

The Comparison of Acute Clinical Outcome between 30 and 40 Sessions of Hyperbaric Oxygen Therapy for Management of Visible Hematuria from Radiation-Induced Hemorrhagic Cystitis

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Abstract

Background: Radiotherapy is one of the most popular treatments for pelvic malignancy, which causes patients suffering from the adverse effect such as cystitis, hematuria, proctitis, hematochezia and distal ureteric stricture. The hematuria condition from radiation-induced hemorrhagic cystitis is the most common adverse event suffering the patients, losing properties, wasting time, and deteriorating quality of life. One of the most effective treatments for radiation-induced hemorrhagic cystitis is the hyperbaric oxygen therapy with no necessity for patients to be hospitalized, no need of anesthesia use, and also non-invasion. However, it requires that patients spend 90 - 120 minutes a day for 40 days administered out-patient treatment session. The transportation cost as well as the accommodation one will greatly burden the self-pay health care patients. In addition, there is still no definite standardized number of HBOT treatment session assignment at present. **Objectives:** To compare the treatment outcome (bladder mucosal characteristics, red blood cells in urine) between 30 and 40 sessions of HBOT for treatment of radiation-induced hemorrhagic cystitis. **Methods:** Prospective cohort observational study of patients (n = 15) who were diagnosed with radiation-induced hemorrhagic cystitis that were treated with hyperbaric oxygen therapy in Somdechprapinklao Hospital between October 2020 and September 2021. We compared the parameter about hemoglobin concentration, red blood cell number in urine during the course of HBOT treatment every 10 sessions and cystoscopic finding severity as EORTC/RTOG classification for radiation-induced hemorrhagic cystitis in **Table 1** before treatment, and after 30 and 40 sessions of

treatment. **Results:** From 15 of treated patients, 93.3% of patients had evidence of posterior wall lesion. The mean duration from radiotherapy (radiation and brachytherapy) to the first episode gross hematuria is 112 months. This study shows no statistically different cystoscopic findings as EORTC/RTOG classification for radiation-induced hemorrhagic cystitis after 30 and 40 sessions of HBOT ($p = 0.653$) and statistically significant improvement after the treatment of more than 30 sessions ($p = 0.008$). No relationship was found with the hemoglobin concentration and red blood cell number in urine during the course of HBOT. **Conclusions:** Radiation-induced hemorrhagic cystitis can be treated with HBOT. There is no different treatment outcome between 30 and 40 sessions of HBOT.

Keywords

Radiation-Induced Hemorrhagic Cystitis, Irradiation Cystitis, Hematuria, RIHC, Hyperbaric Oxygen Therapy, HBOT

1. Introduction

Radiotherapy is one of the most often used treatments of pelvic malignancies such as initial stage of cervical cancer, localized or locally advanced prostate cancer, and rectal cancer. However, the adverse events of radiation are still frequent for example proctitis, ureteric stricture, and hemorrhagic cystitis. Many patients with irradiation cystitis suffer from frequent hospitalization for bladder irrigation, blood transfusion, chronic pain or obstructive uropathy from clot retention that would be treated with cystoscopy with clot evacuation and fulguration. Some patients might have failed with conservative treatments that are necessary to be treated with hyperbaric oxygen therapy (HBOT) which is a standard treatment for radiation-induced hemorrhagic cystitis, according to the guidelines from a number of international associations, such as: American Urological Association (AUA), European Association of Urology (EAU), and Canadian Urological Association (CUA) [1].

Based on “Canadian Urological Association Best Practice Report for Diagnosis and Management of Radiation-Induced Hemorrhagic Cystitis” which was published in Canadian Urological Association Journal 2019 and Campbell-Walsh-Wein Urology 12th edition, which was used as standard textbook for urologists, initiate evaluation with cystourethroscopy for evaluation urinary bladder pathology and additionally tissue biopsied of suspected cancer-invasive lesion and fulgurate on bleeding site [2]. In case of ongoing hematuria or blood clot retention, it would be treated with continuous bladder irrigation (CBI) with normal saline solution, aluminous salt solution or hyaluronic acid. If gross hematuria persists, the patient will be treated with hyperbaric oxygen therapy [3]. Bilateral nephrostomy might be performed in case of continuous gross hematuria during the course of HBOT. If there were a persistent bleeding after a complete course of HBOT, the

treatment would be aggressively progressed to 1% - 4% formalin solution and cystectomy with urinary diversion.

Hyperbaric oxygen therapy (HBOT), the principle of treatment applying high concentration of oxygen diffusion into the tissue causes a better healing process, strengthening tissue, stimulating strength neovascularization, and better decreasing tissue edema. Several studies found 80% - 90% of the patients respond to this treatment within 5 years, and 27% of the patients completely respond and delay time to recurrent gross hematuria to 2.5 years [4] [5] [6] [7] [8].

Somdechprapinklao Hospital, the Royal Thai Naval Medical Department has potential and experience of hyperbaric oxygen therapy to be used to treat the naval officers whose Royal Thai Navy military mission operating in deep-water (SEAL tactical combat operation) or high-altitude parachuting and non-military population (such as scuba diving, high altitude hiking or rescue mission) and in case they suffer from decompressive sickness or "Caisson disease" a barotrauma caused by a rapid alteration of pressure of water or air that results in nitrogen air-bubble in blood stream. Moreover, the role of HBOT could be used for any treatment of hard-to-heal wound from vasculopathy. Thus, radiation-induced hemorrhagic cystitis is one of the conditions that can be treated with HBOT when failures from previous conservative treatments exist [9]. Somdechprapinklao Hospital currently serves for the patients from Thai nationwide. In 2018 and 2019, the number of patients who had been diagnosed irradiation cystitis totaled 113 and 151 respectively, and be treated with HBOT 56 and 73.

For an HBOT treatment procedure, patients have to be assigned in the therapy chamber for 40 times, 90 minutes/time as a standard regimen. Each HBOT administration costs 2700 baht. National health care policy of Thailand does not cover the treatment cost for all patients requiring HBOT. The patients who are not entitled for government health welfare must have to pay not only for all medical treatment cost, but also for travel fare from their residences to the hospitals, or for the accommodation near the hospitals during a course of treatment. From literature reviews among HBOT for radiation-induced hemorrhagic cystitis treatment, the patient received an average of 29 - 33 HBOT sessions [4] [6] [10] [11] [12].

We aimed to make a comparison of clinical outcomes of the administration of HBOT between 30 and 40 sessions. If the result of this study shows indifference in outcome, it would be used as an evidence to decrease the number of treatment sessions, lessen a lot of time and save a lot of money, and it can also minimize adverse consequences, such as: tympanic membrane rupture, barotrauma. The decrease of treatment waiting time and decrease of treatment cost will definitely ensure an improvement of life quality of patients.

2. Methodology

2.1. Study Population

This study was conducted in the patients who were diagnosed with radia-

tion-induced hemorrhagic cystitis and treated with HBOT at Center of Hyperbaric Medicine, Somdechprapinklao Hospital, the Naval Medical Department, from October 2020 to September 2021 as a prospective observational cohort study. The study protocol obtained an approval from the Institution-Review Board of the Naval Medical Department, the Royal Thai Navy. COA-NMD-REC0.24/63.

Inclusion criteria were the patients who have been treated with radiation or a brachytherapy for pelvic cancer, aged 20 - 75 years, confirmed radiation-induced hemorrhagic cystitis, without contraindication for HBOT such as chronic obstructive pulmonary disease (COPD) or severe bronchial asthma, untreated pneumothorax, ongoing chemotherapy course, history of previous ear nose throat surgery, epilepsy, retinitis, uncontrolled hypertension, uncontrolled heart failure, Claustrophobia, and convenient patient for HBOT.

Exclusion criteria were the patients who have active or progressive cancer associated bladder and severe hematuria causing emergent surgical correction or urinary diversion with ileal conduit or ureterostomy.

2.2. Patient Preparation

All patients were evaluated with urinalysis, complete blood count with platelet count, coagulogram for exclusion of medical cause, flexible cystoscopy for diagnosis and exclusion of malignant lesion.

2.3. Intervention

All patients were assigned cystoscopy for a diagnosis of irradiation cystitis and classified as EORTC/RTOG classification of radiation-induced hemorrhagic cystitis as shown in **Table 1**, then later sent to the Center of Hyperbaric Medicine for further evaluation by maritime physicians for prescribing HBOT. The patients were exposed to 100% oxygen at 2 atm, in multiphased hyperbaric chamber, for 90 minutes, once daily, 5 days a week. The patients were appointed to follow-up cystoscopy after attention of HBOT for 30 and 40 sessions for inspecting bladder mucosa as EORTC/RTOG classification for radiation-induced hemorrhagic cystitis. Urinalysis and complete blood count were evaluated before starting HBOT and every 10 sessions of HBOT until the treatment completion.

Table 1. Classification of radiation-induced hemorrhagic cystitis [1].

EORTC/RTOG classification (European Organization for Research and Treatment of Cancer/RTOG: Radiation Therapy Oncology Group)

1	2	3	4	5
Slight epithelial atrophy; minor telangiectasia; microscopic hematuria	Moderate frequency, generalized telangiectasia; intermittent macroscopic hematuria	Severe frequency and dysuria, generalized telangiectasia (often with petechiae), frequent hematuria with decreased bladder capacity	Necrosis/contracted bladder, severe hemorrhagic cystitis	Death directly due to hemorrhagic cystitis

2.4. Outcome Measurement

Analyzed variables included sex, age (years), primary malignant disease, time between RT and hematuria (months), type of radiation administration, radiation dose, involved bladder wall, cystoscopic findings as EORTC/RTOG classification of radiation-induced hemorrhagic cystitis.

The primary clinical outcome compares the grading of bladder mucosa from cystoscopic findings after 30 and 40 HBOT sessions, categorized as grading as EORTC/RTOG classification of radiation-induced hemorrhagic cystitis include grade 1 as “mild”, grade 2 as “moderate”, grade 3 as “severe”, and grade 4 as “necrosis” and also to compare RBCs in urine every 10 HBOT sessions.

2.5. Data Analysis

Clinical data were analyzed using SPSS, version 25. Descriptive statistics demonstrated as frequencies, percentage, mean, and median. Chi-square test was used. Statistical significance was considered for p -value < 0.05 .

3. Results

3.1. Sample Characteristics

In total, 16 patients underwent HBOT in our hospital during October 2020-September 2021 and excluded one patient because of incomplete session of HBOT. The patient characteristics were shown in **Table 2**. From remaining patients in this study were 12 females and 3 males, aged between 49 - 80 years. The most common indications for pelvic radiation were cervical cancer (80%), colorectal cancer (13.3%), and prostate cancer (6.7%). With a mean radiation dose was 28.4 Fractions (20 - 39 fractions). A mean time between radiation to hematuria was 112 months. The most often involved bladder walls from radiation were posterior wall (93.3%), left lateral wall (80.0%), right lateral wall (73.3%), and trigone (53.3%). Pretreatment grading of severity according to EORTC classification for radiation-induced hemorrhagic cystitis in our samples showed 4 patients of grade 2, 10 patients of grade 3, and 1 patients of grade 4.

3.2. Outcomes

There was no significant difference between 30 and 40 sessions of HBOT with severity grading on cystoscopic findings as EORTC/RTOG classification ($p = 0.653$) [shown in **Table 3**] but either 30- or 40-sessions of HBOT showed statistically significant improvement compared with before HBOT ($p = 0.008$) [shown in **Table 4**]. There was no significant difference in relations of radiation dose and grading of severity according to EORTC/RTOG classification ($p = 0.662$) [shown in **Table 5**]. There was no significant difference in the level of red blood cell in urinalysis every 10 sessions of HBOT until completion 40-sessions ($p = 0.276$) [shown in **Table 6**].

Table 2. Patient characteristics.

Gender (%)	Female	12 (80.0)
	Male	3 (20.0)
Average age (Yrs.)		64.4 (49 - 80)
Primary disease (%)	Cervical cancer	12 (80)
	Colorectal cancer	2 (13.3)
	Prostate cancer	1 (6.7)
Average time from radiation to first hematuria episode (Months.)		112 (1 - 280)
Mode of radiotherapy (%)	Radiation only	4 (26.7)
	Brachytherapy only	0 (0)
	Radiation and brachytherapy	11 (73.3)
Average of radiation dose (Sessions)		28.4 (20 - 39)
Involved bladder wall, Patients (%)	Anterior	3 (20.0)
	Dome	6 (40.0)
	Posterior	14 (93.3)
	Right lateral	11 (73.3)
	Left lateral	12 (80.0)
	Trigone	8 (53.3)
EORTC/RTOG Classification of hemorrhagic cystitis before HBOT, Patients (%)	1	0 (0)
	2	4 (26.7)
	3	10 (66.7)
	4	1 (6.6)

Table 3. Comparison clinical outcome of HBOT 30 and 40 sessions as EORTC/RTOG classification.

HBOT	30 Sessions	40 Sessions	<i>p</i> -value
EORTC/RTOG classification			
<i>Mild (Grade 1)</i>	6 (40%)	8 (57.14%)	0.653
<i>Moderate (Grade 2)</i>	6 (40%)	4 (28.57%)	
<i>Severe (Grade 3)</i>	3 (20%)	2 (14.29%)	

Table 4. Comparison clinical outcome of before HBOT and after HBOT 30 and 40 sessions as EORTC/RTOG classification.

HBOT	Before HBOT	After HBOT 30 sessions	After HBOT 40 sessions	<i>p</i> -value
EORTC/RTOG classification				
Mild (Grade 1)	0 (0%)	6 (40%)	8 (57.14%)	0.008*
Moderate (Grade 2)	4 (26.67%)	6 (40%)	4 (28.57%)	
Severe (Grade 3)	10 (66.67%)	3 (20%)	2 (14.29%)	
Necrosis (Grade 4)	1 (6.66%)	0 (0%)	0 (0%)	

Table 5. Relation of number of radiation dose and clinical outcome before HBOT as EORTC/RTOG classification.

Radiation dose (Sessions)	20 - 29 sessions	30 - 39 sessions	<i>p</i> -value
<i>EORTC/RTOG classification</i>			
Mild (Grade 1)	3 (20%)	1 (6.67%)	0.662
Moderate (Grade 2)	6 (40%)	4 (26.66%)	
Severe (Grade 3)	1 (6.67%)	0 (0%)	

Table 6. Comparison of red blood cell in 10-sessions interval HBOT urinalysis.

<i>HBOT</i>	10 Sessions	20 Session	30 Sessions	40 Sessions	<i>p</i> -value
<i>Urinalysis (Blood)</i>					
None	6 (46.15%)	6 (40.00%)	10 (71.43%)	9 (64.29%)	0.276
1+	2 (15.38%)	1 (6.67%)	0 (0.00%)	1 (7.14%)	
2+	1 (7.69%)	2 (13.33%)	3 (21.43%)	3 (21.43%)	
3+	4 (30.77%)	6 (40.00%)	1 (7.14%)	1 (7.17%)	

4. Conclusion

Radiation-induced hemorrhagic cystitis (RIHC) from treatment of pelvic malignancies (cervical cancer, prostate cancer, and colorectal cancer) in 15 patients who were treated in Somdechprapinklao Hospital between October 2020 and September 2021 found that the most often involved bladder walls from radiation were posterior and both lateral walls. Either 30 or 40 sessions of HBOT significantly decreased severity of RIHC according to EORTC/RTOG classification. Although there was no significant difference in outcome between 30 and 40 sessions but their trend to more decrease severity with an increased number of HBOT sessions. Level of red blood cell in urinalysis cannot be used as a treatment monitoring.

5. Discussion and Limitations

The radiation dose which is categorized into 20 - 29 sessions and 30 - 39 sessions (Table 5), does not relate with bladder mucosal grading on cystoscopic findings because the severity of bladder mucosa may result from many factors such as bladder characteristics during radiation (distension or collapse), previous treatment for hemorrhagic cystitis (Fulguration, Intravesical chemical treatment), and total radiation dose.

The Red Blood Cell (RBC) in urinalysis after 30-and 40-HBOT sessions were not different but there were reduced compared with pretreatment and in early treatment session (Table 6).

The number of samples in this study from the calculation was 44 patients. From data collection from medical record in Somdechprapinklao Hospital from 2019 to 2020, the patients who were diagnosed with irradiation cystitis with he-

maturia (ICD-10: N30.91) were 113 and 151 patients respectively and treated with HBOT were 56 and 73 patients but in our study, the target number of samples could not be achieved because of COVID-19 outbreak in Thailand resulting in a limited number of patient recruitment and referrals from other hospitals. Treatment cost of HBOT was unaffordable for some of our patients due to un-coverage of their medical insurance. The number of samples in our study that was lower than the desired ones caused a lower power of confidence of this research and assumingly led to an inaccurate conclusion.

Our study is prospective cohort study that can be used as a pilot study for further investigation about HBOT in the future as a randomized—controlled trial. Test of the relations of HBOT session in this study was performed in the same samples. The measurement method as a cystoscopic finding based on surgeon's experience might be varied. The number of radiation doses and times between radiation and hemorrhagic cystitis data was collected from patients' recalls that might not be accurate.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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