Hyperbaric Chamber as Complementary Treatment to Standard Therapy for Brain Tumors: beneficial or not?

Abstract

Introduction: Hyperbaric oxygen therapy (HBO) is a therapeutic intervention that consists of exposing the patient to pure concentrations of oxygen (O₂) at increased atmospheric pressure. Objective: The present study aims to investigate whether the use of oxygen therapy through the hyperbaric chamber increases the effectiveness of the standard treatment of brain tumors when compared to no therapy, providing references for interventions aimed at these tumors. Methods: A search was carried out in PubMed, Medline, SciELO, Cochrane and Web of Science databases using these terms “hyperbaric oxygenation”, “hyperbaric oxygen therapy”, “brain cancer”, “brain tumor”, “glioma” with the aid of the Boolean operators OR (OR) and AND (AND). The most adequately related to the objectives of this work resulted in 22 articles in Portuguese, English and Spanish, using the PRISMA criteria. Results: Analysis on adjunctive hyperbaric oxygen therapy (HBO) in the treatment of brain tumors has been made, pointing out clinical benefits and rare risk including generalized tonic-clonic seizures due to CNS oxygen toxicity. Conclusion: The hyperbaric chamber is significantly useful in the adjunctive treatment of brain tumors, with tumor remission. However, its use in pediatric neuro-oncology patients with elevated ICP should be reviewed, emphasizing the need for greater caution in recommending use.

Keywords: Brain tumor; Glioma; Hyperbaric Oxygen Therapy

Resumo

Introdução: A oxigenoterapia hiperbárica é uma intervenção terapêutica que consiste em expor o paciente a concentrações puras de oxigênio (O₂) a uma pressão atmosférica aumentada. Objetivo: O presente estudo tem como objetivo investigar se o uso da oxigenoterapia por meio da câmara hiperbárica aumenta a eficácia do tratamento padrão de tumores cerebrais quando comparado à ausência de terapia, fornecendo referências para intervenções voltadas a esses tumores. Métodos: Foi realizada uma busca nas bases de dados PubMed, Medline, SciELO, Cochrane e Web of Science com os termos “hyperbaric oxygenation”, “hyperbaric oxygen therapy”, “brain cancer”, “brain tumor”, “glioma”.

Keywords: Tumor cerebral; Glioma; Terapia Oxigenoterapia Hiperbárica
INTRODUCTION

Hyperbaric Oxygen Therapy (HBO) is a therapeutic intervention that consists of exposing the patient to pure concentrations of oxygen (O₂) at increased atmospheric pressure. Current indications approved by the Undersea and Hyperbaric Medical Society (UHMS) suggest that patients breathe close to 100% oxygen while in a pressurized chamber of at least 2 atmospheres absolute (ATA), which is defined as the sum of pressure atmospheric and gauge pressure inside the hyperbaric chamber.

The therapeutic bases of hyperbaric oxygenation result from three factors: when breathing 100% oxygen, a positive gradient is created, which favors diffusion from hyperoxygenated lungs to hypoxic tissues. Due to the high pressure, the blood concentration of O₂ increases according to Henry’s Law (the amount of dissolved gas is directly proportional to its partial pressure) and reduces the size of gas bubbles in the blood following the Boyle-Mariotte Law (the product between volume and pressure is always constant).

In summary, the creation of a hyperbaric environment with pure O₂ allows a significant increase in blood and tissue oxygen delivery, even without the contribution of hemoglobin. Thus, HBO provides several effects in the body, being used to correct tissue hypoxia, chronic hypoxemia and to help in the clinical management of several pathological processes, such as tumor tissues.

One of the indications for the use of HBO is in the treatment of gliomas. Gliomas are the most common malignant brain tumors. They originate from intracranial neutral glial cells. Aggressively and fatally, glioma growth causes diffuse recombination of functional brain networks. Among them, glioblastoma is the most aggressive and malignant. Due to the high metabolic state of tumors and the abnormal disturbance of blood vessels, the level of oxygen demanded by tumor cells is considerably higher than the oxygen supply, which generates tumor tissue hypoxia, leading to greater malignancy and tumor recurrence.

The standard treatment strategy for gliomas is surgery plus chemotherapy and/or radiotherapy. Despite the significant advances achieved in multi-modality therapy for gliomas, the overall prognosis of patients is still poor, resulting in median survival of less than 15 months. Furthermore, there are many side effects of radiotherapy or chemotherapy and its related costs are high. One of the main issues contributing to ineffective medical treatment of cancer is the occurrence of local hypoxia within central tumor areas. In this sense, it is particularly important to find a more successful treatment or an adjuvant treatment. Hypoxia plays a role in malignant glioma resistance to radiotherapy. During radiation, oxygen serves as a crucial and potent radiosensitizer in the chemical reaction that damages the DNA of cancer cells. The application of HBOT can help to overcome the problem of oxygen deficiency in regions with little oxygen in the neoplastic tissue.

The present study aims to investigate whether the use of oxygen therapy through the hyperbaric chamber increases the effectiveness of the standard treatment of brain tumors when compared to no therapy, in order to provide references for interventions aimed at these tumors.

METHODS

For the development of this systematic review, the research question was elaborated using the PICO strategy. According to Webster and Watson, an effective literature review creates a solid foundation for the advancement of knowledge, facilitates the development of theory in areas where research already exists, and contributes to the discovery of areas where research is needed.

Palavras-chave: Tumor cerebral; Glioma; Oxigenoterapia hiperbárica
Based on the classification presented by Gil, regarding the objectives, the present work is characterized as a descriptive and exploratory research since it aims to identify the characteristics of certain variables related to the scientific production on the subject. With regard to the approach to the problem, a qualitative and quantitative approach was adopted for data collection and analysis which, according to Minayo, this type of research makes it possible to describe the phenomena observed by the researcher as well as to substantiate these views through of evidence.10,11

Data collection was carried out by surveying articles published in national and international scientific journals on the subject of Hyperbaric Oxygen Therapy and available in the PubMed, Medline, SciELO, Cochrane and Web of Science databases. Queries were carried out in this database between September 21 and 25, 2022. To carry out the searches, MeSH Terms and logical search operators (also called Boolean Operators) were used, which are intended to facilitate the search process through greater incisiveness in the results. Table 1 brings examples of each operator.12

The search was carried out with the aid of the Boolean operators OR (OU) and AND (AND), in addition to the filters made available by the search tool of the Portals of journals mentioned above. The temporal cut of the study corresponded to the period of the last 10 years, aiming, thus, to analyze the development of publications on the referred theme in the context of the new millennium. The terms selected for the search were “hyperbaric oxygenation”, “hyperbaric oxygen therapy”, “brain tumor”, “glioma” with their correspondences in English, Spanish and Portuguese, in order to allow words with the same radical to be included in the search results. After carrying out the initial search, using the criteria above mentioned in the “Title” field, and the use of filters “Creation date: 2000 to 2022”, “Type of resource: Articles”, with only journals referring to neoplasms restricted to the brain, and 80 potentially eligible papers were selected. The articles resulting from this refined search had their titles read as a way of identifying those directly aligned with the proposed theme, discarding those related to other themes and duplicate articles. We excluded 58 duplicate studies, which were indexed in more than one collection, as well as studies whose population did not contain only patients with neoplasms restricted to the brain. The final number of articles that were the focus of the study and that were analyzed in more detail was 22 studies.

Table 1. Logical Search Operators (Boolean).

<table>
<thead>
<tr>
<th>OPERATOR</th>
<th>MAIN FUNCTION</th>
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<tbody>
<tr>
<td>AND (AND)</td>
<td>Used to group the terms, allowing the expansion of searches.</td>
</tr>
<tr>
<td>OR (OR)</td>
<td>Used to restrict the search, performing the intersection of sets of works that have combined terms.</td>
</tr>
<tr>
<td>NOT (NO)</td>
<td>Used to exclude a certain subject within the searches, excluding what comes before it and excluding what comes after it.</td>
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Source: Based on Pizzani et al.12

Subsequently, the 22 articles on the topic of Hyperbaric Oxygen Therapy had their titles, abstracts, keywords and methodology sections read and subsequently were classified according to 7 categories, namely: (1) authors; (2) year of publication; (3) scientific journals in which the articles were published; (4) research objectives and results; (5) study framework: theoretical or theoretical-empirical; (6) type of research: qualitative, quantitative or multimethod research; and (7) thematic approach. Then, the data obtained were presented and discussed in order to meet the perspectives of the objectives proposed in this work.

RESULTS

The characteristics and main findings of the selected studies are shown in Table 2. Below are the following evaluations under hyperbaric oxygen therapy, including several topics such as: radiology in malignant gliomas, atopic energy metabolism in glioblastoma, rehabilitation of brain tumors after surgery and effects on TNF-α and IL-6 levels, intracranial pressure during oxygen therapy, pharmacokinetics for the cure of malignant gliomas of carboplatin, adjuvant therapy for glioma, pediatric neuro-oncology, intensity-modulated radiotherapy, complementary and alternative medicine for the treatment of gliomas in radiation-induced brain injury in children, radiotherapy after hyperbaric oxygenation associated with beta-interferon and nimustine hydrochloride to treat supratentorial malignant gliomas, adjuvant therapy in the treatment of malignant tumors, including brain tumors, combination with fluosol, multi-agent chemotherapy, fractionated stereotactic radiotherapy with gamma unit, radiotherapy after hyperbaric oxygenation with chemotherapy for high-grade gliomas, alteration of oxygen pressure in glioblastoma tissue and partial seizure caused by hyperbaric oxygen therapy.
Table 2. Characterization of included studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Objective</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al.</td>
<td>Evaluate radiology after hyperbaric oxygenation for malignant gliomas.</td>
<td>Radiotherapy combined with hyperbaric oxygen in 9 patients showed that 50% of the patients evolved with tumor regression and 4 of these patients evolved with the complete disappearance of the malignant gliomas. Radiotherapy without hyperbaric oxygen in 12 patients showed that 4 patients had tumor shrinkage, but all 12 patients died within 36 months.</td>
</tr>
<tr>
<td>Augur et al.</td>
<td>To evaluate atopic energy metabolism in experimental glioblastoma VM-M3.</td>
<td>Hyperbaric Oxygen Therapy can reverse the hypoxic phenotype of tumors and reduce growth. We hypothesized that combination therapy of a ketogenic diet, hyperbaric oxygen, and oxaloacetate could reduce or eliminate the need for temozolomide in patients with glioblastoma multiforme.</td>
</tr>
<tr>
<td>Hou et al.</td>
<td>To evaluate hyperbaric oxygen in the rehabilitation of brain tumors after surgery and effects on TNF-α and IL-6 levels.</td>
<td>The comprehensive treatment effect of hyperbaric oxygenation is significant. It can inhibit the expression of inflammatory factors in serum and reduce the speed of cerebral arterial flow, and effectively reduce the number of patients with cerebral spasm. It can reduce the functional neurological deficit and improve the patients’ quality of life. Therefore, it is worthy of clinical popularization.</td>
</tr>
<tr>
<td>Kohshi et al.</td>
<td>Assess intracranial pressure during hyperbaric oxygen therapy.</td>
<td>The reduction in ICP is initially due to direct cerebral vasoconstriction caused by hyperoxia and is mainly maintained by reduced hypocapnia during hyperbaric oxygen inhalation. Caution is required when giving Hyperbaric Oxygen Therapy to patients with an elevated ICP and/or who are artificially breathing.</td>
</tr>
<tr>
<td>Suzuki et al.</td>
<td>To evaluate the pharmacokinetics of the increased efficacy against malignant gliomas of carboplatin combined with hyperbaric oxygenation.</td>
<td>The efficacy of intravenous administration of 400 mg carboplatin/m² body surface area over 60 minutes combined with Hyperbaric Oxygen Therapy. Hyperbaric Oxygen Therapy prolongs the biological residence time of carboplatin. Mean residence time for carboplatin may be useful in predicting continuation or modification of chemotherapy and/or clinical antitumor effects in patients with malignant gliomas.</td>
</tr>
<tr>
<td>Xue et al.</td>
<td>Evaluate adjuvant therapy for glioma: hyperbaric oxygen therapy.</td>
<td>Hyperbaric Oxygen Therapy is widely used in various types of adjunctive therapy disease states, and existing studies confirm the effectiveness of Hyperbaric Oxygen Therapy in combination with surgery, radiotherapy, chemotherapy, and photodynamic therapy.</td>
</tr>
<tr>
<td>Aghajan et al.</td>
<td>To evaluate hyperbaric oxygen therapy in pediatric neuro-oncology.</td>
<td>Safety and efficacy in pediatric patients is less understood.</td>
</tr>
<tr>
<td>Yahara et al.</td>
<td>Evaluating radiotherapy using IMRT increases after hyperbaric oxygen therapy with chemotherapy for glioblastoma.</td>
<td>Combination radiotherapy therapy using intensity-modulated radiotherapy (IMRT) boosters following Hyperbaric Oxygen Therapy with chemotherapy was a viable and promising treatment modality for patients with glioblastoma. The results warrant further evaluation to clarify the benefits of this therapy. The 2-year overall survival and progression-free survival rates in all patients were 46.5% and 35.4%, respectively.</td>
</tr>
<tr>
<td>Pangal et al.</td>
<td>Evaluate complementary and alternative medicine for the treatment of gliomas.</td>
<td>Level I or II evidence is lacking for complementary and alternative medicine for the treatment of glioma, representing future research directions to optimally advise and treat patients with glioma.</td>
</tr>
<tr>
<td>Chuba et al.</td>
<td>To evaluate hyperbaric oxygen therapy for radiation-induced brain injury in children.</td>
<td>Hyperbaric Oxygen Therapy may prove to be an important adjunct to surgery and steroid therapy.</td>
</tr>
<tr>
<td>Beppu et al.</td>
<td>To evaluate hyperbaric oxygenation combined with interferon-beta and nimustine hydrochloride to treat supratentorial malignant gliomas.</td>
<td>Therapy with hyperbaric oxygenation and nimustine hydrochloride and radiotherapy could be applied especially to patients with poor prognostic factors, due to its short treatment period, its permissible toxicity and identical response to patients with good prognostic factors.</td>
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It is known that tissue hypoxia is one of the most important factors related to the worst prognosis and low therapeutic efficacy, basically related to two main issues, the first concerns the effectiveness of temozolomide (TMZ), the most commonly used chemotherapeutic agent, which has less action on the glioma due to the low levels of oxygen in the tumor cells. Another point is that due to tumor hypoxia there is an abnormal angiogenesis, which is responsible for creating a vicious cycle of greater hypoxia, generating a smaller effect pharmacologic action of TMZ, with...
this the tumor cells again trigger an abnormal angiogenesis resulting in an important tumor increase\textsuperscript{8,14,21}.

In this sense, studies have indicated adjuvant possibilities to standard treatment, such as the inhibition of hypoxia-inducing factors (HIFs), or increasing the ability of red cells (RBCs) to carry oxygen through transfusions and administration of erythropoietin, among other techniques (16), but good results were not obtained and what has been concluded is that the best solution to combat tumoral and peritumoral hypoxia is the use of HBO\textsubscript{2}, since in the present study 21 patients were evaluated, where 12 of these received standard treatment while another 9 were submitted to the association of RT (radiotherapy) plus HBO\textsubscript{2}, these obtained favorable results in tumor regression. Another study carried out with the objective of reducing hypoxia through an association between Fluosol and a hyperbaric chamber, since with the offer of 100% O\textsubscript{2} associated with perfluorochemicals, the glioma becomes more sensitive to radiation\textsuperscript{22}. The use of TMZ is a determining factor in the survival and recovery after chemotherapy of patients, depending on the dosage, this drug has toxic effects and becomes largely responsible for weight loss in patients undergoing treatment due to its side effects in the gastrointestinal tract. In order to minimize dosages and consequent adverse effects, tests were carried out in which an association of HBO\textsubscript{2}, ketogenic diet and oxaloacetate was made for the treatment of GBM, a combination that is capable of generating hyperoxia that makes the glioma more sensitive, in addition to reducing the supply of glucose and to reduce tumor metabolism, thus obtaining effective tumor regression even when using low doses of TMZ\textsuperscript{14}.

Another important issue to be addressed concerns to tissue lesions after tumor resection, which occur during the surgical procedure, small lesions in physiological tissues with the presence of mutation-free cells, that is, cells that are crucial for the proper functioning of the entire nervous system central nervous system (CNS) after suffering the trauma these tissues need an adequate O\textsubscript{2} support for their restructuring. In this sense the association of HBO\textsubscript{2} would be able to suppress the oxygen demand for the cellular mitochondria and providing a renewal fast and effective tissue treatment which, consequently, will reduce the damage caused by a loss of healthy nervous tissue, thus being able to increase the survival of these patients\textsuperscript{5,6}.

The results of effective improvement in the pO\textsubscript{2} level after using the hyperbaric chamber vary according to several factors, such as number of sections, duration of each section, age and sex of the individual. However, the study shows very important data, where it was seen that after the use of HPO\textsubscript{2} there is a significant increase in pO\textsubscript{2} in tumor and peritumor cells that lasts for 15 minutes. In this sense it can be concluded that the institution of radiotherapy should be performed immediately after the supply of 100% O\textsubscript{2} offered during the session, thus preventing apoptosis due to hypoxia, which is a consequent reaction after exposure to radiation, and also increasing tumor sensitivity to radiotoxic effects\textsuperscript{26}.

The lactic acid that is released due to cell apoptosis caused by tissue hypoxia is directly related to a worse prognosis, shown capable of reducing tissue hypoxia which will decrease cell death and consequently the levels of lactic acid will be reduced\textsuperscript{6}.

Once the advantages and good results of using a hyperbaric chamber have been seen, it is necessary to deepen and understand about possible side effects, an important point is the fact that hyperoxia is not capable of increasing the tumor size, since such cancer cells do not depend on high levels of O\textsubscript{2} for their multiplication. Questions related to the risk of seizures are made and a study carried out with a group of 49 patients undergoing a hyperbaric chamber found that none of them had a change in the seizure threshold, the main reactions observed were tinnitus and nausea in 7 and 5 patients, respectively. During the hyperbaric chamber sessions there is also a decrease in ICP (intracranial pressure), such effect is initially due to a vasoconstriction induced by a state of hyperoxia and later due to the reduction of hypocapnia, thus concluding that the use of HBO\textsubscript{2} should be done with caution in patients who have high intracranial pressure or are using artificial respiration\textsuperscript{5,15,27}.

Scientific studies and research are fundamental for innovation and better therapeutic and prognostic results in patients affected by this pathology. In this sense, several movements are taking place on how to improve the survival of patients with gliomas. Results from several studies lead us to understand the numerous benefits, the prognostic improvement, and the safety of using HBO\textsubscript{2} associated with standard treatment.
CONCLUSION

It was shown that the use of the hyperbaric chamber as an adjunct treatment to the standard therapy for brain tumors was beneficial, since patients who used it showed significant improvements in terms of tumor control and remission, with low incidence of side effects. Its aid in the results obtained in radiotherapy and chemotherapy has also been proven as a potentiator of the sought effects.

However, there is still no evidence that could lead to the conclusion of the same beneficial picture in the use of these therapeutics in pediatric neuro-oncology. At the same time, it is worth mentioning careful administration, and if possible avoided, in patients who have high ICP and/or are in the process of artificial respiration.

REFERENCES


Mateus Gonçalves de Sena Barbosa, MS
Medical student
Atenas University Medical School
Passos, Minas Gerais, Brazil
E-mail: mateusgonsb@gmail.com
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