A narrative review of adjuvant therapy for glioma: hyperbaric oxygen therapy

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Abstract

Glioma is a kind of common malignant tumor in neurosurgery and has a high mortality and morbidity rate, which poses a serious threat to the health of people all over the world. Surgery is the preferred treatment for patients with glioma, radiotherapy or chemotherapy can be used after surgery. Although there are clear therapeutic protocols, the efficacy and safety of these protocols are clinically proven, a large number of patients are still dissatisfied with the treatment and the health of the patient remains unsatisfactory. Therefore, it is crucial to look for other treatments or complementary treatments. In the modern medical treatment, hyperbaric oxygen (HBO) therapy is widely used in various kinds of pathological state of adjuvant therapy, and existing studies confirm the efficacy of HBO therapy in combination with surgery, radiotherapy, chemotherapy, and photodynamic therapy. Studies have shown that HBO can inhibit the growth of tumor tissue as an adjunctive therapy. This provides novel insights into the clinical treatment of glioma patients. Although HBO is not licensed for use in cancer treatment, as a kind of adjuvant therapy, the treatment effect of HBO can be accepted by the patients and its cost lower, which could be regarded as an ideal safe treatment.

Key words: adjuvant therapy; central nervous system; chemotherapy; glioma; hyperbaric oxygen therapy; hypoxic; radiotherapy; temozolomide

doi: 10.4103/2045-9912.318861

How to cite this article: Xue T, Ding JS, Li B, Cao DM, Chen G. A narrative review of adjuvant therapy for glioma: hyperbaric oxygen therapy. Med Gas Res. 2021;11(4):155-157.

Introduction

The main diseases of the central nervous system can be classified into two categories: brain tumors and cerebrovascular diseases. Both of them have extremely high mortality and disability.[1] Cerebrovascular disease can mainly be divided into hemorrhagic stroke and ischemic stroke. Hemorrhagic stroke accounted for about 20% of all strokes,[2] and ischemic stroke accounted for 80%.[3,4] Gliomas account for 40–50% of the central nervous system tumor. Glioma is a malignant tumor originating from intracranial neutral glial cells. As an aggressive and fatal malignancy, the growth of glioma causes diffuse recombination of brain functional networks.[5] Among them, glioblastoma was the most aggressive and malignant.[6] Despite significant advances have achieved in multi-modality therapy for glioma, the overall prognosis of glioma patients remains poor.[7,8] The standard treatment strategy for gliomas is surgery plus chemotherapy or radiation.[9] Even so, the prognosis was poor, with an average survival time of less than 15 months.[10] In addition, the side effects of radiotherapy or chemotherapy are obvious and the related costs are relatively expensive, so it is particularly important to find a better treatment or adjuvant treatment.

Hyperbaric oxygen (HBO) has become an adjunct therapy for a variety of diseases and is suitable for a variety of medical conditions.[11] It is worth mentioning that HBO therapy has been unanimously approved in the treatment of chronic radiation injuries. As is known to all, hypoxia plays an important role in the development of cerebrovascular disease.[12,13] With the further study of the tumor, hypoxia of tumor tissue has become a recognized fact.[14] And hypoxia promotes the growth of tumor tissue.[15,16] Numerous studies have demonstrated that HBO can improve the efficacy of radiotherapy or chemotherapy in glioma patients combined with radiotherapy or chemotherapy (such as temozolomide (TMZ)).[17,18] Existing study has shown that performing radiotherapy immediately after HBO with chemotherapy was safe with virtually no late toxicity for high-grade gliomas.[19] This treatment strategy may be promising and merits further investigation. Clinically, glioma patients may have partial nerve function defects after operation. Therefore, patients need HBO for postoperative rehabilitation and can also amplify the effects of radiotherapy or chemotherapy.

Therefore, this paper comprehensively describes the application of HBO therapy as an adjuvant therapy for other therapeutic schemes in the treatment of glioma, so as to provide a sound decision for clinical treatment. In this review, literature searches were performed on PubMed, and articles that were published until August 2020 were included.

The Compatibility of Hyperbaric Oxygen Therapy with Mainstream Treatments

HBO therapy and chemotherapy

As an oral imidazolidazinone methylator, TMZ can inactivate the DNA repair enzyme O6-alkylguanine-DNA alkyltransferase and is the preferred chemotherapy drug for the clinical

treatment of glioma.[20] TMZ improves survival in glioma patients and prolongs progression-free survival after surgical treatment.[9] However, due to the toxicity of TMZ, its therapeutic dose is limited.[21] Because of the high degree of malignancy of gliomas, the 5-year survival rate under current standard treatment is still less than 8%.[22] Therefore, it is urgent to improve the traditional chemotherapy drugs for glioma. Hypoxia may be one of the reasons why glioma is resistant to TMZ.[17] Modern medical science generally believes that hypoxia is conducive to tumor growth, and can promote the formation of blood vessels in tumor tissues, and improve tumor invasiveness.[23] A relevant study has shown that the increase of lactic acid is closely related to the poor prognosis of glioma.[24] HBO therapy is expected to overcome hypoxia in the hypoxic region of tumor tissue. Studies have shown that HBO therapy alone does not inhibit tumor growth, while TMZ combined with HBO significantly inhibits tumor growth (**Table 1**).

Two mechanisms have been proposed for TMZ combined with HBO therapy. On the one hand, tumor tissue hypoxia tends to decrease after HBO treatment, and some hypoxic areas return to normal oxygen supply, while the increase of oxygen concentration in tumor tissue makes tumor tissue more sensitive to chemotherapy drugs.[28] On the other hand, HBO may enhance the cell cycle arrest effect of chemotherapeutic drugs. TMZ alkylates guanine in genomic DNA at position O6 inducing impaired DNA repair and G_2/M arrest.[29] When TMZ is used to treat glioma cells, the number of cells blocked in G_2/M phase is: hypoxia (18%), normal oxygen (27%) and hyperbaric oxygen (23%). Therefore, it can be concluded that HBO therapy can enhance the affinity of tumor cells to TMZ.[25] Study has shown that inflammation plays an important role in the development of tumors, which mainly through a variety of inflammatory factors. When Nimustine was used in combination with HBO, it was found that the expression of many inflammatory factors was reduced and the growth of tumor tissue was inhibited. Therefore, HBO therapy also played an important role in inhibiting the inflammatory response (**Table 1**).

HBO therapy and radiotherapy

Radiotherapy utilizes the so-called classical oxygen effect in tumor treatment. Under radiation, water molecules break down to form hydrogen ions and hydroxyl groups, the hydrogen ions react with oxygen, forming highly stable hydrogen peroxide and hydroxyl radicals, which damages the DNA chain, causing cell death. It follows that the effect of radiotherapy is closely related to the oxygen content in tumor tissue. It was observed that mice breathing pure 1 atmosphere absolute (1 atmosphere absolute = 101.325 kPa) oxygen required a one-third smaller dose of X-rays than mice that were breathing air to achieve similar cancer regression.[30] HBO combined with radiotherapy may have two functions: one is to enhance the effect of radiotherapy as a sensitizer. Second, it can reduce the damage of delayed radiotherapy as a therapeutic agent.[31,32] The incorporation of HBO and radiotherapy can reduce tumor growth, improve tumor local control and prolong survival time.[33] It is obvious that the lack of oxygen in tumor tissues is caused from insufficient blood flow. It is generally accepted that there are two mechanisms of radiation resistance due to hypoxia: limited diffusion and chronic hypoxia. This is mainly due to the oxygen is hard to reaching the distal vessels of the tumor and the transient vascular obstruction caused by acute hypoxia.[34] It is well known that the Radio-sensitivity of tumors is determined by the partial pressure level of oxygen and can be significantly increased in the presence of small amounts of oxygen.[11] Due to low oxygen consumption and low blood flow, the internal oxygen partial pressure of glioma decrease relatively slow after decompression. We hypothesized that concentration of

Table 1: The effect of HBO on glioma

Study subject	Modeling	Treatment	Conclusion
Male BALB/c nude mice	Rat glioma C6 cell line was inoculated into a nude mouse to establish the subcutaneous tumor model.	HBO treatment under 2.5 atmospheres absolute for 2 h on 1, 3, and 5 d in the related groups,	The significant inhibition of tumor growth and cell proliferations was observed in TMZ combined with HBO groups.[25]
Nude mice	The human glioma stem/progenitor cell line SU3 was subcutaneously injected in the flank of the nude mice.	The treatment regimen consisted of a 5–10 min ramp-up to 2.5 atmospheres absolute pressure in a 100% O_2 environment, followed by sustaining for 90 min at this pressure prior to a 10- to 20-min decompression phase.	HBO could inhibit glioma cell proliferation and inflammatory cell infiltration.[26]
Male Sprague-Dawley rats	Rat C6 cells were injected into right caudate nucleus of each rat.	Rats in the HBO therapy group were treated with HBO at 2, 4, 6, 8, 10, and 12 d after surgery.	HBO alone may promote tumor growth, it is recommended that HBO should be combined with radiotherapy or chemotherapy.[27]
Forty-one newly diagnosed cases of adult glioma	–	All 41 patients completed a total dose of 60 Gy radiotherapy immediately after HBO with one course of concurrent chemotherapy.	Performing radiotherapy immediately after HBO with chemotherapy was safe with virtually no late toxicity for high-grade gliomas. This treatment strategy may be promising and merits further investigation.[19]
Twenty-nine gliomas patients	–	15 min of compression with air, 60 min of 100% oxygen inhalation using an oxygen mask at 2.5 atmospheres absolute and 10 min of decompression with oxygen inhalation.	Radiotherapy after HBO exposure improved the survival of patients with malignant gliomas.[11]

Note: 1 Atmosphere absolute = 101.325 kPa. HBO: Hyperbaric oxygen; TMZ: temozolomide.

oxygen in the tumor after decompression can still maintain a period of time. According to this hypothesis, HBO combined radiotherapy can increase the sensitivity of tumor tissue for radio-therapy, and would not damage normal brain tissue, which can be concluded that this novel combination therapy can be very effective for the glioma patients treatment.[35]

Conclusion and Prospect

To sum up, as a kind of auxiliary treatment, HBO therapy for glioma has the advantages of safety, cheap and effective, but its mechanism and possible side effects has not yet been fully elucidated, which requires more basic research to study the exact molecular mechanism, and a lot of clinical cases for retrospective study were also needed. HBO therapy has not yet been approved for clinical use. However, we believe that HBO therapy will certainly enter the clinic as a safe and reliable treatment in the near future.

Author contributions
Manuscript writing: TX; manuscript revision: JSD, BL; manuscript drafting: DMC, GC. All the authors read and approved the final version of the manuscript for publication.
Conflicts of interest
The authors have no conflicts of interests to declare.
Financial support
None.

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Date of submission: May 14, 2020
Date of decision: May 23, 2020
Date of acceptance: June 18, 2020
Date of web publication: June 28, 2021