of oxygen levels in tissues resulting in angiogenesis, increased collagen formation, and an increased number of fibroblasts [7]. The angiogenesis is correlated, at least in part, to the macrophages of the affected tissue, which react to the steep oxygen gradient achieved in a hyperbaric environment [7]. The increase in fibroblasts and collagen creates a connective tissue framework for the new vessels [8]. The elevated level of oxygen also supports the regeneration of damaged tissue, as well as reducing edema, necrosis, and leukocytic infiltration [9].

HBOT is an effective treatment modality in radiation-induced HC. Its overall effectiveness in various pathologies has manifested in many clinical studies and trials [4, 5, 6]. More research is needed to delineate and define the clinical effectiveness and benefits of HBOT in each disease entity. The purpose of this study is to evaluate the efficacy of HBOT in radiation-induced HC.

MATERIAL AND METHODS

Between the years 2006 and 2010, ten patients (seven men and three women) with radiation-induced HC as a consequence of standard methods of treatment were subjected to HBOT. Their average age was 68.9 years; age-range 54-81 years. In these patients, four men were initially treated with radio-hormonal therapy or radiation therapy because of prostate cancer. Patients in this group received 50 Gy of teleradiotherapy, with an additional dosage of 20-24 Gy. Three men were treated with radiation therapy for cancer of the bladder. Patients in this group received 50 Gy of teleradiotherapy with an additional dosage of 16 Gy. Two women were treated for cervical cancer and one for endometrial cancer. In the case of cervical and endometrial cancers, 30 Gy of brachy-

Table 1. Patient characteristics

Number of patients	Age	Sex	Primary neoplastic disease	Total radiation dosage (Gy)	Previous treatments	Number of treatments	Effect	Follow-up (months)
1	65	F	Cervical	30 B + 45 T	TUC, C, E, K	60 +60	+	25
2	68	M	Bladder	50 T +16 T	TUC, C, E, K	25	+	14
3	75	M	Prostate	50 T + 20 T	TUC, C, E, K	30	+	14
4	61	M	Prostate	50 T + 24 T	TUC, C, E, K	60	+	48
5	79	M	Bladder	50 T + 16 T	TUC, C, E, K	25	–	31
6	68	F	Endometrial	30 B + 50 T	TUC, C, E, K	14	–	35
7	81	M	Prostate	50 T + 24 T	TUC, C, E, K	36	+	31
8	54	F	Cervical	30 B + 50 T	TUC, C, E, K	60	+	30
9	70	M	Prostate	50 T + 24 T	TUC, C, E, K	8	–	10
10	68	M	Bladder	50 T + 16 T	TUC, C, E, K	57	–	7

Abbreviations: M = male, F = female, TUC = transurethral coagulation, C = cyclonamine, E = exacyl, K = vitamin K, B = brachytherapy, T = teleradiotherapy

therapy with 45-50 Gy of teleradiotherapy were utilized (details in Table 1).

Patients in which radiation induced HC was present were initially treated for cancer using radiotherapy and in some cases with additional brachytherapy – Table 1 contains the details of this treatment – and hematuria was recognized with an average onset of 4.3 years (0.5-8) after radiotherapy. Prior to the advent of HBOT, treatment of radiation-induced HC was initially performed utilizing cystoscopic electrocoagulation, oral etamsylate, tranexamic acid, and vitamin K. However, a follow-up performed at 7-48 (average 24.5) months revealed that this approach only resulted in temporary improvement, as reappearance of hematuria was observed in all patients. Each patient received cystoscopic confirmation of HC, as well as exclusion of urinary tract infection and bladder cancer. One patient received treatment with palliative intent due to persistent hematuria, seeing as the cancer was advanced and no additional treatment with intention of cure was planned. The other patients were without detectible presence of cancer. Additionally, five of the patients required blood transfusions due to low hemoglobin values. The transfusions were given both before and during HBOT, but were not required after.

The HBOT was performed in a DELTA HAUX-QUADRO 2700 hyperbaric chamber, engineered to minimize claustrophobia. The treatment schedule consisted of five sessions a week, with a duration of 90 minutes per session. During the sessions, patients were provided with 100% O_2 at a pressure of 253312.5 Pa (2.5 atm). Sessions were continued until the hematuria disappeared, or until the patient requested to terminate the treatment. The average number of HBO treatments was 43.4 (8-60) [43.5 (8-120)]. One patient received a total of 120 treatments in two sets of 60, interspaced by four months between each series and two other patients completed a series of 60 treatments. The efficacy of the treatment was assessed every six months by visually evaluating the degree of hematuria. In case of any suspicions of hematuria, a general urine test was performed.

RESULTS

Complete resolution of hematuria was achieved in six of the ten patients (60%). The maximum follow-up after hyperbarotherapy was 18 months. None of these patients showed signs of hematuria upon completion of HBOT, including the patient that received 120 treatments. Four patients who suffered from bladder, endometrial, or prostate cancers, were withdrawn from the treatment. In one of the patients with primary bladder cancer, treatment was discontinued because of increasing hematuria and suspicion of bladder cancer recurrence. The other three patients who discontinued their treatments prematurely due to coexisting morbidities had lessened or incomplete cessation of the hematuria. The four patients who had no complete resolution of symptoms were the same patients who did not complete the treatment. A follow-up did not occur in this group. These patients suffered from bladder, endometrial, and prostate cancers. None of the patients experienced a claustrophobic event.

DISCUSSION

According to current standards of treatment, electrocoagulation, with or without pharmacotherapy, is the first step in the treatment of HC. Formalin (40% formaldehyde) is the most effective intravesical hemostatic agent [10]. Conjugated estrogens have a success rate of 60-85% in the treatment of hematuria in HC. The efficacy of conjugated estrogens applies to different etiology of HC and it should be noticed that these results using post high dose chemotherapy are not directly applicable to radiocystitis [11]. Pentosan polysulfate, tranexemic acid, aminocaproic acid, alprostadil, dinoprost, silver nitrate, and aluminum can also be used [12-16]. When the hematuria cannot be controlled using electrocoagulation or pharmacotherapy, selective embolization of hypogastric arteries can be performed. If this fails, cystectomy and supravesical diversion of urine may have to be performed to control the hematuria.

Although many studies have shown the benefit of HBOT in the treatment of radiation-induced HC, especially in patients who have failed other forms of management, HBOT is currently not included in standard treatment [2, 3, 17-20]. In the literature on the subject, studies report complete resolution-rates range from 76-100% [1, 3, 21-25]. Although, our study demonstrated slightly lower rates of complete resolution (60%), it is clear that the treatment contributed significantly to the healing process and health of the patients. In addition to its high efficacy, HBOT is safe and well tolerated by patients. Side effects are rare and generally well tolerated by the patients [9, 17]. They include pharyngotympanic tube problems, pneumothorax, air emboli, as well as CNS and pulmonary oxygen-toxicity [9].

Furthermore, the benefits of HBOT are relatively long lasting when compared to standard methods of treatment. A study by Del Pizzo involving 11 patients, with a mean follow-up of 5.1

years, showed an asymptomatic period of 2.5 years in eight of the patients, following treatment with HBOT [26]. After five years of observation, five out of the eight patients had a recurrence of hematuria and required supravesical urinary diversion. Many questions regarding patient selection to HBOT remain, as factors such as age, total irradiation dose, and duration of hematuria influence the outcome of HBOT. Furthermore, there is a lack of data evaluating the effect of HBOT in smoking patients or patients with chronic disease.

It should be remembered that HC may be caused by pharmacotherapy, such as cyclophosphamide. Moreover clotting and coagulation profiles in all cases of HC should be performed to rule out hematuria due to clotting and coagulation disorders [27].

There is no general consensus on the cost-effectiveness of HBOT compared to standard methods of treatment, although investigations on the subject seem to suggest that HBOT is more cost-effective than standard methods of treatment. In a study similar to this one, Norkool et al treated 14 patients with radiation-induced HC using HBOT. They concluded that the average cost per patient was $10,000 to $15,000, comparing favorably to the cost of multiple conservative treatments to control symptoms [28]. A review article by Wang et al. claims that HBOT significantly reduces the length of the patient's hospital stay, amputation rate, and wound care expenses in musculoskeletal disorders, making it is a cost-effective modality [29]. Concerning the treatment of soft tissue radiation necrosis using HBOT, Boykin et al. showed that HBOT achieved a reduction in patient charges by greater than 30% when compared to traditional management [30].

In a study by Hampson et al. where a hypobaric treatment was used, a positive outcome occurred in 94% of patients with osteoradionecrosis of the jaw (n = 43), 76% with cutaneous radionecrosis that caused open wounds (n = 58), 82% with laryngeal radionecrosis (n = 27), 89% with radiation cystitis (n = 44), and 63% with gastrointestinal radionecrosis (n = 73). A positive outcome of 100% was seen in patients who were treated with oral surgery in a previously irradiated jaw (n = 166) [31].

Cianci et al also reported that a reduction in expenses in the treatment of thermal-burn patients with adjunctive HBOT [32]. A study by Chuck et al., concerning HBOT use in diabetic foot ulcers, concludes that HBOT is cost-effective compared with standard care. The authors also mention that additional HBOT capacity would be needed if it were to be adopted as the standard care throughout Canada [33].

CONCLUSIONS

In conclusion, HBOT seems to be a promising treatment alternative in refractory hematuria caused by radiation-induced HC. Many studies have shown that HBOT is a cost-effective alternative in various pathologies, including radiation-induced HC. However, questions regarding its cost and availability may determine the future of HBOT. More cost-benefit analyses should be performed before a definite conclusion can be reached.

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