

Oxygen Hyperbaric Therapy in Patients with Radiation Proctitis

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ABSTRACT

Background: Cervical cancer is the most common female malignancy in developing countries, including Indonesia. It usually occurs at the age of 20 years, reaches the peak incidence at the age of 35-55 years, and afterwards, the incidence declines. Radiotherapy is the most important treatment method in cervical cancer, especially for local advanced stage or stage IIB-IVA. It is also effective for the early stage. Oxygen hyperbaric therapy (OHBT) is defined as 100% oxygen (O₂) administration of 2-3 ATA (Absolute Atmospheres) pressures in a high-pressure room. OHBT accelerates wound healing by improving oxygen perfusion around the wound and by increasing angiogenesis through Nitric Oxide Synthetase (NOS).

Methods: The study was conducted at Cipto Mangunkusumo hospital, while OHBT was provided at Dr. Mintoharjo Navy Hospital. Block randomization was performed, resulting 32 patients in OHBT group and 33 patients in control group; both groups were at normal distribution. The prevalence of radiation proctitis in OHBT and control group was determined using chi-square test.

Results: By comparing the prevalence of radiation proctitis between OHBT and the control group, show that OHBT could decrease proctitis prevalence by $p = 0.03$.

Conclusions: This study indicates that OHBT may reduce the prevalence of radiation proctitis. The OHBT is save and secure to the patients.

Keywords: OHBT, cervical cancer, radiotherapy, radiation proctitis

INTRODUCTION

Radiation proctitis usually occurs in patients with cancer, who have radiation therapy in pelvic region. According to Lashner,¹ more than 50% patients with cancer receive radiation therapy. Radiation therapy in pelvic region usually causes late adverse effect, i.e. radiation proctitis in 5-10% patients. Gilinsky² reported that acute adverse effect and late adverse effect caused by radiotherapy occur in 50-78% and 2.5-25% cases, respectively. The incidence of radiation proctitis depends on radiation dose, fractionation, the width of radiation area, and radiation techniques.

The prevalence of cervical cancer (Ca cervix) is quite high in women with low socio-economic status³ and it is commonly found in developing countries, including Indonesia.^{3,4} In order to reduce

morbidity and mortality of cervical cancer, prevention and therapeutic efforts should be initiated, which include reducing or eliminating contact to carcinogenic agents, screening, early detection of radiation cases, and decreasing adverse effect, as well as enhancing disease recovery.⁴

Radiotherapy method in cervical cancer with local advanced stage includes 25 five-weekly external radiation with two Gy (200 cGy)/day dose. Later, the next radiotherapy includes brachithery (after loading techniques) with 2 x 85 Gy (850 cGy) dose. Total hysterectomy without lymphadenectomy is performed for cervical cancer stage Ia₁ and stage Ia₂. While radical hysterectomy with lymphadenectomy or radiotherapy is carried out in patients with cervical cancer stage Ib and IIa.⁵

Radiation-induced tissue damage in rectal area occurs by dose > 6,000 Rad.^{6,7} Rectal tissue damage includes radiation proctitis, which may be acute or chronic, as well as acute and chronic adverse effect.^{8,9} Radiation-induced tissue damage will cause platelet aggregation and inflammation reaction, resulting hypoxia, hypocellular and hypovascular state, which eventually causes tissue damage.^{7,10}

Oxygen hyperbaric therapy (OHBT) is defined as 100% oxygen (O₂) administration of 2-3 ATA (Absolute Atmospheres) pressures in a high-pressure room. OHBT is used for treatment of decompression sickness—a disease caused by diving activity. In addition, it may be also used for treatment of tissue injury by enhancing wound healing and reducing hypoxia condition around the wound.^{11,12} OHBT improves tissue oxygenation around the wound by increasing collagen synthesis, upgrading leukocytes ability to kill bacteria, and increasing angiogenesis; which eventually form neovascularization in the wound tissues.¹² OHBT increases and improves micro vascular blood flow and capillary density through *ischemic-reperfusion model* by reducing neutrophils affinity to venule endothelial and arteriole vasoconstriction.^{12,13} Administration of OHBT with 2-3 ATA for 2 hours will increase Nitric Oxide (NO) level about 4-5 times greater.¹⁴

Oxygen hyperbaric therapy (OHBT) increases granulation formation around the wound tissue, accelerates angiogenesis and enhancing local synthesis of NO and prostacyclin. OHBT protects blood vessel endothelial, prevents proliferation of vascular smooth muscle cells, increases survival of endothelial cells, reduces thrombosis events and suppresses anti-inflammation effects.¹⁴

In 2001, Lisbon Consensus, a consensus between The European Society for Therapeutic Radiology and Oncology (ESTRO) and The European Committee for Hyperbaric Medicine (ECHM), evaluated study results which were in accordance with evidence-based medicine criteria and found that OHBT utilization in cancer radiation may be beneficial.¹⁵

OHBT, which is given for 20 times administrations, is intended to improve the tissue damage induced by radiation. The radiation-induced tissue damage starts to recover in the 8th OHBT session, which eventually gets better up to the 20th session.¹⁶

METHODS

This study was conducted in patients with cervical cancer (Ca cervix), who had have radiotherapy in pelvic region at Cipto Mangunkusumo hospital, and who had fulfilled the eligibility criteria. All patients signed written informed consent form. Later, a routine blood examination, rectosigmoidoscopy and endoscopic

biopsy for histopathology examination with HE staining were performed to determine the diagnosis of radiation proctitis.

By using block randomization, patients were randomized into two groups; there were some patients with OHBT and some patients without OHBT (as control group)

ELIGIBILITY CRITERIA

Inclusion criteria

- Patient with cervical cancer who had finished pelvic radiation therapy, in accordance to the therapeutic protocol of Division of Radiotherapy, Cipto Mangunkusumo hospital, in 1-6 months period of time
- Age < 55 years
- Stage I-III B
- Signed written informed consent form

Exclusion criteria

- Pneumothorax
- Patient with metabolic disease: diabetes mellitus, malnutrition, and other chronic disease
- Depression
- Refuse to participate in the study

Evaluation of histopathologic features

Evaluation of rectal histopathologic features by Hematoxyllin Eosin (HE) staining.

Materials and study subjects

The study was performed in patients with cervical cancer (Ca cervix) who had finished their pelvic radiation therapy at Division of Radiotherapy, Cipto Mangunkusumo hospital. All patients signed written informed consent form and then the study was conducted. Later, a routine blood examination, endoscopy and endoscopic biopsy followed by histopathology examination with HE staining were performed to determine the diagnosis of proctitis radiation. By using block randomization, the patients were randomized into two groups; there were some patients with OHBT and some patients without OHBT (as control). Afterwards, an evaluation and 6 months follow-up were performed.

The diagnosis of radiation proctitis was established based on history of pelvic radiotherapy, with or without clinical symptoms such as abdominal pain, diarrhea, anorexia and nausea. In addition, the rectosigmoidoscopy revealed erythema, edema, teleangiectasis, erosion, and ulcer in rectal mucosa. While pathology anatomy examination revealed greater amount of inflammation cells, followed by two major histologic appearances with Tsang and Rotterdam modification,¹⁷ i.e. hyalinated lamina propria, fibrotic sub-mucosa, vascular ectasia, fibrinoid necrosis of blood vessel wall and atypical fibroblasts.

Statistical analysis

Proportional test for radiation proctitis with Tsang, Rotterdam¹⁷ modification was performed in two subject groups, i.e. OHBT group and control group, after pelvic radiation. Data was analyzed by using chi-square (χ^2) test for two independent groups.

RESULTS

Between July 2004 and January 2006, there were sixty-five patients with cervical cancer and had finished pelvic radiation in outpatient clinic at Department of Obstetric and Gynecologic Oncology and Radiotherapy Cipto Mangunkusumo hospital who were eligible for the study. Afterwards, block randomization was performed; resulting 32 patients with OHBT treatment and 33 patients as the control group who had have symptomatic treatment as well as vitamin B and C as necessary.

Statistical analysis was estimated by using statistic software program, i.e. SPSS 11 for Windows. First measurement was performed between one to six months after pelvic radiation. The next measurement was performed one to two months later, with 32 patients in treatment group and 33 patients in control group. The third measurement was conducted six months after the first measurement, with 26 patients in OHBT group and 21 patients in control group. The third measurement included histopathology examination of rectal tissue by HE staining.

Table 1. Demographic data of patients with cervical cancer (n = 65)

Variables	Group		p
	OHBT (n = 32) Mean \pm SD	Control (n = 33) Mean \pm SD	
Age (years)	47 \pm 5.5	44.7 \pm 6.2	0.117
Body weight (kg)	57.1 \pm 14.4	54.3 \pm 10.4	0.372
Body height (cm)	153.6 \pm 6.2	153.1 \pm 4.8	0.097
Hemoglobin level (g/dL)	12.2 \pm 6.1	12.2 \pm 5.2	0.781
Leukocytes count ($10^3/\mu\text{L}$)	8 \pm 1.8	7.9 \pm 1.8	0.784
Platelets ($10^3/\mu\text{L}$)	219 \pm 43	222 \pm 42	0.772
Total radiation dose	6637.5 \pm 446.3	6724.2 \pm 687.4	0.550

Note: significant different at $p < 0.05$

Sample characteristics and demographic data distribution of the study variables

Patients in OHBT group had no significant difference in mean value of age, body weight, body height, total radiation dose, and hemoglobin level compared to the control group, with $p > 0.05$ (table 1).

Results of variables measurement

Data of the study variables were analyzed, i.e. the prevalence of post-OHBT radiation proctitis compared to the control group.

Correlation between OHBT and the prevalence of radiation proctitis

Forty-six patients of sixty-five patients in this study were evaluated for the OHBT effect on radiation proctitis (26 patients had received OHBT, 20 patients were in the control group). In the OHBT group, there were six patients (13%) who had radiation proctitis on the sixth month period. While in the control group, there were 11 patients (23.9%) who had this complication (table 1). Statistical analysis by chi-square test indicated that OHBT significantly decreased the prevalence of radiation proctitis ($p = 0.026$).

Table 2. The prevalence of proctitis radiation in OHBT group and control in sixth months after treatment

Group	Proctitis Prevalence		Total	p
	Yes	No		
OHBT	6 (13%)	20 (43.5%)	26 (56.5%)	0.026
Control	11 (23.9%)	9 (19.6%)	20 (43.5%)	
Total	17 (37%)	29 (63%)	46 (100%)	

DISCUSSION

Evaluation on the efficacy of Oxygen Hyperbaric Therapy (OHBT) in reducing proctitis - the adverse effect of radiation - is very relevant to be done; considering radiation proctitis recovery is still difficult to obtain and until now, there is no standard therapy for it. In addition, radiotherapy is still the most important therapy in management of cervical cancer, along with surgery and chemotherapy.^{18,19}

Seventy-five eligible subjects were included in this study, i.e. 35 patients in OHBT group and 40 patients in control group. In treatment group, three patients were unable to complete the therapy procedures because they were unable to fulfill 20 regular visits during the study. In control group, seven patients were unable to follow the evaluation; four patients were out of town - they had difficulty to come and visit regularly and three patients were withdrawn their selves from the study without any explanation. Thirty two patients had OHBT procedures more than 18 times. However, in the evaluation six months later, there were only 26 patients in the study; 6 patients were died at home because of their illness. In control group, there were 33 patients. After one to two months post-radiation evaluation, there were still 33 patients. After 6 months evaluation, there were 21 patients in this study, while 10 patients were died at home without any clear explanation, possibly because of their own illness. While two patients transmigrated, out of province, and had difficulty to come back for the study.

In addition, the result of homogeneity test of adverse effect and radiation proctitis indicates that we use samples with similar variation population, with $p > 0.05$. Therefore, the samples were eligible for further statistical analysis.

In this study, the average age in OHBT group was 47 years; while the average age in control group was 45 years. According to Aziz,⁴ the most prevalent case was at the age of 35-55 years in Jakarta. Therefore, this study is in accordance with the data in Jakarta.

There are some clinical parameters evaluated in patients with post-radiation cervical cancer who have OHBT, i.e. hyperbaric oxygen reduces the prevalence of proctitis. Radiation proctitis is established based on history of radiation, with or without clinical symptoms: diarrhea, abdominal pain, and tenesmus. Endoscopic examination reveals mucosa erosion and teleangiectasis, as well as two major histopathologic criteria, i.e. ectasis of vascular blood vessels and hyalinated lamina propria according to Tsang and Rotterdam¹⁷ modification. There are 13% proctitis of 32 patients in OHBT group and there are 24% proctitis of 33 patients in the control group; with $p = 0.026$. Hence, OHBT administration as much as 20 times in 6 months period, after pelvic radiation, may reduce the prevalence of radiation proctitis in patients with cervical cancer.

This result is as the same as with the case series reported by Feldmeier²⁰ - that indicates OHBT may improve radiation proctitis in four of seven patients. While Mayer¹⁵ reported his case series that five patients with rectal bleeding recover by OHBT administration. Reports of nine scientific publications with 114 case series, indicates that in patients with radiation proctitis, 41 patients (36%) recover, 68 patients (60%) get well after OHBT treatment for 20-50 times.²⁰ In this study, with 65 subjects, OHBT administration may decrease the prevalence of radiation proctitis in six months after pelvic radiation of cervical cancer compared to patients without OHBT.

CONCLUSIONS

Radiation proctitis usually occurs in patients with cancer, who have radiation therapy in pelvic region. Proctitis radiation therapy is often unfinished and very difficult, however OHBT is an alternative treatment, since it is save and secure. Compared to the control, OHBT reduces the prevalence of radiation proctitis.

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