

Role of hyperbaric oxygen in glioma: a narrative review

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Abstract

Gliomas are common brain mass with a high mortality rate. Patients with gliomas have a severely bad outcome, with an average survive duration less 15 months because of high recurrent rate and being resistant to radio-therapy and chemistry drugs therapy. Hyperbaric oxygen is extensively taken as an adjuvant treatment for various disease conditions. To know the characteristics of hyperbaric oxygen as a remedy for gliomas, we find that, in general, hyperbaric oxygen shows an obviously positive effect on the treatment of gliomas, and it can also relieve the complications caused by postoperative radiotherapy and chemotherapy of gliomas. Whereas, several researches have shown that hyperbaric oxygen promotes glioma progression.

Key words: adverse; complication; efficacy; glioma; HBO; hyperbaric oxygen; mechanism; treatment

doi: 10.4103/2045-9912.324589

How to cite this article: Wang WJ, Ding JS, Sun Q, Xu X, Chen G. Role of hyperbaric oxygen in glioma: a narrative review. *Med Gas Res.* 2022;12(1):1-5.

INTRODUCTION

Gliomas are the most frequent primary intracranial masses and have a potential feature of invasive growing,¹ which accounts about 30% intracranial or spinal masses, characteristic 80% of malignancy in brain.² Glioma is next to stroke³ which can be caused by carotid artery stenosis⁴ and leptomeningeal disorder.⁵ Causing cognition dysfunction,⁶ stroke can be conducted by ¹³C magnetic resonance imaging.⁷ Stroke is researched in many animal experiments,⁸ and optogenetic stimulation could reduce neuronal nitric oxide synthase expression after stroke.⁹ Cerebral organoids repair ischemic stroke brain injury,¹⁰ glycyrrhizin prevents hemorrhagic transformation and improves neurological outcome in ischemic stroke¹¹ and exo-transplantation of endothelial-specificity progenitor cells reduced ischemia damage.¹² Compared with stroke, it is very difficult to cure the glioma, which is currently treated with surgical resection, accessorial radio-therapy or chemistry drugs therapy like generation II alkylating agent temozolomide (TMZ) are usually used after operation.¹³ Despite a lot of therapy with many surgical resection times, radio-therapy and chemistry drugs therapy having effects, the curing effectiveness is not ideal because of high recurrence rates and being resistant to radio-therapy and chemistry drugs therapy.¹⁴ Hyperbaric oxygen (HBO), which is taken as an adjuvant cure for different disease conditions, usage of 100% oxygen gas burdening increased atmospheric pressure. HBO can be taken to treat inadequate wounds healing, sickness of decompression and poison of carbon monoxide.¹⁵ Tumor hypoxia is an important factor involving promoting glioma invasion,¹⁶ which promotes bad changes of metabolism and intensifies and apoptosis, and angiogenesis.¹⁷ The alters are adjusted by hypoxia induced factor-1, depended on the cellular

oxygenation level, can be inhibited by HBO.¹⁸ Thus, we want to delve into the effect of HBO in the treatment of glioma. We searched PubMed for relevant articles published until 2020.

THE EFFICACY OF HYPERBARIC OXYGEN IN GLIOMA

The experiments and clinical studies are shown in **Additional Table 1**.

Experimental research

A pre-clinical research report shows that initial HBO treatment can change the hypoxic microenvironment of gliomas, where the proportion of CD133⁺A2B5⁺ cells was significantly reduced, and can also reduce the stemness-associated characteristic of cancer stem cells by the expression of stemness-related genes like Nanog and oncostatin M. However, their outcomes disclosed that primary HBO treatment upregulated transforming growth factor- β , but the scale of CD133⁺ cells did not change obviously, which was minor different from the previous research.²⁷ Xie et al.²³ take advantage of the naked mice without health immune reaction with transplanted glioma in paws to investigate whether vitexin, which is a suppressor of hypoxia induced factor-1 α , could strengthen irradiation-therapy sensing of HBO on glioma. Surprisingly, they found the results focused were significantly reduced compared with groups without HBO. Thus, vitexin can accelerate HBO to sensitize the glioma irradiation-therapy, and representing HBO has wide usage in the treatment of gliomas. However, the research found no precise effect of vitexin on the pentose phosphate pathway in this study, which needs deeper study.²³ Zeng et al.¹⁹ explored underlying mechanism of the combination treatment of porous silicon nanoparticles burdened with TMZ and HBO therapy. The experiments *in vitro* present that NCH421-K and



C-type-6 cells had added sense, and the expression of stem-like cell markers and hypoxia related molecules were decreased in the combined dealing. Investigation *in vivo* shows that it has obvious tumor-killing effects in mouse burdening C6 tumor, which is in line with *in vitro*.¹⁹ Zembrzuska et al.²⁰ concluded that the combination of isothiourea derivative-HBO shows a promisingly potential therapeutic approach for malignant glioma treatment. They tested the efficacy of different oxygenic states playing cellular toxicity on bromide-drugs curing the Type-98-G glioblastoma. Cell proliferation could be reduced and the T98G cell sensitivity to bromide-drug was increased by HBO. In the same time, hypoxia induced factor-1 α expression levels were decreased under HBO. While protein kinase D1 phosphorylation and activation exhibit no significant changes in the other researches.²⁰ Xie et al.²² improved the density of oxygenic gas in tumor and the tumor-killing scale was escalated to 84.2% within the TMZ-loaded porous silicon nanoparticles combined with HBO. In response to TMZ-loaded porous silicon nanoparticles treatment with HBO, the viability of hypoxia-induced glioma C6 cells were decreased and cell cycle was stuck at G2/M period, which represents HBO as an adjuvant to TMZ nanoparticle could inhibit glioma growth.²² Lu et al.²⁹ established a green fluorescent protein transgenic nude mice bearing human glioma model to investigate the efficacy of the combined effects of nimustine and HBO. They found that HBO therapy can suppress glioma cell growing and pro-inflammatory cell infiltrating, and exert a sensitizing effect on nimustine therapy partially through promoting oxygen pressure in tumor tissues and lower expression levels of hypoxia induced factor, tumor necrosis factor, interleukin, vascular endothelial growth factor, matrix metalloproteinase 9, and nuclear factor- κ B.²⁹ Lu et al.³⁰ explored whether HBO combined with irradiation decreases the capability of U251 glioblastoma cells for relapse and metastasis. Results showed that the clonogenic survival diminished by 70% through the combination of HBO and irradiation, the accumulated distance travelled by cells reduced by 11% with their combination, and combination lowered travel by 41%. Thus, HBO could strengthen the effect of irradiation on clonogenic survival. Aiming to explore whether HBO can help medicine distribution and strengthen the consequence of TMZ, Lu et al.²⁹ treated cultured glioma U251 cells with TMZ and HBO. Results presented that combination treatment together restrained existence and conducted apoptosis and death of U251 cells by decreasing the deep of factor to help vessel formation and multidrug resistance-associated protein-1. They accepted the conclusion that the association of TMZ and HBO may be a helpful curing for glioma with poor outcomes. The research just focused on experiment *in vitro*, thus, *in vivo* animal or human studies are required to prove the effect of HBO on glioma. Dagistan et al.³⁸ tested the combination efficacy of TMZ associated with HBO in gliomas disease pattern of rats by three-dimensional syringe of C-6-type Lac-Z-type rattus gliomas into the Wistar rats' brain. Level of Ki67 was significantly decreased and the total necrotic area ratio was decreased significantly in tumor tissue of the combination treatment of TMZ and HBO. Stuhr et al.²⁶ established BT-type-4C rat glioma xenografts to explore

the function of hyperoxic treatment on it. Hyperoxic treatment can cause less than 60% reduction in tumor growth and induced a significant increase in the fraction of apoptotic cells (~21%). At the same time, the mean vascular density was reduced in the central parts of the tumors. Regarding the biological effects of HBO on tumors, the therapeutic implications may be more complex. HBO treatment may recruit hypoxic tumor cells into the pool of proliferative cells. This should in turn lead to enhanced tumor growth and eventually increased neovascularization. Also, athymic nude rats lack normal immune system, which could not simulate the condition of patients clinically.²⁶

Clinical research

A pilot study showed that all nine patients with malignant gliomas receiving the treatment of radiotherapy combined with HBO showed more than 50% regression of the tumor, and in 4 of them, the tumors disappeared completely. Kohshi et al.³³ operated a clinical test to look for the effectiveness of eradication-therapy associated by HBO in patients burdening poor gliomas. Twenty-nine patients were included in the research, where 11 of 15 patients (73%) treated with HBO showed \geq 50% tumor regression and just 4 of 14 other patients (29%) showed tumor regression. The median survivals in patients with and without HBO were 24 and 12 months, respectively. The trial suggested that HBO has benefits on the treatment of malignancy. However, eradication must be applied quickly following decompression. Aghajani et al.⁴³ included seven patients treated with HBO therapy, four of whom showed the clinical improvement, indicating that HBO therapy is good and well-tolerated in children and young adult people burdening central nervous system masses. Clinical tests are required to explore the safety and efficacy of HBO therapy in pediatric central nervous system mass.⁴³ Aiming to exam the feasibility and efficacy of radiotherapy using intensity modulated radiotherapy boosts after HBO therapy with chemotherapy in patients with glioblastoma, Yahara et al.²¹ observed 24 patients treated with the combined therapy. However, local disease progression was recognized in more than half of the patients. The results justify further evaluation in prospective trials including a dose escalation of intensity-modulated radiotherapy to clarify the benefits of this combined treatment in patients with glioblastoma.²¹ Kiyotaka et al.³¹ included 14 anaplastic astrocytoma patients and 11 glioblastoma multiforme patients, undergoing gamma fractionated stereotactic radiotherapy immediately following HBO therapy (2.5 atmospheres absolute for 60 minutes) to reduce the complications. The middle survival time after fractionated stereotactic radiotherapy anaplastic astrocytoma glioblastoma multiforme patients, demonstrating that gamma fractionated stereotactic radiotherapy and the efficacy of HBO is necessary. Since their trial is a preliminary study, further investigation is needed to confirm this point.³¹ Beppu et al.⁴² carried out a second period research of eradication dealing besides HBO united by interferon-beta associated with nimustine-hydrochloride to deal with bad gliomas supratentorially. Respectively, 35 of 39 patients underwent a complete schedule of HBO combined with interferon-beta and nimustine hydrochloride therapy, and thirty patients (77%) either maintained or increased Karnofsky

Performance Scale during HBO combined with interferon-beta and nimustine hydrochloride with a time of 68 days. At same time, the rate were 50% for glioblastoma, 30% for anaplastic astrocytomas were 43%, and median time of tumor progression were 38 weeks for glioblastoma patients, 56 weeks for anaplastic astrocytoma patients, and overall were 43 weeks. Finally, further studies should be performed by cooperative groups using a prospective randomized trial to strictly confirm that HBO/interferon- β and nimustine hydrochloride therapy was beneficial for patients with malignant glioma.

THE ADVERSE EFFECT OF HYPERBARIC OXYGEN IN GLIOMA

Wang et al.²⁴ established gliomas pattern of C57BL-type-6J mouse behind HBO dealing. Results showed that HBO accelerated the growing of exotransplanted GL261-type-Luc in the gliomas mouse pattern, and thymus reactive oxygen species levels were significantly upregulated. Suppressor T/cytotoxic T lymphocytes were also reduced in HBO-treated set. In this research, HBO helped severe gliomas growing in the mice pattern.²⁴ Ding et al.³⁶ treated male Sprague–Dawley rats with or without HBO after glioma cell inoculation. Results demonstrated that HBO-treated rats had larger tumor volume and more water in the cerebellum compared with control rats. The intra-tumoral expression of vascular endothelial growth factor, hypoxia induced factor-1 α and intra-tumoral micro-vessel density were all taller in HBO-treated rats to control rats, whereas the apoptosis was shorter in HBO-treated rats to controls.³⁶ Wang et al.²⁵ constructed an ex-transplanted glioma-pattern intracranially at C57BL/6J to look for influence of HBO. Bio-luminescent images demonstrated that HBO increased the growing of intracranially exo-transplanted GL261-Luc cell and yet suppressed the necrosis death of the transplanted gliomas.²⁵ Doherty et al.²⁸ reported a patient after resection of anaplastic astrocytoma and 5580 cGy of total external-beam radiation treatments with brain radiation necrosis who underwent HBO therapy and developed a partial seizure during treatment. The probable mechanism is that HBO inhibits glutamic acid decarboxylase, which is the critical enzyme for synthesizing the inhibitory neurotransmitter gamma-aminobutyric acid, and HBO increases the cerebral blood flow.²⁸

ROLE OF HYPERBARIC OXYGEN IN TREATMENT OF ANY COMPLICATIONS

Haji and Frenkel³⁵ reported a case that a male patient aged 62 suffered irradiation inducible retinal ischemic disorder following received irradiation to gliomas. The patient received focal laser, intravitreal triamcinolone, and HBO therapy, and besides receiving HBO-therapy, visual of him acuity supported to twenty/fifty and fluorescent angiography showed improvement in retinal affusion. Darakchiev et al.³⁷ included 34 patients with recurrent glioblastoma multiforme to investigate the safety and efficacy of permanent iodine-125 seed implants and carmustine wafers in patients with recurrent glioblastoma multiforme. Eight patients (24%) developed brain necrosis, and were successfully treated with surgery or HBO therapy.³⁷ Boschetti et

al.⁴¹ described a woman who was 42 years having not well vision on left sight, and same states and signs also followed in other eye after stereotactic radiosurgery because of unsuccessful neurosurgery. After HBO therapy, her vision steadily started to improve.⁴¹ Hulshof et al.³⁴ included 7 patients with acknowledge error behind irradiation in the research, and demonstrated that HBO treat was excellent and leading a perfect advancement of acknowledge function within 1 to 7 patients, whereas mild but not obvious advancement overall. Thus, more researches are required to explore the efficacy of HBO on the treatment of cognitive impairment after brain irradiation.³⁴ During evaluating the efficacy of permanent iodine-125 brain stem implants in children, Chuba et al.³⁹ observed that a patient had necrosis without tumor found on biopsy after 36 months, and successfully treated with HBO therapy.³⁹ Also, five of six surviving patients who has radiation-induced necrosis were improved by clinical and imaging criteria after HBO therapy, and one patient was alive with tumor present at last follow-up.

CONCLUSION

Overall, HBO therapy has significant efficacy on the prognosis of gliomas, whatever in experimental or clinical research. The main mechanism maybe is that the highly level hypoxia induced factor-1 α in masses is related to the anti-oxidation ability and related to the sensitivity of irradiation-therapy, and HBO therapy could suppress the level of hypoxia induced factor-1 α which promotes the expression of vascular endothelial growth factor, matrix metalloproteinase-9, multi-medicine resistant protein-1.³⁰ Partial mechanism of HBO on treatment of glioma is shown in **Figure 1**. However, the adverse effect never could be ignored, which indicates that HBO therapy is just an adjuvant therapy and more experimental and clinical researches, especially randomized controlled trials, are needed to be conducted. The potential mechanisms, whether HBO treatment inhibits or promotes the progression of glioma, is unsolved. The future research direction may focus on the mechanism why the HBO treatment could promote the invasion of glioma and its downstream molecule independent of hypoxia induced factor-1 α signal pathway.

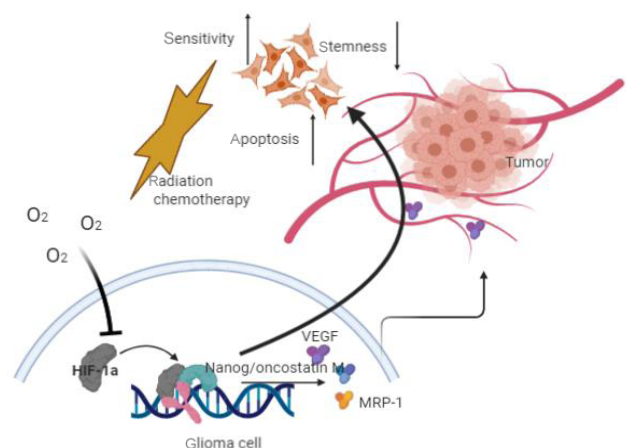


Figure 1: The partial mechanism of hyperbaric oxygen on treatment of glioma.
Note: HIF-1 α : Hypoxia-inducible factor-1 α ; MRP-1: multidrug resistance-associated protein-1; VEGF: vascular endothelial growth factor.



Author contributions

Manuscript drafting: QS and XX; manuscript writing: WJW; manuscript revision: JSD and GC. All authors read and approved the final version of the manuscript for publication.

Conflicts of interest

The authors declare that they have no competing interests.

Financial support

None.

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Plagiarism check

Checked twice by iThenticate.

Peer review

Externally peer reviewed.

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Additional file

Additional Table 1: Summary of experiments and clinical studies of HBO treatment in glioma

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Date of submission: July 1, 2020

Date of decision: July 10, 2020

Date of acceptance: July 29, 2020

Date of web publication: August

30, 2021

Additional Table 1: Summary of experiments and clinical studies of HBO treatment in glioma

Study	Year	<i>In vitro</i> study/ <i>in vivo</i> preclinical study/clinical study	Outcome
Zeng et al. ¹⁹	2019	NCH-421K, C6	TMZ/PSi NPs together with HBO and photothermal therapy is a possible curing approach for glioma.
Zembrzuska et al. ²⁰	2019	T98G glioblastoma multiforme cell line	The combined usage of isothiourrea derivatives and HBO shows a promising therapeutic way for malignant glioma treatment.
Yahara et al. ²¹	2017	24 patients with glioblastoma multiforme	The combined therapy of radiotherapy using intensity modulated radiotherapy behind HBO with chemistry drug therapy was a possible and promising cure modality for people with glioblastoma.
Xie et al. ²²	2018	Glioma C6 cell	The together dealing with TMZ/PSi NPs and HBO is a good curing approach for glioma.
Xie et al. ²³	2020	Nude mice with paw-transplanted glioma	Vitexin could cooperate with HBO to make the glioma radiotherapy sensitive.
Wang et al. ²⁴	2018	C57BL/6J mice, GL261-Luc cell	HBO treatment accelerated the growing of trans-exogenous-planted bad gliomas, suppressed death.
Wang et al. ²⁵	2015	C57BL/6J mice, GL261-Luc cell	HBO induced reactive oxygen species translocation, suppressed CD3 β T lymphocyte development, help bad gliomas growing intracranially brain gliomas mice pattern.
Stuhr et al. ²⁶	2007	BT4C rat glioma	Increased oxygenic pressures in experimental gliomas, taking advantage of normobaric and simple HBO therapy, caused a significant reduction in tumor growth.
Song et al. ²⁷	2019	Basal ganglia glioma rat model	Initial HBO treatment can change the hypoxic micro-environment and affect the stemness-associated characteristic of cancer cells.
Doherty et al. ²⁸	2005	Clinical case report	A patient received surgery of astrocytoma and 5580 cGy of total outside radiation dealing with brain irradiation mortify who has HBO therapy and had a partial seizure during treatment.
Lu et al. ²⁹	2016	Green fluorescent protein transgenic nude mice, SU3 human glioma cells	HBO therapy can suppress glioma cell proliferating and pro-inflammatory cell infiltrating, and exhibit a good reactive on nimustine treatment.
Lu et al. ³⁰	2012	U251 glioma cells	TMZ and HBO together made death of glioma-cell, maybe via less vessels with suppression of medicine tolerance.
Kohshi et al. ³¹	2007	14 anaplastic astrocytoma and 11 glioblastoma multiforme	Gamma fractionated stereotactic radiotherapy following HBO therapy has a good survival benefit for patients with badly recurrent severe gliomas.
Kohshi et al. ³²	1999	29 patients with malignant glioma	Irradiation after HBO seems to be a useful form of treatment for malignant gliomas, but irradiation should be administered immediately after decompression.
Kohshi et al. ³³	1996	21 patients with malignant glioma	HBO is an okay part of radiotherapy to bad gliomas.
Hulshof et al. ³⁴	2002	7 cognitive impairment after brain irradiation patients	HBO treatment was reliable and leading an obviously meaningful improving of cognition function in 1/7 patients.
Haji and Frenkel ³⁵	2010	Clinical case report	HBO treatment improves retinal affusion on people who suffer radioactive inducible retina ischemic disease.
Ding et al. ³⁶	2015	Male Sprague–Dawley rats with glioma cell inoculation	HBO alone may promote tumor growth, and is therefore not better to treat patients with gliomas with neuro-deficits or diseases with HBO alone.
Darakchiev et al. ³⁷	2008	34 patients with recurrent glioblastoma multiforme	The use of adjunct therapy combined with carmustine wafers and permanent iodine-125 seeds resulted in survival that compares favorably with data from similar studies performed in patients with recurrent glioblastoma multiforme.
Dagistan et al. ³⁸	2012	Wistar rats with C6/LacZ glioma cell	The combination of HBO with TMZ produced an important reduction in glioma growth and effective approach to the treatment of glioblastoma.
Chuba et al. ³⁹	1998	28 children have had iodine-125 implants for central nervous system tumors	In one patient who received an implant alone for midbrainlow-grade astrocytoma, necrosis without tumor was found on biopsy after 36 mon. He was successfully treated with HBO therapy.
Chuba et al. ⁴⁰	1997	Patients with radiation-induced necrosis	HBO therapy may prove to be an important adjunct to surgery and steroid therapy for central nervous system radiation-induced necrosis.
Boschetti et al. ⁴¹	2006	Clinical case report	HBO treatment was instituted promptly and vision started stably improving.
Beppu et al. ⁴²	2003	18 patients with a diagnosis of WHO grade 3 or 4 gliomas	HBO was the optimal procedure for oxygenation, but its benefit was reduced over time.
Beppu et al. ⁴²	2003	39 patients of malignant glioma	The present study suggested that HBO/interferon-beta and nimustine hydrochloride cure can be managed to patients especially who had sad prognostic features, because its treatment time is short, its toxicity is permissible and responses to patients with so-so characteristics are identical.
Aghajan et al. ⁴³	2019	Seven patients with gliomas	HBO therapy is safe and well-tolerated in pediatric and young adult patients with central nervous system tumors.

Note: HBO: Hyperbaric oxygen; PSi NPs: porous silicon nanoparticles; TMZ: temozolomide.