

Does Hyperbaric Oxygen Administration Decrease Side Effect and Improve Quality of Life after Pelvic Radiation?

Suyanto Sidik*, Daldiyono Hardjodisastro**, Rianto Setiabudy***, Soehartati Gondowirdjo****

ABSTRACT

Aim: to evaluate the influence of HBOT to the side effect and quality of life after pelvic radiation.

Methods: this is an open randomized, parallel, prospective study conducted in Department of Obstetry and Gynecology, Oncology Division and Department of Radiotherapy. Endoscopy procedure was performed in Department of Internal Medicine and tissue biopsy in Department of Pathology Anatomy. The hyperbaric oxygen therapy (HBOT) was done in Dr. Mintohardjo, Navy Seal Hospital Jakarta. The side effect was measured using LENT SOMA scale ratio, the quality of life used the Karnofsky score. The difference of two mean was analyzed using student *t* test.

Results: of 32 patients undergoing HBOT and 33 patients as control, the ratio of ASE of control group was 44.1±28.2%, HBOT group was 0.7±30.1%; $p < 0.001$; the LSE of control group was 33.6±57.6%, HBOT group was -19.6±69.4%; $p = 0.008$. Quality of life of control group after intervention was 4.5±10.7%; HBOT group was 19.7±9.6%; $p < 0.001$. After 6 months of intervention the quality of life was 2.5±16.1% in the control group, and HBOT group was 15.2±14.7%; $p = 0.007$.

Conclusion: the study showed that HBOT decreased acute and late side effect, also improved the quality of life of patients with proctitis radiation.

Key words: HBOT, LENT SOMA ratio, Karnofsky score.

INTRODUCTION

Proctitis radiation is commonly found in cancer patients undergoing radiation therapy in pelvic area. Lashner¹ found more than 50% of cancer patients undergoing radiation. The late side effects (LSE) of proctitis radiation was found in 5-10% of patients receiving pelvic radiation. Gilinsky² reported acute side

effects (ASE) of radiation therapy occurred in 50-78% of cases and LSE in 2.5-25% of cases. The occurrence of proctitis radiation depends on dosage, fractionation, area and technic of radiation.³ Reducing the side effect will improve cure rate.⁴ Radiotherapy on local late stadium of cervical cancer was external radiation 2Gy (200 cGY) per day, with frequency of 5 times a week, and a total of 25 times. After that it was continued with brachytherapy (afterloading technic) using dosage of 2 x 8.5Gy (850 cGY).⁵

Acute side effect (ASE) of pelvic radiation are diarrhea, abdominal pain, tenesmus and hematochezia which occur in the first month after radiation. The late side effects are the sign of ASE in severe form (abdominal pain, diarrhea with mucus and blood, and small form of fecal mass). The symptoms occurred within 6 months after radiation.^{6,7} Monfardini⁸ reported quality of life among cancer patients receiving treatment using Karnofsky score. American Society for Therapeutic Radiology and Oncology reported the importance of scoring system in ASE and LSE due to radiation using the Late Effect Normal Tissues Subjective Objective Management and Analytic (LENT SOMA) scale.⁹

The treatment of LSE of radiation is difficult and most of the time doesn't succeed due to complexity of tissue damage after radiation. Efforts are performed to improve this condition; the hyperbaric oxygen (HBO) is one of the way.¹⁰ HBO procedure consist of delivering 100% oxygen (O₂) with pressure between 2-3 atmosphere absolute (ATA) in High Pressure Chamber (HPC). Wound healing improved by reducing the tissue hypoxia around the wound.¹¹⁻² HBOT administration of 2-3 ATA in 2 hours will increase NO (Nitric Oxide) of 4-5 times higher.¹³

In 1960, HBOT was done for the first time in Indonesia by Navy Seal in Surabaya. Loedin¹⁴ in 1969, studied the use of HBOT in tetanus patients. Lisbon consensus in 2001 between ESTRO (European society for therapeutic radiology and oncology) and ECHM (European committee for hyperbaric medicine)

* Department of Internal Medicine, Hyperbaric Medicine, dr. Mintohardjo Navy Hospital, Jakarta, ** Department of Internal Medicine, *** Department of Pharmacology, **** Department of Radiology, Faculty of Medicine University of Indonesia-dr. Cipto Mangunkusumo Hospital, Jakarta

recommended the use of HBOT in cancer patients receiving radiation therapy.¹⁵⁻¹⁷ The objectives of this study was to evaluate the influence of HBOT to side effect and quality of life of patients after pelvic radiation.

METHODS

This is an open randomized, parallel, prospective study among neck cervical cancer patients aged \leq

55 years old, stage I – IIIB that had received pelvic radiation following the protocol in Radiology Department, Sub division of Radiotherapy, School of Medicine University of Indonesia, Cipto Mangunkusumo hospital, from July 2004 until January 2006. The Exclusion criteria: pneumothorax, metabolic disease, diabetes mellitus, malnutrition, other chronic diseases, depression and not willing to join the study. To subjects agreeing to join the study, informed consent form was signed.

Table 1. The LENT SOMA scale

No.		Grade 1	Grade 2	Grade 3	Grade 4
1	Tenesmus	> 1 weeks	< 4x every week	Every day	Always
2	Stool frequency	2 – 4 x per day	4 – 8 x per day	> 8 x per day	Loss of sphincter control
3	Abdominal pain	sometimes > 1x per week	< 4 x tiap week	Colic every day	Difficult to cure
4	Feces consistency	Solid	soft	Mucoid watery	oftenly/always watery
No	Objective	Grade 1	Grade 2	Grade 3	Grade 4
5	Bleeding	Occult	Sometimes > 2 x per minggu	everyday	Massive
6	Ulcer	area < 1cm ²	area > 1cm ²	Deep ulcer	Perforation /fistula
7	Stricture	> 2/3 n Φ dilatation	1/3 – 2/3 n Φ dilatation	< 1/3 diameter	complete obstruction
No	Management	Grade 1	Grade 2	Grade 3	Grade 4
8	Tenesmus and stool frequency	Sometimes ? 2, anti diarrhea > 2 times per week	anti diarrhea > 2 per week routinely	often, anti diarrhea per day	Intervention surgery, permanent colostomy
9	Pain	Sometime not narcotics	Routine, non narcotics	Routine Narcotics	Intervention surgery, permanent colostomy
10	Bleeding	Soft Fecal, iron treatment	Sometimes transfusion	Often Transfusion	Intervention surgery, permanent colostomy
11	Ulcer	Diet modification, soft fecal	Sometime steroid	Steroid enema	Intervention surgery, permanent colostomy
12	Stricture	Diet modification	Sometime dilatation	Always dilatation	Intervention surgery, permanent colostomy
13	Sphincter control	Sometimes use tool	Often use tool	Always use tool	Intervention surgery, permanent colostomy

Table 2. Quality of Life with Karnofsky Scale

Functional Capability	Degree of Activity
Normal activity	100 % - normal no complaint No abnormality
Does not need special care	90 % - complaint with minimal symptom 80 % - normal with few symptoms
Not able of working Stayed home Needing assistance most of the time	70 % - capable of self-caring Not capable of normal activity or working 60 % - need assistance, most of the time could provide self-caring 50 % - need help and medication support
Not able of self-caring Need hospitalization or other supported care	40 % - need help and special care 30 % - need hospitalization 20 % - severely ill, hospitalization, active medication supports were needed 10 % - coma 0 % - death

In 65 patients fulfilling the inclusion criteria, the block randomization was performed and resulted in 32 patients received HBOT and 33 patients as control group. Side effect was measured using LENT SOMA scale. Routine laboratory test will be performed in all subjects, rectosigmoidoscopy and biopsy through endoscopy, clinical scoring of quality of life were measured by the Karnofsky score.

Data were analyzed using SPSS 11 program. First evaluation was performed from the first until six months after pelvic radiation. Second evaluation was performed in the first until two months later in both group (32 patients in HBOT group and 33 patients in control group). Third evaluation was performed within six months after the first evaluation of 26 patients receiving HBOT and of 21 control patients. Quality of life was measured with Karnofsky score and ratio of side effect using the LENT SOMA scale.

Place and Time

The study was conducted in Radiotherapy Department. Endoscopy procedure was done in Gastroenterology Division, Department of Internal Medicine; histopatology was performed in Department of Patology Anatomy, School of Medicine, University of Indonesia, Cipto Mangunkusumo Hospital. The HBOT was performed in Dr. Mintohardjo, Navy Seal hospital Jakarta. Every patient was prospectively followed for 6 months.

Statistical Analysis

First step of the study was analyzed using the ratio of LENT SOMA scale (appendix 1) and statistical analysis was performed using two different mean unpaired t tests. Second step of the study measured the Karnofsky score (appendix 2) and statistical analysis was done using two different mean unpaired t tests.

RESULTS

Among cervical neck cancer patients from Oncology polyclinic, Department of Obstetry and Gynecology that had performed pelvic radiation in Radiotherapy Department Cipto Mangunkusumo Hospital, we determined the stadium, recorded the side effect of radiation clinically using LENT SOMA scale and performed endoscopy in gastrointestinal division, Department of Internal Medicine. The quality of life was determined by the Karnofsky score. The results of demographic characteristic are showed in table 3.

The characteristic and total dose of radiation between the two groups are similar. (Table 3)

Table 3. Demographic Characteristic

Variable	Group	
	HBOT Mean \pm SD	Control Mean \pm SD
Age (years)	47 \pm 5,5	44,7 \pm 6,2
Body weight (kg)	57,1 \pm 14,4	54,3 \pm 10,4
Body height (cm)	153,6 \pm 6,2	153,1 \pm 4,8
Hemoglobin concentration (g/dL)	12,2 \pm 6,1	12,2 \pm 5,2
Leucocyte count ($10^3/\mu\text{L}$)	8 \pm 1,8	7,9 \pm 1,8
Trombocyte count ($10^3/\mu\text{L}$)	219 \pm 43	222 \pm 42

The first evaluation conducted before HBOT included recording of quality of life using Karnofsky score, side effect using LENT SOMA scale, later called K-1 and Lent-1, the results are shown in table 4.

Table 4. First Evaluation Before HBOT

Variable	Group	
	HBO (mean \pm SD)	Control (mean \pm SD)
K-1	73.8 \pm 6.0	74.6 \pm 8.3
Lent-1	7.7 \pm 2.0	6.8 \pm 2.3

K-1 : Quality of life before intervention
Lent-1: Side effect before intervention

This study will analyze the difference mean before and soon after intervention, reported in percentage. Any difference of quality of life and side effect, before and after HBOT will be later called $\Delta K21$ and $\Delta Lent21$.

The difference ratio before intervention and on 6 months will be reported in percentage. The study will report also the difference in quality of life, side effect after 6 months, after intervention and will be called as $\Delta K31$, $\Delta Lent31$, $\Delta MVD31$. (Table 5)

The variables analyzed will include quality of life and side effect.

Table 5. Quality of Life and Side Effect Soon After Intervention and on 6 Months

Variable	Group		P
	HBO	Control	
$\Delta K 21$ (%)	19.67 \pm 9.64	4.53 \pm 10.74	<0.001
$\Delta K 31$ (%)	15.27 \pm 14.74	2.47 \pm 16.11	0.007
$\Delta Lent 12$ (%)	44.12 \pm 28.22	0.71 \pm 30.16	<0.001
$\Delta Lent 13$ (%)	33.64 \pm 57.64	-19.69 \pm 69.44	0.008

$\Delta K 21$ = ratio of quality of life before and soon after intervention
 $\Delta K 31$ = ratio of quality of life before and soon after 6 months of intervention
 $\Delta Lent 12$ = ratio of side effect before and soon after intervention
 $\Delta Lent 13$ = ratio of side effect before and soon after 6 months of intervention

DISCUSSION

Short term effect of HBO was vasoconstriction and followed by vasodilatation; increased oxygen supply that reduced tissue oedema, activated phagocytosis function, increased the effect of anti inflammation,¹⁵⁻¹⁷ and the long term effects were neovascularization^{17,18} induced collagen production through fibroblast as shown by wound healing and tissue regeneration on radiation.

A total of 75 subjects with cervical neck cancer after pelvic radiation eligible for the study were grouped as followed: 35 patients received HBOT and 40 patients

are taken as control. In the first group, 3 patients failed to complete treatment procedure due to difficulty to attend regular visit to receive treatment. In the control groups, 7 patients were failed to evaluate; 4 patients were lived outside Jakarta and not available to be followed up and 3 patients were dropped out. Among 32 patients receiving HBOT, most of them received HBOT for more than 18 times, but during 6 months follow up only 26 patients still on the study, and 6 patients were died. All patients were in control group, were still in the study of 1 until 2 months after radiation. During followed up time of 6 months 9 patients died and 2 patients moved out to other city.

In this study, the evaluation of clinical parameter among subjects of cervical neck cancer after radiation was discussed as follows:

Side Effect Improvement After Radiation

The LENT SOMA scale was used to evaluate ASE. We calculated the percentage of different mean of ASE soon after HBOT and before the statistical analysis showed significant different ($p < 0.001$) compared to control group.

It showed that HBOT strongly reduced ASE after pelvic radiation. This result supported by the study of Feldmeier¹⁷ that showed serial cases of 8 patients after pelvic radiation, 7 patients experienced proctitis, 4 of those patients were improved. One patient had enteritis and did not showed any improvement

The LSE of pelvic radiation was calculated from percentage of difference mean of side effect occurred in 6 months after intervention and before HBOT. The results were compared to control group. The statistical analysis showed significant different ($p = 0.008$). This findings were similar to studies by Mayer¹⁶ and Feldmeier¹⁷ that showed HBOT reduced side effect and transfusion after pelvic radiation. Gouello reported retrospective study of 36 patients and 2 of 3 patients with chronic complaints in GIT tract were improved after HBOT.

Quality of Life Improvement After Radiation

We found improvement in quality of life among cervical neck cancer after radiation using the Karnofsky score. The statistical analysis using unpaired t-test showed the mean of Karnofsky score before and after intervention ($\Delta Karnofsky1-2$) in HBOT group were significantly different compared to control ($p < 0.001$). The same results also showed after 6 months of intervention ($p = 0.007$). These results were supported by the study of Mayer et al¹⁶ that HBOT reduced the severity of symptoms due to radiation that improved the quality

of life. Marx^{18,19} had explained the tissue injury after radiation that resulted in 3H: hypoxia, hypocellular, hypovascular, and HBOT will increased oxygen perfusion and increase neovascularization in the injured tissue.

The study limitation was the design; patients were aware of their treatment, so the subjective bias from patients could be influenced by the results.

CONCLUSION

The HBOT procedure yield hyperoxia, hypervascular and hypercellular that improved the tissue damage after pelvic radiation. This condition will decreased acute and late side effect showed by LENT SOMA scale and improved quality of life shown by Karnofsky score.

REFERENCES

- Lashner BA. Miscellaneous diseases of the colon. In: Grendell JH, Mc Quard KR, Friedman SC, eds. *Current diagnosis & treatment in gastroenterology*. Stamford: Appleton & Lang; 1996. p. 427–33.
- Gilinsky NH. The Natural history of radiation induced proctosigmoiditis an analysis of 88 patients. *Q J Med*. 1983; (52):40–53.
- Perez CA. Cervix uterine. In: Perez CA, Brady LW, eds. *Principles and practice of radiation oncology*. Philadelphia: Lippincott-Raven Publisher; 1998. p. 3, 1733–819.
- Aziz MA. Skrining dan deteksi dini kanker serviks. In: Ramli HM, Umbas R, Panigoro SS, eds. *Deteksi dini kanker*. Jakarta: Balai Penerbit FKUI; 2000. p. 97-112.
- Azis MF, Kampono N, Syamsuddin S, dkk. Standar pelayanan medik kanker serviks preklinik, preinvasif, invasif. *Buku penuntun–pelayanan–pendidikan–penelitian Subbagian Onkologi Ginekologi*. Jakarta: FKUI; 1998. p. 74–90.
- Fajaringando LF. Morphology of radiation effects on normal. In: Perez CA, Brady LW, eds. *Tissues in principles and practice of radiation oncology*. Philadelphia: JB Lippincott Co; 1992;2: 114–23.
- Bentzen SM, Overgaard J. Clinical manifestations of normal tissue damage. In: Steel GG, ed. *Basic clinical radiobiology*, London: The Bath Press; 1997. p. 87–97.
- Union Internationale Control Cancer. Evaluation of the cancer patient and the response to treatment. In: Monfardini S, et al, eds. *Manual of cancer chemotherapy*. Geneva. 1981;3:17–26.
- American Society for Therapeutic Radiology and Oncology. LENT SOMA scales for all anatomic sites. *Int J Radiat Oncol Biol-Phys*. 1995;30:1049-92.
- Mitchell RN, Cotran RS. Acute and chronic inflammation. In: Kumar V, Cotran RS, Robbins SL, eds. *Basic pathology*. Philadelphia: WB Saunders Co; 2003;7:33–59.
- Juarez EC. Hyperbaric oxygen therapy. *J Am Academy General Physic*. 2003;4:3;1–6.
- Jain KK. Hyperbaric oxygen therapy in wound healing, plastic surgery, and dermatolog. In: Jain KK, ed. *Hyperbaric medicine*. Göttingen: Hogrefe & Huber Publishers; 2004;3:147–66.
- Smith S. Physiological and pharmacological basis of hyperbaric oxygen therapy. In: Bakker DJ, Cramer FS, eds. *Hyperbaric text book of surgery preoperative care*. USA: Best Publishing Co; 2002. p. 63–110.
- Loedin AA. Hyperbaric oxygenation (HBO²) penelitian tentang penggunaannya pada penyakit tetanus, disertasi. Surabaya: Univ. Airlangga, 1969.
- Sumen G, Cimsit M, Eroglu L. Hyperbaric oxygen treatment reduces collagen induced acut inflammation in rats. *Eur J Pharmacol*. 2001;431:265-8.
- Mayer R, Hamilton-Farrell MR, Van der Kleij AJ, et al. Hyperbaric oxygen and radiotherapy. *Strahlenther Onkol*. 2005; 2:113–23.
- Feldmeier JJ, Hampson NB. A systematic review of the literature reporting the application of hyperbaric oxygen prevention and treatment of delayed radiation injuries: an evidence based approach. *Undersea & Hyperbaric Med J*. 2002; 29:1:4–30.
- Marx RE, Ehler WJ, Tayapongsak P, et al. Relationship of oxygen dose to angiogenesis induction in irradiate tissue. *The Am Jour of surgery*. 1990;160:519-24.
- David LA, Sandor GKB, Evans AW, Brown DH. Hyperbaric oxygen therapy and mandibular osteoradionecrosis: a retrospective study and analysis of treatment outcomes. *Br J Oral Maxillofacial surg*. 2003;23;3:173-6.