



Is there a role for hyperbaric oxygen as primary treatment for grade IV radiation-induced haemorrhagic cystitis? a prospective pilot-feasibility study and review of literature

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ABSTRACT

Purpose: To examine the safety and efficacy of hyperbaric oxygen as the primary treatment for Grade IV radiation-induced haemorrhagic cystitis.

Materials and Methods: Hyperbaric oxygen was prospectively applied as a primary treatment option in 11 patients with Grade IV radiation cystitis. Primary endpoint was the incidence of complete and partial response to treatment. Secondary endpoints included the duration of response, the correlation of treatment success-rate to the interval between the onset of haematuria and initiation of therapy, blood transfusion need and total radiation dose, the number of sessions to success, the avoidance of surgery and the overall survival.

Results: All patients completed therapy without complications for a mean follow-up of 17.82 months (range 3 to 34). Mean number of sessions needed was 32.8 (range 27 to 44). Complete and partial response rate was 81.8% and 18.2%, respectively. However, in three patients the first treatment session was not either sufficient or durable giving a 72.7% rate of durable effect. Interestingly, all 9 patients with complete response received therapy within 6 months of the haematuria onset compared to the two patients with partial response who received therapy at 8 and 10 months from the haematuria onset, respectively ($p = 0.018$). The need for blood transfusion ($p = 0.491$) and the total radiation dose ($p = 0.259$) were not correlated to success-rate. One patient needed cystectomy, while all patients were alive at the end of follow-up.

Conclusions: Early primary use of hyperbaric oxygen to treat radiation-induced grade IV cystitis is an effective and safe treatment option.

ARTICLE INFO

Key words:

Hyperbaric Oxygenation;
Radiation; Cystitis

Int Braz J Urol. 2014; 40: 296-305

Submitted for publication:
November 28, 2012

Accepted after revision:
September 17, 2013

INTRODUCTION

The inhalation of oxygen in high percentages and under high pressure has been extensively applied to the prevention and treatment of complications after radiation therapy (1). Recently, the European Society for Therapeutic Radiotherapy and

Oncology and the European Committee for Hyperbaric Medicine underlined the indications of hyperbaric oxygen therapy (HBO) in the treatment of radio-induced lesions in normal tissue (1), including the prevention of osteoradionecrosis after dental extraction, the treatment of mandibular osteoradionecrosis in combination with surgery and the treatment of

haemorrhagic cystitis resistant to conventional treatments. All studies published on HBO therapy for radiation cystitis are not randomized or controlled. The majority constitutes retrospective reviews and case series (2-13), with only one study being prospective in nature (14). In all these studies HBO was used as a secondary treatment option. However, experimental (15-17) and clinical studies (2-13) indicate that HBO may correct the underlying pathophysiology of radiocystitis, leading to permanent cure. We present the first prospective series on hyperbaric oxygen therapy of radiation cystitis in patients who have not received any previous treatment.

MATERIALS AND METHODS

Inclusion/Exclusion criteria

Since September 2007 we have prospectively enrolled 11 patients with grade IV post-radiation haematuria morbidity, according to the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) acute and late radiation morbidity scoring criteria for radiation-induced haemorrhagic cystitis (Table-1) (18). As a consequence, all patients suffered from severe haemorrhagic cystitis with haematuria requiring transfusion. Furthermore, we have prospectively classified our cases into two groups according to transfusion needs prior to HBO treatment;

the first group included patients who required 1-6 units of packed red cells and the second included patients who required more than 6 units of packed red cells, respectively. All patients should have not had any prior treatment of the radiation cystitis, apart from bladder irrigation. Patients with severe emphysema or other severe chronic obstructed airway disease, a history of spontaneous pneumothorax, a history of tympanic membrane spontaneous perforation or otological reconstruction were excluded from the current study. Moreover, patients with active viral infection, history of treatment with cisplatin or doxorubicin, active bladder malignancy and uncorrected bleeding disorders were not considered eligible for our study.

Evaluation and Treatment

On admission to hospital all patients underwent full blood count and complete clotting and biochemistry profile measurements. Urine samples for common urinalysis, culture and cytology were also sent to laboratory. Computed tomography (CT) or Magnetic Resonance Imaging (MRI) of the abdomen was scheduled for all patients to access the status of the underlying malignancy and to exclude other bladder pathology. All patients underwent cystoscopy under anaesthesia

Table 1 - Classification of haematuria events for both acute and late radiation morbidity scoring criteria for radiation-induced haemorrhagic cystitis.

Haematuria morbidity	Radiation morbidity	
	Acute* (RTOG**)	Late* (RTOG/EORTC***)
Grade I	NA	Minor telangiectasia (microscopic haematuria)
Grade II	NA	Generalized telangiectasia (macroscopic haematuria)
Grade III	Gross haematuria with or without clot passage	Severe generalized telangiectasia (frequent macroscopic haematuria)
Grade IV	Haematuria requiring transfusion	Severe haemorrhagic cystitis
Grade V	Death from uncontrolled haematuria	Death from uncontrolled haematuria

* Acute morbidity defined as treatment related complications occurring within 90 days from first radiotherapy session

** RTOG: Radiation Therapy Oncology Group

*** EORTC: European Organization for Research and Treatment of Cancer

and bladder biopsies were taken by one surgeon to confirm histological changes consistent with radiation cystitis and to exclude bladder malignancy.

Based on the results of previous studies (2-14), all patients were initially scheduled to receive 30 HBO sessions in a walk-in multiplace hyperbaric chamber with intend to increase them up to 45 until the haematuria resolved. Patient would receive 100% oxygen at a 1.8 atmospheres absolute pressure per session for 90 minutes per day, five days a week- Monday to Friday, schedule which is compatible with the definition of HBO therapy according to the Undersea and Hyperbaric Medicine Society (19). When complete response to HBO was reached the treatment was ceased. In case of improvement only or relapse of haematuria during follow-up, therapy was planned to re-initiate under the same schedule. In case no benefit was gained from the initial treatment, more than 45 treatments needed, severe complications occurred, or the patient declined further therapy, HBO was considered as a failure and the plan was to refer the patient for having another treatment, either conservative or surgical. During treatment all patients were closely monitored. Serum glucose measurements were planned as needed in diabetic patients to exclude hypoglycemia.

Within 4 weeks of treatment completion, all patients underwent cystoscopy under anesthesia and bladder biopsy by the same surgeon to confirm treatment result and/or to compare with the pre-treatment status.

Study endpoints

Primary endpoint was the success rate measured by the incidence of complete and partial response to treatment. Complete response was defined as the complete cessation of bleeding and the lack of need for transfusion in combination with the disappearance of endoscopic findings and concomitant normal bladder findings in repeat biopsies. Partial response was defined as a decrease in the grade of RTOG/EORTC scoring criteria mainly the existence of microscopic haematuria or the persistence of mild macroscopic haematuria not requiring transfusion or other urgent treatment. Secondary endpoints included the duration of HBO response without need for further

treatment, the correlation of the time interval between initiation of HBO therapy and the onset of haematuria to the success rate of HBO therapy, the correlation of blood transfusion need to HBO success rate, the correlation of total Gys received to the HBO success rate, the number of sessions needed to achieve success, the avoidance of surgery and the overall survival.

Statistical analysis

Descriptive statistics and comparisons were made using the SPSS 12 statistical package with $p < 0.05$ being significant. Statistical analysis was performed using the chi-square and t test, as appropriate.

RESULTS

Since September 2007 ten men and one woman were enrolled in our study. Mean patient age was 71.7 years (range 56 to 82). Indications for radiation therapy included prostate cancer for all male patients and bladder cancer for the female patient. Mean radiation dose was 74.45 Gy (range 66 to 80). Mean interval between completion of radiation therapy and onset of haematuria was 9.8 months (range 4 to 14). Mean interval between completion of radiation therapy and the onset of HBO therapy was 13.11 months (range 6 to 22 months). Mean transfusion need prior to and during the treatment was 8.18 red blood cells packs (range 3 to 16). More specifically 4 patients have been transfused with ≤ 6 units and 7 patients with > 6 units.

Pretreatment patient evaluation revealed no bladder infection or tumor. Bladder biopsy revealed diffuse mucosal edema, vascular telangiectasia, submucosal haemorrhage, interstitial fibrosis and fibrosis of smooth muscle, histological findings consistent with post-radiation cystitis. Severe ischemia of the bladder wall, a result of obliterative endarteritis, was also present.

All eleven patients completed HBO therapy without suffering any complications and were followed up for a mean period of 17.82 months (range 3 to 34). Mean HBO therapy sessions were 32 (range 27 to 44). Nine men had complete response while the last man and the woman experi-

enced partial response with marked improvement in their haematuria (grade II). One patient from the complete response group had a recurrence of grade II haematuria at 6 months of follow-up and received 18 additional HBO treatments. All these patients remained with complete response for the rest of the follow-up. The male patient with the partial response received 35 additional treatments and he has not had haematuria since then. The female patient experienced severe haematuria 6 months after the end of HBO therapy and following a full consent she chose cystectomy and urinary diversion for her treatment.

Post-hyperbaric treatment cystoscopy revealed a subjectively normal bladder mucosa in all men, which was confirmed by a histologically normal mucosa in only the 7 patients who had complete response. The male and the female with partial response showed improved but persistent findings of radiation cystitis. Cystectomy specimen revealed a T2G3N0M0 transitional cell carcinoma of the bladder.

Regarding our study endpoints, complete response rate was 81.8% and partial response rate was 18.2%, giving an overall success rate of primary therapy, as defined in our study, of 100%. However, as mentioned above, in three patients the first treatment session was not either sufficient or durable giving a 72.7% rate of durable effect. Interestingly, all 9 patients with complete response received HBO therapy within 6 months of the haematuria onset compared to the two patients with partial response who received HBO therapy at 8 and 10 months from the haematuria onset, respectively ($p < 0.018$). The need for blood transfusion was not correlated to the complete or partial response to HBO ($p = 0.491$). Total radiation dose was not correlated to complete or partial responses to HBO therapy ($p = 0.259$). All patients were alive at the end of follow-up.

DISCUSSION

Bladder complications may occur within 2 months to > 20 years following completion of pelvic radiotherapy (1,14). Their incidence ranges from 5 to 12%, with haemorrhage presenting in up to 9% of cases (1). Severe RTOG/EORCT grade III or

worse bladder morbidity has been reported at 1% at 5 years, 1.4% at 10 years and 2.3% at 20 years following radiotherapy for cervical cancer (20). Radiation for prostate cancer may lead to moderate or severe haematuria in 3-5% of cases (10,12).

Traditionally, severe radiation cystitis has been treated in various ways (1). Bladder irrigation almost always constitutes the first-line treatment. Intravesical instillations with alum, silver nitrate, phenol or formalin have been used as a second-line treatment. Several oral and intravenous agents are administered either concomitantly or as a third-line option. Among them the most commonly applied are aminocaproic acid, traxenamic acid, corticosteroids, estrogens, antibiotics, prostaglandins and sodium pentosanpolysulphate. However, these treatments do not cure the radiation-induced cystitis, nor prevent recurrence of severe haematuria. Moreover, some of them may have serious systematic side effects or may exacerbate bladder fibrosis which was initiated by radiation treatment, leading to a small-capacity bladder (1,2-14). A recent Cochrane Database systematic literature review on non-surgical interventions for late radiation cystitis in patients who have received radical radiotherapy to the pelvis concluded that in the absence of randomized controlled studies it is impossible to set definitive rules for treatment (21). In case of intractable haemorrhage arterial embolization or ligation and/or cystectomy represent definitive treatment, at the cost of increased morbidity.

Pelvic radiotherapy initially causes mucosal edema and inflammation. Telangiectasia, submucosal haemorrhage and interstitial fibrosis follow. Obliterative endarteritis of small blood vessels leads to acute and chronic ischemia of the bladder wall and eventually to smooth muscle fibrosis due to cellular hypoxia (22). Hyperbaria related to HBO therapy increases bladder's tissue oxygen tension (14). Hyperoxia enhances neovascularization and growth of normal tissue (6,10,15,17). Angiogenesis is stimulated by tissue macrophages responding to the steep oxygen gradient (15). Tissue oxygen remains near normal levels for many years following HBO therapy, implying that the angiogenesis is essentially permanent (10). Vasoconstriction and cease of bleeding and improvements of tissue healing and immune function constitute ad-

ditional beneficial effects of HBO (6,12,15-17). For these reasons, HBO is the only treatment which is believed to reverse the vascular radiation-induced pathophysiology (15,22).

Several series of radiation-induced haemorrhagic cystitis treated with HBO have been reported (2-14). Tables 2 and 3 present indications and results for most of them. The vast majority are retrospective in nature. Endpoints have been set prospectively in only one study (14). These included recurrence of severe haematuria, cystectomy, or death. Forty patients were recruited, all of which had had previous unsuccessful treatments for radiation cystitis. In addition, although a mean transfusion need of 8.2 units per patient was reported, a specific classification system of haematuria morbidity was not used and patients presented with various haematuria grades according to RTOG/EORTC criteria, leading to a diversity of results. Similar to our study, a classification of the severity of haematuria according to transfusion needs was used. However, no statistical analysis was provided and HBO failure was seen only in 3 patients with a mean transfusion need of 25.7 units. Finally, neither the total Gys received nor the time interval elapsed from initiation of HBO therapy to onset of haematuria, were correlated to HBO success rate. Overall, haematuria disappeared completely or improved in 37 patients (92.5%). With a median follow-up of 23 months, in 9 patients haematuria recurred, representing a recurrence rate of 0.12/year (14). Bladder preservation was achieved in 36 of patients. Based on their results the authors inferred in their conclusion that HBO should not be reserved only for severely affected and conventional therapy-resistant patients.

The retrospective study with the most significant numbers included 62 patients, with a follow-up of 10-120 months (10). Among these patients, all had previous treatments while only 8 (13%) required pre-hyperbaric oxygen blood transfusion. Of the 57 patients to be evaluated, 49 (86%) presented with a complete disappearance or a notable improvement of their haematuria. Again, based on their results the authors inferred in their conclusion that early HBO should be considered before repeated instillations of chemicals leave the bladder fibrotic, contracted and non-compliant. Another important retrospective study

on 60 patients with intractable to other conservative treatments radiation cystitis, showed an overall 80% complete or partial response to HBO after 12 months of follow-up (11). Having used similar response criteria to our study, the authors showed that HBO success rate has not been impaired by the modality and timing of pelvic radiotherapy or by previous intravesical treatment. Younger age, higher radiation dose and treatment within 6 months from the onset of haematuria were associated with a favorable HBO outcome. The later, also having been shown retrospectively in other studies (8), was confirmed in our study, in a prospective manner. Tables 2 and 3 summarize data and results for the most of the rest large retrospective studies. All these studies have confirmed the efficacy and safety of HBO therapy.

Our study has several drawbacks. First of all, it is neither randomized nor controlled. However, as cystectomy represents the alternative definitive treatment for radiation cystitis we believe it will be difficult for urologists to randomize patients. Secondly, due to strict inclusion criteria, the number of patients enrolled in our study is small and conclusions should be made with caution. Thirdly, the follow-up in our series is considered short. Although durable results up to 10-years have been published (6), HBO success rate may drop from 73% to 27% as follow-up increases from 2.5 years to 5 years (7). As our study is still ongoing, we believe these drawbacks will become weaker upon time.

Taking into consideration the aforementioned drawbacks, current study remains important for several reasons. It is the second prospective study in literature and the first on only haematuria grade IV patients. It is the first study using HBO as primary therapy to radiation-induced cystitis and the first in which post-treatment cystoscopic and histologic findings were included to study's endpoints and were documented for all patients. Several conclusions can carefully be drawn from the current study. Primary treatment of severe post-radiation haemorrhagic cystitis with HBO has proved to be effective and safe both for the bladder structure itself and for patients. Initiation of therapy within 6-months of haematuria onset will be of patient's benefit. HBO's success

Table 2 - Material and methods of studies on hyperbaric therapy in the treatment of radiation-induced bladder complications.

Series (Reference)	No. patients	Prospective /Retrospective	Mean Radiation dose (range) (Gy)	Symptoms / Grade of Haematuria (n = number of patients)	Number of patients transfused	Average Blood units per patient (range)	Mean (range) interval from radiation to symptoms (months)	Mean (range) interval from radiation to HBO therapy (months)	Mean (range) interval from haematuria to HBO therapy (months)
Nakada (3)	6	Retrospective	60 ± 4.3	Haemorrhagic cystitis	NA	NA	NA	20.8±3.6	NA
Norkool (4)	14	Retrospective	66.82 (45-100)	Haemorrhagic cystitis	1	3	NA	NA	NA
Lee (5)	20	Retrospective	62 (52-90)	Haemorrhagic cystitis n = 19 Frequency, urgency n = 1	NA	NA	114 (24-312)	NA	NA
Weiss (6)	13	Retrospective	46.87 (40-69.74)	Haemorrhagic cystitis	9	2.7 (2-7)	NA	69.23 (12-216)	NA
Del Pizzo (7)	11	Retrospective	75 (60-96)	Intractable haematuria n = 11 Pain n = 2 Urgency/ Incontinence n = 1	11	3.3 (2-15)	84 (16-144)	NA	NA
Mathews (8)	17	Retrospective	66	Haemorrhagic cystitis	8	NA	NA, (2-180)	NA	≤ 2 n=11 > 2 n=6
⁹ Mayer (9)	11	Retrospective	⁴ 69.27 (66-70)	² Grade 2 n = 2 Grade 3 n = 6 Grade 4 n = 2	2	NA	⁵ 15.84	52.1 (11.1-145.3)	NA

Corman (10)	62	Retrospective	NA	¹ Haemorrhagic cystitis	8	4 (1-7)	48 (0-355)	63 (2-360)	NA
Chong (11)	60	Retrospective	NA	² Grade 1-2 n=16 Grade 3-4 n=44	NA	NA	NA	NA	≤ 6 n=28 > 6 n=32
Neheman (12)	7	Retrospective	64	¹ Haemorrhagic cystitis	NA	NA	NA	NA, (3-180)	NA
Yoshida (13)	8	Retrospective	56.6 (42-70)	Haemorrhagic cystitis	3	NA	NA	NA	8.9 (3-34)
Beyers (14)	40	Prospective	61.05	Haemorrhagic cystitis	30	8.2 (0-36)	53.1 (4-253)	NA	NA
Present study	11	Prospective	74.45 (66-80)	² Grade IV n=11	11	8.18 (3-16)	9.8 (4-14)	13.11 (6-22)	3.36 (1-10)

¹ = No specific symptoms; number of blood transfusions not mentioned; no grade of haematuria morbidity

² = RTOG/EORTC haematuria morbidity grades

³ = Three patients had combined proctitis and cystitis

⁴ = Refers to the mean and range of maximum dose of radiation

⁵ = Median value

NA = Not Available

Table 3 - Results of studies on hyperbaric therapy in the treatment of radiation-induced bladder complications.

Series (Reference)	Mean (range) of HBO treatments	Mode of HBO sessions (absolute atmospheres/ Minutes per session/ Sessions per week)	Criteria for response	Complete Response (patients/ %)	Partial response (patients / %)	Recurrence after complete response (patients, %)	Cystez	Mean (range) Follow-up (months)
Nakada (3)	45 (20-61)	2/90-120/7	Complete or partial improvement of haematuria and cystoscopic findings	5 (83.3%)	-	0 (0%)	0 (0%)	12 ± 1.2*****
Norkool (4)	28 (9-58)	2.4/90/5-6	Complete or partial improvement of haematuria	8 (57%)	2 (14%)	1 (12.5%)	1 (7.1%)	19.07 (10-42)
Lee (5)	44 (10-87)	2.5/100	Complete or partial improvement of haematuria, frequency, urgency Changes in cystoscopic findings	16(80%)	2 (10%)	0 (0%)	1 (5%)	14 (5-41)
Weiss (6)	55.38 (34-60)	2/120/7	Complete or partial improvement of haematuria	12 (92.3%)	-	2 (15.38%)	1 (7.7%)	30 (4-102)
Del Pizzo (7)	40 (28-64)	2/90/5	Presence or absence of haematuria, urgency and pain	3 (27.2%)*	5 (45.4%)*	1 (33.3%)*	8 (72.7%)*	5.1***** (3.2-8.5)
Mathews (8)	14 (NA)	2-2.5/90/5	Complete or partial improvement of haematuria	13 (75%)	2 (11%)	NA	NA	21 (9-60)
Mayer (9)	26.5 (18-31)	2.2-2.4/60/7	RTOG/EORTC Haematuria morbidity grades	6 (54.5)	3 (27.27)	NA	1 (9%)	17.7 (2.2-51.6)
Corman (10)**	33 (9-68)	2.4/90/5-7	Complete or partial improvement of haematuria	21 (34%)	28 (45%)	6 (10.5%)*	0 (0%)	NA

Chong (11)	NA	2.36/90/5	Complete response: Absence of haematuria	44 (73.35)	4 (10%)	NA	NA	At least 12 (NA)
Partial response: Reduction in RTOG/EORTC grade								
Neheiman (12)	30 (18-57)	2/90/5	Complete or partial improvement of haematuria	100%*	100%*	2 (28.55) *	0 (0%)	24 (3-53)
Yoshida (13)	19 (10-42)	2/90/5	Complete or partial response of haematuria	6 (75%)	0 (0%)	1 (12.5%)	2 (25%)	15.5 (2-31)
Beyers (14)	20 (NA)	3/90/5-6	Recurrence of severe haematuria, Cystectomy, death	30 (75%)	7 (17.5%)	3 (10%)	5 (12.5%)	23 (1-74)
Present study	32.8 (27-44)	1.8/90/5	Complete response: No haematuria, Normal cystoscopy Normal histology Partial Response: Reduction in RTOG/EORTC Grade No urgent treatment	9 (81.8%)	2 (18.2%)	1 (11.1%)	1 (9%)	17.82 (3-34)

* Results refer to complete and partial response in combination

** Data available on 57 out of 62 patients

*** Data refer to 5.1 years median follow-up

**** Data refer to 2.5 years median follow-up

***** Median value

***** ± Standard error

NA = Data not available

rate is not correlated to the degree of blood transfusion need or radiation dose. Finally, we support the findings of previous series (2,4), indicating that when HBO fails, the urologist should think of other underlying causes such as malignancy.

CONCLUSIONS

Early primary use of hyperbaric oxygen to treat radiation-induced grade IV haematuria is an effective and safe treatment option. Increase in patient recruitment and longer follow-up is warranted to extract permanent conclusions. Prospective randomized controlled trials will eventually provide information of high-level of evidence.

CONFLICT OF INTEREST

None declared.

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