

Hyperbaric oxygen therapy as adjunctive strategy in treatment of glioblastoma multiforme

Lei Huang^{1,2,#,*}, Warren Boling^{1,#}, John H. Zhang^{1,2,3,#}

1 Department of Neurosurgery, School of Medicine, Loma Linda University, Loma Linda, CA, USA

2 Department of Basic Sciences, Division of Physiology, School of Medicine, Loma Linda University, Loma Linda, CA, USA

3 Department of Anesthesiology, School of Medicine, Loma Linda University, Loma Linda, CA, USA

*Correspondence to: Lei Huang, M.D., lhuang@llu.edu.

orcid: 0000-0002-7211-8337 (Lei Huang)

#These authors contributed equally to this work.

Abstract

Glioblastoma multiforme (GBM) is the most common type of malignant intracranial tumor in adults. Tumor tissue hypoxia, high mitotic rate, and rapid tumor spread account for its poor prognosis. Hyperbaric oxygen therapy (HBOT) may improve the sensitivity of radio-chemotherapy by increasing oxygen tension within the hypoxic regions of the neoplastic tissue. This review summarizes the research of HBOT applications within the context of experimental and clinical GBM. Limited clinical trials and preclinical studies suggest that radiotherapy immediately after HBOT enhances the effects of radiotherapy in some aspects. HBOT also is able to strengthen the anti-tumor effect of chemotherapy when applied together. Overall, HBOT is well tolerated in the GBM patients and does not significantly increase toxicity. However, HBOT applied by itself as curative strategy against GBM is controversial in preclinical studies and has not been evaluated rigorously in GBM patients. In addition to HBOT favorably managing the therapeutic resistance of GBM, future research needs to focus on the multimodal or cocktail approaches to treatment, as well as molecular strategies targeting GBM stem cells.

Key words: glioblastoma; hyperbaric oxygen; radiotherapy; apoptosis; inflammation; tissue oxygenation

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INTRODUCTION

Glioblastoma multiforme (GBM) is the most common type of malignant intracranial tumor in adults. The overall prognosis is poor even in patients receiving complete surgical resection combined with radio-chemotherapy.^{1,2} Tumor tissue hypoxia activates transcription factors that support cancer cell survival and migration, contributing to radiotherapy/chemotherapy resistance.³⁻⁵ Hypoxic tumor volumes were inversely correlated to the GBM progression time and survival.⁵ Previous studies demonstrated that a hypoxic microenvironment promoted and maintained GBM stem cells phenotypes favoring the development of radiotherapy and chemotherapy insensitivity.^{6,7} Enhancing the tumor oxygenation may offer an adjunctive therapeutic strategy to overcome the unfavorable effects of hypoxia on GBM treatment.⁸

Hyperbaric oxygen therapy (HBOT) is a treatment that delivers 100% oxygen at a pressure greater than atmospheric pressure at sea level.⁹ The net effect of HBOT consists of increases in partial pressure of oxygen (PO₂) within the blood and subsequent mitochondrial metabolism/tissue oxygenation.¹⁰ HBOT have used in a variety of diseases and shown benefits to the outcomes.⁹⁻¹² The rationale to apply HBOT to cancer is that hyperbaric oxygen (HBO) may help improve oxygen tension within the hypoxic regions of the neoplastic tissue. However, HBOT alone may not offer a curative effect against tumors.^{13,14} HBOT has often been investigated as an adjuvant treatment to potentiate radio- and chemotherapy effects in the treatment of cancer.¹⁵

In this review, we summarize the effects of HBOT when used in combination with the standard therapeutic modalities in the setting of GBM.

GLIOMA TISSUE HYPOXIA AND RATIONALE FOR HBOT APPLICATION AS ADJUNCTIVE THERAPY TO RADIOTHERAPY

The hyper-proliferation feature of GBM cancer cells results in the formation vessel-remote and subsequent highly hypoxic area. Although the low PO₂ of tumor tissue can stimulate vascularization, the neovascularization, usually consisting of abnormal occluded vessels or capillaries, may further promote the formation of tumor tissue hypoxia.^{16,17} In the GBM patients, peritumoral tissue had a significantly higher PO₂ values than intratumoral tissues.¹⁸ Such hypoxic microenvironment favors the rise of hypoxic tumor cells which are adaptive to low PO₂.^{17,19,20} The response and the adaptation of cells to hypoxia are controlled by low PO₂ activated transcription factor of hypoxia-inducible factor 1 (HIF-1) and autophagy induction.^{21,22} A correlation between higher HIF-1 alpha (HIF-1α) protein level and transcriptional activity in GBM cell lines has been reported.²² Autophagy mechanism has also been associated with GBM cancer cell resistance to hypoxic stress.¹⁷ Intratumor hypoxia represents a major mechanism of tumor resistance to radiotherapy and/or chemotherapy in GBM.^{23,24} Given that HBOT is a medical intervention to improve the dissolving O₂ level in blood plasma, it may increase the sensitivity of hypoxic GBM tissues to irradiation and/or chemotherapy by raising intratumoral oxygen tension. In GBM patients, normobaric 100% O₂ inhalation (15 minutes at rate of 3 or 6 L/min) did not significantly improve the PO₂ in both peri- and intratumoral tissues. HBOT (60 minutes at 2.8 atmospheres absolute (ATA); 1 ATA = 101.35 kPa) significantly increased

and maintained the PO₂ in both peritumoral and intratumoral tissues for 35 minutes and 30 minutes, respectively.¹⁸

However, neovascularization is one of the long-term effects associated with HBOT.²⁵ The potential tumor-enhancement of HBOT is needed to be precluded. In two comprehensive reviews of published preclinical and clinical data, both Feldmeier²⁶ and Moen²⁷ consistently concluded that there were no evidences to suggest the correlation between intermittent HBOT exposure and malignant growth or metastases. Bennett et al.²⁸ further reviewed the benefit and potential risks of HBOT as radiosensitizer when applying either simultaneously with or immediately following radiation therapy on various solid tumors including head and neck cancer and urinary bladder cancer but not GBM. In their conclusion, some evidences supported that HBOT improved local tumor control and mortality as well as reduced local tumor recurrence in head and neck cancer. The HBOT efficacy may only be evident when radiotherapy is given in a small number of sessions and each with a relatively high dose. The significant adverse effects of oxygen toxic seizures and severe tissue radiation injury associated with HBOT demanded a cautious interpretation.²⁸

CLINICAL STUDY

HBOT applied by itself as curative strategy against GBM has not been evaluated rigorously in GBM patients. All the clinical studies evaluated the treatment effects applied HBO as adjunctive therapy to radio- and/or chemotherapy in post-surgical GBM patients. Two specific modalities of HBOT-radiotherapy combination were investigated including radiation during HBOT and radiation within 15 minutes after HBOT. Overall, the total of 11 clinical studies were all conducted in relative small patient population and most were lacking of control groups in the study design. Comparing to radiotherapy during HBOT, the application of post-surgical radiotherapy within 15 minutes after HBOT was commonly used as a standard approach with better performance feasibility and less toxicity to normal surround tissues. When applying radiation right after HBOT in post-operative GBM patients, there was insignificantly toxicity directly associated with HBOT except for middle ear barotraumas or tympanitis. In some aspects, HBO as an adjunctive therapy seems to strengthen the efficacy of radio-chemotherapy either applied initially or in the recurrent GBM tumors. However comprehensive evaluations are definitely needed to validate such findings in series of well design clinical trials with a large sample size.

The clinical trials and main findings are shown in **Additional Table 1**.

Radiation during HBOT

The clinical trials first investigated the synergistic effect of simultaneous administration of radiotherapy and HBOT. In 1977, a pilot controlled clinical trial evaluated the effect of performing radiotherapy during HBO exposure against previously untreated GBM.²⁹ A total of 80 untreated glioblastoma patients were enrolled in which 38 patients received radiotherapy treatment with HBO and 42 patients in atmospheric air. Radiotherapy combined with HBO had a tendency toward improved 18- and 36-month survivals while the toxicity of

HBO was well tolerated by most of the patients. Serious side effects such as radiation necrosis and convulsive seizures were observed in some patients.²⁹ Following this early study, a single arm phase I trial investigated the use of Fluosol and radiation during HBOT in 16 patients with anaplastic astrocytoma or GBM.³⁰ Patients received radiotherapy treatment in an HBO chamber at 3 ATA with 6 Gy weekly fractions following Fluosol administration. No significant chronic toxicities were observed. The results demonstrated that HBO could be safely used adjunctively to radiation and Fluosol in the treatment of human brain tumors.³⁰ However, the combination regimen of performing radiation during HBO exposure has not been applied as a standard treatment because of practical difficulties for radiation set-up and potential risk of increased radiation side effects within surrounding normal tissues.³¹

Radiation subsequent to HBOT

Given that oxygen pressure was a major factor impacting radiosensitivity, Beppu et al.¹⁸ demonstrated that HBOT (60 minutes at 2.8 ATA) significantly increased and maintained the PO₂ in both peritumoral and intratumoral tissues for 35 minutes and 30 minutes, respectively. The PO₂ was greater than 30 mmHg (1 mmHg = 0.133322 kPa) at 15 minutes after HBOT, suggesting maximal radio-sensitivity.³² This finding provided a rationale for starting radiation within 15 minutes of HBO decompression when applying HBO as an adjunctive therapy to radiation. Kohshi et al.^{33,34} reported the clinical studies applying radiotherapy immediately after HBO in post-operative patients with malignant gliomas. While local irradiation combined with nitrosourea-based chemotherapy was administered in control group of 14 patients, HBOT was administered prior to radiation in an HBOT group of 15 patients. The authors concluded that radiation treatment within 15 minutes but not 30 minutes after HBOT decompression significantly improved median survivals from 12 months in control group to 24 months in HBOT group, as well as decreased tumor regression.³⁴ The HBOT benefit was confirmed in a single arm phase II study in which a modified radiotherapy 15 minutes after HBOT (60 minutes at 2.8 ATA) combined with interferon-beta and nimustine were administered in the post-operative patients with supratentorial malignant gliomas.³⁵ Approximately 76.9% of total 36 patients maintained or increased Karnofsky performance scale with tolerable toxicity. The response rates for glioblastoma, anaplastic astrocytoma were 50% and 30%, respectively.³⁵ Ogawa's team³⁶⁻³⁸ consistently reported the tolerance and beneficial effects of HBOT addition to radiotherapy in serial single arm studies of non-previously treated patients. A prospective single arm clinical trial of 21 patients indicated that radiotherapy less than 15 minutes after HBOT (30–60 minutes at 2.8 ATA) with nimustine chemotherapy was feasible for high-grade gliomas.³⁶ During HBOT, middle ear barotrauma was occurred in 14% of patients, which required tympanostomy with tube placement.³⁶ Furthermore, the study was expanded to a phase II trial in which the efficacy and toxicity of radiotherapy immediately after HBOT with chemotherapy consisting of procarbazine, nimustine and vincristine administered during and after radiotherapy.³⁷ A total of 41 patients (31 patients with glioblastoma and 10 patients with grade 3 gliomas) were enrolled. All 41



patients were able to complete a total radiotherapy dose of 60 Gy immediately after HBOT (30–60 minutes at 2.8 ATA) with one course of concurrent chemotherapy. In a total of 30 assessable patients, there were no serious side effects including nonhaematological or late toxicities.³⁷ Long-term follow-up of these patients showed that the median overall survival times in all 57 patients,³⁹ patients with glioblastoma, and 18 patients with Grade 3 gliomas, were 20.2 months, 17.2 months, and 113.4 months, respectively. The authors concluded that radiotherapy delivered 15 minutes after HBO (60 minutes at 2.5 ATA) with multiagent chemotherapy was safe, with virtually no late toxicities, and seemed to be effective in patients with high-grade gliomas.³⁸ Such survival benefits appeared to also exist in high-grade gliomas patients with recurrence from previous radiotherapy with chemotherapy.³⁹ Consecutive patients with recurrent high-grade gliomas who had previously received radiotherapy with chemotherapy (14 patients with anaplastic astrocytoma and 11 with GBM) had fractionated stereotactic radiotherapy less than 7 minutes after HBOT (60 minutes at 2.5 ATA) that resulted in actuarial median survival time of 19 months for patients with anaplastic astrocytoma and 11 months for patients with GBM.³⁹ Most recently, a study investigated the effects of the combined therapy of radiotherapy using post-operative intensity-modulated radiotherapy boosts immediately after HBOT (60–90 minutes at 2 ATA) with chemotherapy. The result showed a 2-year overall survival of 46.5% and progression-free survival rates of 35.4%. HBOT was tolerated by most of the 24 patients except for one patient who developed Grade 2 aural pain.⁴⁰

Only one study evaluated the effect of HBOT as adjunctive therapy to chemotherapy alone. In 6 patients with malignant or brainstem gliomas, HBOT (60 minutes at 2 ATA) was able to prolong the biological residence time of carboplatin chemotherapy.⁴¹

Serious side effects such as radiation necrosis and convulsive seizures were observed in some patients when performing radiotherapy during HBOT.²⁹ Overall, permissible toxicity except for middle ear barotraumas or tympanitis were associated directly with HBOT if radiotherapy was applied after HBOT.³³⁻³⁹

Eligibility criteria, standard procedure of HBOT adjunctive to radiotherapy in GBM

The aforementioned clinical studies have their own specific inclusion and exclusion criteria. For all the studies which applied post-operative radiation fraction immediately after each HBOT (the current standard modality), the main eligibility criteria were in the following³³⁻³⁹: 1) male or female patients at age of 14–85 years old; 2) histological confirmed glioma diagnosis according to World Health Organization (WHO) criteria; 3) post-operative Karnofsky performance scale (KPS)⁴² greater than 60 or KPS index greater than 40%; 4) not received any previous radiotherapy or chemotherapy or receiving initial post-operative radio-chemotherapy but with evidence of substantial regrowth of lesion (recurrence); 5) no evidence of cardiopulmonary diseases or sinusitis. Some studies have additional enrollment requirements including the absence of infection, normal functions of bone marrow,

kidney and liver.³⁵⁻³⁸ Other studies excluded the patients without residual tumor,^{33,34,39} brain MRI identified post-operative gliosis³³⁻³⁹ or discontinued the HBO/radiation immediately upon the emergency of brain magnetic resonance imaging (MRI)-defined tumor progression at the middle term treatment evaluation.³⁵

The HBOT was administered in either monoplace or multiplace hyperbaric chamber. The chamber was compressed with 100% oxygen for 15 minutes^{33,34,39} or with air for 18 minutes.^{30,36-38} Inhalation 100% oxygen through an oxygen mask for 30–60 minutes at 2.0–2.8 (ATA followed by 15–18 minutes of decompression with oxygen inhalation.³³⁻³⁹ The duration of time from completion of decompression to radiation was within 15 minutes for each irradiant fraction.³³⁻³⁹

PRECLINICAL STUDY

A few preclinical studies have been published focusing on the effects of HBOT alone or as adjunctive therapy against glioma using *in vitro* or *in vivo* model. In U251 glioblastoma cell culture, HBOT strengthened not only the irradiation effect on clonogenic survival,⁴³ but also temozolomide effects on inhibiting glioma cell growth.⁴⁴ The synergistic effects were confirmed in animal model *in vivo*. In a rat model of transplanted with rat C6/Lac Z glioma, a combination of HBO with temozolomide enhanced the treatment efficacy of temozolomide and resulted in a more effective reduction of tumor growth.⁴⁵ In a GFP transgenic nude mice model bearing human glioma, the effects of HBO (2.5 ATA for 90 minutes) in sensitizing nimustine chemotherapy were investigated.⁴⁶ Following 28 days treatment, HBO inhibited inflammation and glioma cell proliferation as well as reinforcing the effects of nimustine therapy. The underlying mechanism was partially through increasing tumor tissue oxygenation and suppressing the HIF-1 α , tumor necrosis factor-alpha (TNF- α), interleukin-1 beta (IL-1 β), vascular endothelial growth factor (VEGF), matrix metalloproteinase-9 (MMP-9) and nuclear factor-kappa B (NF- κ B).⁴⁶

However, the HBO effect alone on gliomas were not conclusive. While some studies demonstrated inhibition effects,^{47,48} the others showed the HBO promoted the tumor growth.^{14,49} After exposing cultured U87 human glioma cells exposed to HBO (3.25 ATA) or normobaric hyperoxia for 60 minutes, the membrane lipid peroxidation and membrane blebbing increased with O₂ concentration as a result of hyperoxia.⁴⁸ In nude rats with transplanted BT4C gliomas, Stuhr et al demonstrated that effects of hyperoxia in suppressing tumor growth.⁴⁷ Treatments of either normobaric 100% oxygen therapy or HBOT at 2 ATA were delivered to the rats three times with 90 minutes/time over 8 days. Resulting from both hyperoxia regimen, the increased PO₂ level in the gliomas tissue significantly suppressed the tumor growth associated with enhanced tumor cell apoptosis, reduced vascular density and down-regulation of angiogenesis genes.⁴⁷ However, the unfavorable direct effect of HBO on a glioma was observed in a mouse model of intracranial transplanted glioma. Using bioluminescent imaging, Wang et al.¹⁴ consistently demonstrated that HBO promoted the growth of intracranial transplanted GL261-Luc glioma cells *in vivo*. In

addition, immunohistochemistry showed the HBO treatment increased the microvessel density and inhibit the apoptosis of the transplanted malignant glioma. In a rat model of glioma, Ding et al.⁴⁹ demonstrated that HBO alone may promote tumor growth. The authors recommended that HBO should be combined with radiotherapy or chemotherapy.

In summary, the preclinical studies on HBOT in treatment of GBM were limited. A few rodent studies support the efficacy of applying HBOT as adjunctive therapy to radio-chemotherapy with underlying mechanism of improved tumor tissue oxygenation and reduced inflammatory response.⁴⁴⁻⁴⁶ However, the application of HBOT alone as therapeutic anti-GBM strategy is not recommended due to the completely opposite findings reported in other studies. The increased tissue hyperoxia by HBOT itself either suppressed^{47,48} or promoted^{14,49} transplanted glioma tumor growth by its effects on tumor cell apoptosis and tissue angiogenesis. Future animal studies are warranted to elucidate the detailed signaling pathways regulated by HBOT alone or in combination with other anti-cancer therapy, which may identify the potential translation targets for further clinical investigation in the settings of GBM.

CONCLUSION AND FUTURE DIRECTION

The clinical and preclinical data suggests that radiotherapy immediately after HBOT may increase the sensitivity of hypoxic tumor cells to radiotherapy to some extent. The addition of HBOT to radiation and/or chemotherapy is tolerated and may be beneficial in patients with GBM. However, most clinical trials were single arm studies with a small sample size of patients. The prospective randomized controlled clinical trials are needed to 1) verify the beneficial effects in larger patient population; 2) optimize the HBOT regimen in combination with different radiotherapy modalities. Due to controversial findings in the preclinical study that HBOT alone may promote the recurrence of GBM, it is recommend that HBOT should be applied as adjunctive strategy to radio and/or chemotherapy in the treatment of post-surgical GBM patients.

Importantly, emerging evidence has demonstrated the importance of cancer stem cells in GBM recurrence and therapeutic resistance.^{7,50} In addition to HBOT approach to improve the hypoxic tumor cells sensitivity to radio- and chemotherapy, basic science and clinical research are needed to develop multimodal treatment approaches that include molecular strategies targeting at GBM stem cells.

Author contributions

LH conceived and drafted the manuscript and WB revised the manuscript. JZ was the corresponding author and participated in conceiving the manuscript. All authors read and approved the final manuscript for publication.

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Open peer reviewer

Sheng Chen, Zhejiang University, China.

Additional file

Additional Table 1: Summary of clinical studies in hyperbaric oxygen therapy as adjunctive strategy in treatment of glioblastoma multiforme.

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