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REVIEW ARTICLE

Hyperbaric Therapy in Patients Undergoing Liver Transplantation: An Integrative Review

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ABSTRACT

Introduction: Patients with liver disease generally have a serious clinical condition that can rapidly worsen, making the wait until liver transplantation or post-surgery a poor prognosis. Hyperbaric oxygen therapy has therefore been described in some studies as an alternative in these cases, as it mitigates the effects of the diseases and liver transplantation. **Objective:** To describe the effects of hyperbaric oxygen therapy in the pre- and post-operative periods of patients undergoing liver transplantation. **Methods:** This is an Integrative Review using the PubMed and Web Of Science databases. The following descriptors were used: "Hyperbaric oxygenation", "Liver transplantation" and "Hyperbaric oxygen therapy" with the Boolean operator "AND", and articles of relevance to the topic were selected. Initially, 49 articles were selected, all published in the last 20 years, in Portuguese and/or English. After analysis, 6 articles matched the proposed objective. **Results:** It can be seen that intraoperative systemic O_2 content affects postoperative recovery in patients undergoing liver transplantation. Early hyperbaric oxygen therapy acts as a protector in reducing the severity of hepatocyte ischemia/reperfusion injury. Hyperbaric oxygen therapy also influences the immune response of patients undergoing liver transplantation, reducing incompatibility. Still on the subject of the immunomodulatory effects of hyperbaric oxygen therapy, this therapy has been shown to be effective in helping to prevent post-operative infections by improving the antibacterial activity of immune cells and increasing the bactericidal effect of antibiotics. In the case of patients on the waiting list for liver transplants, a reduction in the number and intensity of encephalopathy episodes, an improvement in pruritus and a feeling of well-being were observed after treatment with oxygen therapy. In terms of early allograft dysfunction, it was shown that patients with dysfunction had lower O_2 values in the anepathic and neo-hepatic phases when compared to patients without dysfunction in the post-operative period. In addition, during the anepathic phase, the content of the $SatO_2$ level was also lower in the group with dysfunction than in those without. **Conclusion:** Hyperbaric oxygen therapy is beneficial in liver preservation, as it helps to maintain liver function, prolong liver preservation time and improve the outcome of liver transplantation.

Descriptors: Hyperbaric oxygenation; Hyperbaric Oxygenation; Liver transplantation.

Oxigenoterapia Hiperbárica em Pacientes Submetidos ao Transplante Hepático: Uma Revisão Integrativa

RESUMO

Introdução: Pacientes hepatopatas, geralmente, apresentam um quadro clínico grave que pode se intensificar rapidamente fazendo com que a espera até o transplante de fígado ou o pós-cirúrgico tenha má prognósticos. Com isso, a oxigenoterapia hiperbárica é descrita em alguns estudos como uma alternativa nesses casos por mitigar os efeitos das doenças e do transplante hepático. **Objetivo:** Descrever os efeitos da oxigenoterapia hiperbárica no pré e no pós-operatório de pacientes submetidos

ao transplante hepático. **Métodos:** Trata-se de uma Revisão Integrativa na base de dados PubMed e Web Of Science. Foi utilizado os descritores: "Hyperbaric oxygenation", "Liver transplantation" e "Hyperbaric oxygen therapy" com o operador booleano "AND", e selecionados artigos de relevância para o tema. Inicialmente, foram selecionados 49 artigos, todos publicados nos últimos 20 anos, em português e/ou inglês. Após análise, 6 artigos corresponderam ao objetivo proposto. **Resultados:** Pode-se verificar que o conteúdo intraoperatório de O_2 sistêmico afeta a recuperação pós-operatória em pacientes submetidos ao transplante de fígado. A oxigenoterapia hiperbárica precoce atua como protetor na redução da gravidade da lesão de isquemia/reperfusão dos hepatócitos. A oxigenoterapia hiperbárica também influencia na resposta imune do paciente submetido ao transplante de fígado, reduzindo a incompatibilidade. Ainda sobre os efeitos imunomodulatórios da oxigenoterapia hiperbárica, essa terapia se mostrou eficaz no auxílio da prevenção de infecções pós-operatórias por melhorar a atividade antibacteriana das células imunes e aumentar o efeito bactericida dos antibióticos. Tratando-se de pacientes em lista de espera para transplante de fígado, foi observado após tratamento com a oxigenoterapia a diminuição no número e na intensidade dos episódios de encefalopatia, melhora do prurido e sentimento de bem-estar. No quesito disfunção precoce do aloenxerto, foi demonstrado que pacientes com disfunção apresentaram valores mais baixos de O_2 nas fases anepática e neo-hepática, quando comparado com os pacientes sem disfunção no período pós-operatório. Além disso, durante a fase anepática, o conteúdo do nível de $SatO_2$ também foi menor no grupo com disfunção do que nos sem disfunção. **Conclusão:** A oxigenoterapia hiperbárica é benéfica na preservação do fígado, uma vez que ajuda a manter a função hepática, a prolongar o tempo de preservação do fígado e melhorar o resultado do transplante hepático.

Descritores: Oxigenação hiperbárica; Oxigenoterapia hiperbárica; Transplante de fígado.

INTRODUCTION

In 1937, Dr. Alber Behnke, serving in the United States Navy, first suggested using oxygen (O_2) at elevated pressures during recompression therapy currently used in decompression sickness, arterial gas embolism, monoxide poisoning carbon and other conditions. From this point onwards, hyperbaric oxygen therapy (HBOT) was defined as administering O_2 at 100% for up to several hours under 2 to 3 times the atmospheric pressure at sea level inside a hyperbaric chamber. Side effects are rare, and (O_2) toxicity appears mainly when used in high doses and for a longer period than recommended.[1]

The supply of O_2 depends on blood flow and circulating O_2 content, which depends on the hemoglobin level, the partial pressure of O_2 (PaO_2) and the O_2 saturation level ($SatO_2$). The imbalance between O_2 supply and demand results in tissue hypoxia, which, if prolonged, leads to a decrease in the production of adenosine triphosphate (ATP), used for the metabolic homeostasis of organs, and subsequent development of irreversible tissue damage related to organ failure.[2]

HBOT has been widely used as an adjuvant treatment for various pathological conditions, predominantly related to hypoxic and/or ischemic conditions. In Brazil, the indications were regulated by the Federal Council of Medicine, through resolution CFM 1.457/95, in cases of gas embolism, decompression sickness, Fournier syndrome, gas gangrene, necrotizing infections of soft tissues, compromised flaps or grafts, among other indicative situations.[1]

In liver diseases, the use of HBOT has been studied in cases of hepatic artery thrombosis (HAT), acute liver injury, non-alcoholic steatohepatitis (NASH), bacterial infections, fibrosis and cancer. In cases of end-stage liver disease, such as hepatocellular carcinoma and acute liver failure, liver transplantation (LTx) is widely adopted as the definitive treatment. However, there are important challenges that can cause liver graft failure, including ischemia, preservation and reperfusion injury (PRI), and immunological rejection. Therefore, studies have shown that HBOT protects against organ ischemia/reperfusion (I/R) injuries and has immunomodulatory effects.[1,3,4]

Acute cellular rejection (ACR) affects approximately 30 to 40% of patients after LTx. Although ACR is effectively treated with modern immunosuppressive agents, this significantly increases postoperative morbidity and the overall cost of the procedure. Recent evidence suggests a correlation between the severity of ischemia, preservation and reperfusion (LIPR or HIRI) and ACR. Therefore, limiting the severity of LIPR may reduce the incidence of primary graft nonfunction and ACR after liver transplantation (LTx). Based on this, studies have shown that HBOT reduces the severity of LIPR and modulates the humoral and cellular immune response.[5]

It is also worth mentioning that HBOT was also beneficial in the preoperative phase of LTx, while patients are on the waiting list for the procedure, as it mitigates the progression of liver disease to allow longer life until carrying out the transplant.[3]

Therefore, this work aims to analyze the information available in the pre- and post-operative period of patients undergoing LTx, to evaluate its positive and negative effects in these cases.

METHODS

This is an integrative literature review constructed from the following steps: 1) Identification of the topic and elaboration of the research question; 2) Establishment of criteria for inclusion and exclusion of studies; 3) Definition of the information to be extracted from the selected studies; 4) Critical analysis of the included studies based on the levels of evidence; 5) Discussion of results and 6) Presentation of the integrative review.[6]

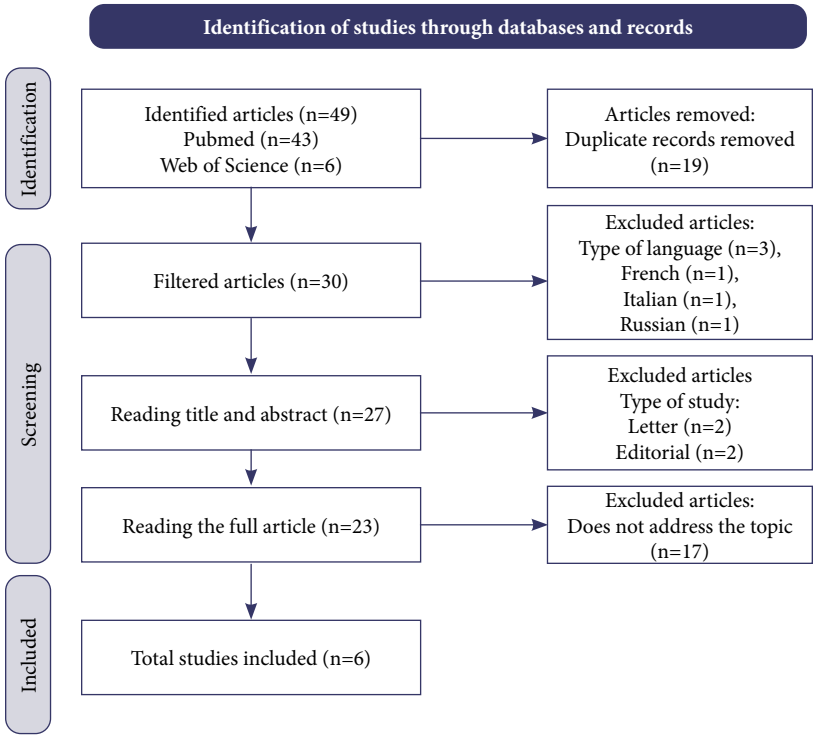
The guiding question was formulated according to the PICO strategy, which represents an acronym for Patient (Person/Problem), Intervention, Comparison and Outcomes (Results). Therefore, the following research question was developed: What are the benefits of using hyperbaric oxygen therapy in patients undergoing LTx?

The bibliographic search was carried out systematically in the following DATABASES - PubMed and Web Of Science. The following descriptors validated by Health Sciences Descriptors (DeCS/MeSH) were used: "Hyperbaric oxygenation", "Liver transplantation", and "Hyperbaric oxygen therapy". The descriptors were exchanged using the Boolean operator "AND" and there was a time-lapse restriction, selecting articles from the last 20 years.

The use of descriptors in English is due to the functioning of the databases and the fact that most indexed articles are available in English, meaning that the search using descriptors in Portuguese limits the results to only articles that provide versions in Portuguese and English.

In PubMed and Web Of Science, the descriptors were used, and the searches were expanded to all fields, finding 43 and 6 articles, respectively, totaling 49 articles.

For the systematic selection of articles, the RAYYAN - Intelligent Systematic Review tool was used, considering the PRISMA Statement 2020 search strategy by the Equator Network's CARE Guidelines for Systematic Reviews, described in Fig. 1.[7]



Source: Elaborated by the authors.

Figure 1. Screening of articles with the PRIMA Statement 2020 flowchart for systematic reviews.

In screening the articles, the screening criteria (inclusion and exclusion) were used, excluding duplicate articles and those that did not fit the focus of the research (hyperbaric oxygen therapy in patients undergoing LTx).

Therefore, the priority of the search was to consider only scientific articles that described the general functioning of hyperbaric oxygen therapy, the protective effects of HBOT on liver ischemia and reperfusion injury, the immunomodulatory effects of HBOT and the possible applications of HBOT in regeneration and LTx.

The articles that fit the theme were analyzed and classified according to the levels of evidence that depend on the methodological approach adopted and, therefore, represent the quality of scientific evidence. This study categorized articles into level 2, which means retrospective and prospective studies, and level 4, which represents narrative review works.

RESULTS

The results were described in Table 1.

Table 1. Summary of studies included in the integrative review.

Author	Periodical/Year	Objective	Kind of study	Results	Level of evidence
KREIMER, F. et al.	ABCD: Arq. Bras. Cir. Dig./2011	To evaluate clinical and laboratory data on liver function in cirrhotic patients on the waiting list for liver transplantation, undergoing hyperbaric oxygen therapy (HBOT)	Prospective study	30% of patients reported a decrease in the number and intensity of spontaneous bacterial peritonitis and gastrointestinal bleeding, and there was no increase in the severity of ascites. Two patients reported improvement in general condition within a few weeks after HBOT sessions.	II
SUN, Y. et al.	International Journal of Medical Sciences/2018	Summarizes the role of HBOT in liver disease and regeneration, discusses HBOT toxicity, and evaluates the potential clinical application of HBOT in the liver.	Narrative review	Most studies have positively evaluated HBOT as an adjuvant treatment for liver injury, non-alcoholic steatohepatitis, fibrosis, cancer and especially for hepatic artery thrombosis. Furthermore, applying HBOT early leads to better results in most situations.	IV
UENO, S. et al.	Langenbecks Arch Surg/2011	To evaluate the utility of acute HBOT after liver resection for patients with HCC to minimize the need for perioperative blood transfusions.	Prospective study	Six patients in the HBOT group who experienced major intraoperative bleeding or fatal hepatic hypoxia (ShvO2 < 50%), ShvO2 and serum lactate levels improved significantly after HBOT. Compared to the control group, the HBOT group showed better changes in ShvO2 serum lactate and bilirubin levels in the first 3 days postoperative after surgery. Furthermore, the HBOT group did not present fatal complications and had a lower incidence of postoperative hyperbilirubinemia than the control group.	II
LEE, M.V. et al.	Medicine/2020	Investigate the role of intraoperative oxygen content in the development of early allograft dysfunction (APD) in patients undergoing living-donor liver transplantation.	Observational study	Lower systemic oxygen content is associated with impaired functional recovery of the graft after living donor liver transplantation. Analysis of intraoperative oxygen contents revealed that patients with postoperative APD had lower oxygen levels in the anhepatic and neohepatic phases compared to patients without postoperative APD. Hemoglobin content and PaO2 during the anhepatic and neohepatic phases and SatO2 during the anhepatic phase were lower in the APD group than in the non-APD group. Analysis of serial changes in oxygen content in each group revealed that oxygen content increased from the prehepatic phase to the anhepatic and neohepatic phases in the non-APD group. However, in the APD group, the oxygen content decreased from the prehepatic phase to the anhepatic and neohepatic phases. In the non-APD group, hemoglobin content increased from the prehepatic phase to the anhepatic and neohepatic phases. However, SatO2 during the anhepatic phase and PaO2 during the anhepatic phase were lower than their respective levels during the pre-anhepatic phase.	II

Continue...

Table 1. Continuation.

Author	Periodical/Year	Objective	Kind of study	Results	Level of evidence
VIJAYARAGAVAN, M. et al.	HPB: The Official Journal of the International Hepato Pancreato Biliary Association/2007	Reviews the rationale for HBO therapy in the field of transplantation with particular emphasis on liver transplantation.	Narrative review	It demonstrated beneficial results about the use of HBO in patients undergoing liver transplantation.	IV
LV, H. et al.	Med Gas Res/2016	Introduce HBOT in liver transplantation, including donors and recipients	Narrative Review	HBO has the ability to increase tissue oxygenation, help preserve the liver during transplantation, and can be applied in different operative phases. The anti-oxidative, anti-inflammatory and anti-apoptosis effects have been proposed as causes of the therapy's efficiency. The correlation between HBOT and immunomodulation is still not exact, despite several studies showing an immunosuppressive effect through HBOT in cases of disease.	IV

HBO(T) Hyperbaric Oxygen Therapy. HCC Hepatocellular carcinoma. ShvO2 Hepatic venous oxygen saturation. APD Early allograft dysfunction. PaO2 Partial pressure of oxygen. SatO2 Oxygen saturation. Source: Elaborated by the authors.

From the analysis of the articles, it can be seen that intraoperative systemic O2 content affects postoperative recovery in patients undergoing LTx. Early HBO acts as a protector in reducing the severity of I/R injury to hepatocytes and, therefore, the effects of the therapy since liver regeneration is closely linked to oxygenation.[1,8]

HBOT also influences the immune response of the patient undergoing LTx, reducing incompatibility. Clinical indicators of general immunosuppression after HBOT include decreased response to antigens, weakened autoimmune responses and slower rejection of allografts.[1] When considering the significant inhibition of the production of gamma interferons (IFN-γ) by lymphocytes present in the peripheral blood within 24 hours after exposure to HBO therapy, this effect is attributed predominantly to the hyperbaric action of the therapy and not to hyperoxemia. Animal studies further demonstrated the depressant effect on IFN-γ through hyperbaric therapy in the absence of hyperoxemia, concluding that the hyperbaric effect operates on the cell's cytoskeleton, reducing IFN-γ without increasing oxygen tension.[3]

Still on the immunomodulatory effects of HBO, this therapy proved to be effective in helping to prevent postoperative infections by improving the antibacterial activity of immune cells and increasing the bactericidal effect of antibiotics.[1] The possibility of HBO therapy in altering the expression of cell surface major histocompatibility complex (MHC) class I antigen.[3]

In the case of patients on the waiting list for LTx, in a study, HBOT was performed in nine sessions lasting 1 hour, in an atmosphere of 100% O_2, under a pressure of 2.8 absolute atmospheres, in these individuals. After treatment, it was observed that 30% of the individuals who underwent HBOT treatment showed a decrease in the number and intensity of encephalopathy episodes. There was no evidence of spontaneous bacterial peritonitis, digestive hemorrhage or changes in the degree of ascites. One in five reported a small improvement in itching, and two in five reported a feeling of well-being for a period of a few weeks after HBOT sessions.[5]

Regarding early allograft dysfunction (APD), the verification of intraoperative O_2, hemoglobin and PaO_2 contents dissolved in arterial blood demonstrated that patients, in one study, with APD had lower O_2 values in the anhepatic and neohepatic phases when compared with patients without APD in the postoperative period. Furthermore, during the anhepatic phase, the $SatO_2$ level content was also lower in the APD group than in the non-APD group.[2]

In the same study, the analysis of changes in O_2 content in each group revealed that in patients with postoperative APD, the O_2 content decreased from the pre-anhepatic phase to the anhepatic and neo-hepatic phases and that the hemoglobin content, $SatO_2$ and PaO_2 during the anhepatic phase were lower than their respective levels during the pre-anhepatic phase. About patients without APD, the analysis of these changes revealed an increase in O_2 content from the neo-hepatic phases, however $SatO_2$ in the neo-hepatic phase and PaO_2 in the anhepatic phase were lower than their respective levels in the pre-hepatic phase in patients without APD.[2]

In the context of investigating the intraoperative prevalence of normal O_2 content, patients with APD had a lower prevalence than those without postoperative dysfunction. The evaluation of changes in the prevalence of normal O_2 content showed that the domain

was greater in the anhepatic and neohepatic phases than in the pre-anhepatic phase in patients without APD, as for the group with APD, there were no significant differences in prevalence between the prehepatic phase and the anhepatic and neohepatic phases.[2,8]

Still in the same study, a model that included O_2 content during the anhepatic phase and the CRP level before surgery was significantly associated with postoperative APD. Also, in the same study, the analyzes recorded that the median duration of hospitalization was longer in the group with APD, being 32 days on average, than in the group without APD, which has an average duration of around 25 days. It is also noteworthy that the incidences of acute kidney injury were around 26.2% in patients without APD and 47.5% in those with dysfunction, and the chances of occurring infection were 6.6% for the group without APD and 18.6% for those with APD, showing higher numbers of incidences in patients with APD. Furthermore, the mortality rate was worse in the APD group at 33.9%, while the group without dysfunction had a 12.5 % mortality rate during the follow-up period.[2]

In another study, to maintain perioperative hemoglobin levels above 7.0 g/dl, red blood cell transfusions were performed in 13 patients in the control group and 13 in the HBO group. The intraoperative and postoperative volumes of erythrocytes, fresh frozen plasma and platelets administered were similar in the HBOT and control groups. HBO therapy was administered to 6 patients who experienced massive intraoperative bleeding. After therapy, low levels of fatal hepatic tissue hypoxia showed significant increases, while serum lactate levels plummeted.[4]

On the other hand, the seven patients in the control group who presented this type of intraoperative bleeding had very low hepatic venous oxygen saturation ($ShvO_2$) and high lactate levels 6 hours after the end of liver resection, which had a similar time to the period after the first HBO. When comparing these two values between the groups, a significant difference was noted in $ShvO_2$ but not significant in serum lactate levels. These differences in $ShvO_2$ and serum lactate levels were clearly noticed during the first 3 postoperative days. Furthermore, changes in serum bilirubin levels in patients undergoing HBOT recovered sooner than in the control group.[4]

Finally, one of the limitations of the present study was that the scientific discussion on the application of HBOT in LTx is still quite restricted to reports of cases of TAH after transplantation and studies involving animals, with not enough prospective randomized and controlled studies published with humans that corroborate the effectiveness of applying this therapy in this situation.

DISCUSSION

HBO management

The critical evolution of patients on the waiting list encourages studies on the use of HBOT in patients with advanced-stage liver diseases on the list as a way of improving their condition and quality of life, perhaps allowing them to reach LTx.

HBO basically acts through two physical factors related to the hyperbaric environment: the mechanical effects of pressure and the increase in oxygenation in tissues. In the hematological system, with the use of HBO, there is an increase in the elasticity of red blood cells, the activity of neutrophils and a reduction in platelet aggregation.[2]

However, oxygen can be toxic, and this is mainly due to the initiation of the chain reaction of free radicals by O_2, which can worsen spontaneously with the consequent lipid peroxidation. The initial phase of HBOT involves the metabolism of lipid peroxidase reaction. The last phase is linked to glutathione oxidation and release of glutathione disulfide (GSSG). GSSG is then reduced through the glutathione reductase reaction, linking to the oxidation of NADPH, which subsequently generates more reactive oxygen species and ultimately leads to cell death. All of these changes by HBOT can cause pathological disruption of biosynthesis. Most of the observed hyperbaric oxygen toxicity has occurred under conditions above 3 atmospheres absolute (ATA), but in clinical application, HBOT is controlled below 2 ATA. However, an antioxidant regimen rich in vitamins C and E can be used to offset oxidative stress in the liver.[2,8]

Protective effects of HBO on hepatic ischemia and reperfusion injury

During LTx, the donated organ goes through a process of ischemia, which is mitigated through the preservation technique, which can cause significant damage to the liver and is subsequently reperfused after implantation in the recipient. Increasing studies indicate that liver I/R is closely related to the onset and severity of acute rejection after LTx.[1]

Early HBO played a protective role in reducing the severity of I/R injury and hepatocyte fibrogenesis by decreasing oxidative stress, ATP energy loss, necrosis or apoptosis, and improving microvascular patency. After I/R injury, HBOT can ensure hepatic homeostasis characterized by decreased neutrophil accumulation and activation and improved mitochondrial function. Furthermore, oxygen therapy facilitated hepatocyte proliferation and regeneration by improving angiogenesis, antioxidant activity, mitochondrial function, and energy metabolism stability.[2,5,8]

Nitric oxide (NO) has a dual role in hepatic I/R injury. Endothelial NO synthase (NOSe) is expressed mainly in case of hypoxia. On the other hand, inducible NO synthase (NOSi) can be activated by interleukin-1(IL-1), tumor necrosis factor α (TNF-α) and

lipopolysaccharides in neutrophils and macrophages, increasing NO production, which can increase vascular permeability and cause tissue damage. The toxic effects of NO derived from iNOS are probably due to the increased production of superoxide radicals rather than the toxicity of NO itself. *In vitro* and *in vivo* studies have demonstrated that HBO is capable of selectively inducing the activation of NOSe and inhibiting the activation of NOSi, exerting protective effects.[1,3]

In liver I/R injury, a large number of inflammatory mediators and chemokines are produced by inflammatory cells that then activate leukocytes, platelets, and endothelial cells. Subsequent expression of adhesion molecules on vascular endothelial cells can promote the adhesion of leukocytes to these endothelial cells, leading to aggregation and infiltration of leukocytes into the cells. HBOT can reduce leukocyte migration and adhesion by decreasing the expression of the adhesion molecules CD11 and CD18, two ligands of intercellular cell adhesion molecule-1 (ICAM-1) expression in endothelial cells, which may attenuate leukocyte adhesion to endothelial cells. Inhibition of endothelial-neutrophil interaction has been attributed as a mechanism underlying the protective effects of HBO on I/R injury(1). Leukocyte adhesion also occurs through upregulating P and E selectins expressed on endothelial surfaces. P-selectin is present in its pre-made form inside cells and therefore regulates and quickly binds to its ligand CD15 on neutrophils. Upregulation of E-selectin requires new synthesis and is, therefore, slower and binds to a molecule on neutrophils.[3]

There is evidence that HBO is capable of inhibiting I/R-induced oxidative stress. This stress occurs due to a large amount of reactive oxygen species produced in cells, mainly in inflammatory cells, causing damage to the cell membrane and organelles via lipid peroxidation, protein nitration and DNA modification. Exposure to 100% normobaric O_2 increases the degree of this injury during reperfusion. Although HBOT increased reactive oxygen species, it reduced lipid peroxidation. HBOT can also inhibit hepatocyte apoptosis in the ischemia phase, but the application of HBOT in the reperfusion phase cannot suppress hepatocyte apoptosis. This can be justified by the fact that HBO administered in the ischemia phase improves the supply of O_2 to tissues, which attenuates the production of reactive oxygen species in the reperfusion phase.[1]

Immunomodulatory effects of HBOT

HBOT treatment have demonstrated efficacy in modulating the immune system during LTx, promoting the suppression of the humoral and cellular immune response. Such effects are related to the repercussion of the hyperbaric tension exerted by HBO on T lymphocytes, a cell that plays a crucial role in immunity. The manipulation of HBOT categorical hyperbaric tension levels allows the improvement of leukocyte activity, more specifically, the cytotoxic class of lymphocytes, T lymphocytes, and acting in an inhibitory manner, interfering with cellular physiology to regulate the normal pattern of behavior.[1,3]

It is noteworthy that the effects of HBOT on lymphocytes are directly related to the pressure used in therapy. HBOT applied at 100 kPa for 60 to 90 minutes has been shown to improve the activity of cytotoxic T lymphocytes. However, this activity was inhibited when HBO was administered at 150 kPa for 30 to 60 minutes. It was also found that, in treating allogeneic stimulator cells with HBO culture, the activity of cytotoxic T lymphocytes, proliferative responses and production of IFN-γ in a mixed lymphocyte reaction was nullified.[1,3]

In one study, the immune function of 12 non-cirrhotic patients undergoing elective hepatectomy due to liver cancer was evaluated after applying 2 cycles of HBOT treatment, with a pressure of 200 kPa and 100% pure O_2, for 60 minutes. Analyzes were performed at 3 hours and 24 hours after hepatectomy. The results indicated a significant decrease and delay in the maximum levels of polymorphonuclear leukocyte elastase (PMNE) and thrombomodulin (TM). Furthermore, elevated expression of CD18, a leukocyte adhesion-related protein, was remarkably suppressed after HBO exposure.[4,9]

HBOT is also recognized for its ability to fight infections. Studies have shown that the functions of neutrophils, especially antibacterial activity, are strongly correlated with O_2 concentration. When PaO_2 exceeds 30mmHg, the destruction capacity of neutrophils remains normal. On the other hand, a PaO_2 lower than 30 mmHg considerably compromises the respiratory burst, a phenomenon that represents the vital activity of immune cells due to possible damage to the mitochondrial respiratory chain. In this way, HBO enhances the antibacterial activity of immune system cells and intensifies the bactericidal power of antibiotics, which, in turn, can significantly contribute to the prevention of postoperative infections.[1]

The modulation of HBO in the immune System can be done based on the relative concentration of high and low-affinity receptors for interleukin-2 (IL-2) on T lymphocytes. Binding to high-affinity receptors stimulates cell proliferation, while the opposite is true for low-affinity receptors. In this way, HBO can change the proportion of these receptors, reducing T cell proliferation.[3]

As for macrophages, HBO conditions the release of TNF-α in macrophages not stimulated by hyperbaric and hyperoxemic components. However, for macrophages exposed to bacterial lipopolysaccharide, only the hyperbaric component is necessary. It is important to note that in some studies, an initial increase in TNF-α and IL-1 secretion was observed in patients with Crohn's disease and in healthy volunteers undergoing HBOT, but this response decreased with continued therapy. Furthermore, the production of IFN-γ by peripheral blood lymphocytes was significantly inhibited for up to 24 hours after exposure to HBOT, and this effect is attributed mainly to the hyperbaric influence of the therapy, in contrast to hyperoxemia.[3]

Another mechanism by which HBO therapy may prevent tissue damage due to reperfusion injury is by providing supplemental O_2 to generate phagocytes that detoxify highly reactive oxygen radicals before they cause damage to reperfused tissues. These phagocytes include superoxide dismutase, catalase, peroxidase and glutathione.[10]

Finally, HBO therapy also exerts an inhibitory effect on the β2 integrin system in neutrophils. The β2-integrin system triggers the adherence of neutrophils to the endothelium of the postcapillary venule through the intracellular adhesion molecule. Inhibition of this process prevents the aggregation of neutrophils in post-capillary venules, thus avoiding the "non-reflux" aspect of reperfusion injuries. Studies have shown that HBO does not affect the number of β2-integrin receptors nor the respiratory burst response of neutrophils, which keeps the general function of these cells intact. However, HBO therapy has been shown to have a distinct inhibitory effect on the β2-integrin system.[10]

HBOT applications in regeneration and LTx

After liver injury, the liver begins regeneration to repair the injury. This process is proportional to O_2 consumption, and after liver injury, metabolism requires an increased amount of O_2 to provide mitochondrial oxidative phosphorylation to restore the hepatic energy load. The increase in portal blood flow and the supply of O_2 produced by arterialization of the portal vein have fundamental effects on hepatic energy metabolism and liver regeneration. In accelerated liver regeneration, O_2 for normal regeneration will be insufficient. Theoretically, HBO can increase O_2 for mitochondrial oxidative phosphorylation, leading to elevated ATP production. In patients undergoing hepatectomy, the effects were attributed to increased vascular endothelial growth factor expression after HBOT.[1]

In one study, the first HBOT was administered 3 hours after completion of hepatectomy and was followed at 24 and 48 hours by repeat treatment. Acute HBOT improved postoperative hepatic hemodynamics and liver function, even in the two patients with severe hypoxia, $Shv0_2 < 50\%$, caused by cirrhosis, operative events and major intraoperative bleeding. Furthermore, postoperative $ShvO_2$ and serum lactate levels in the HBOT group improved compared to those in the control group, specifically during the first 24 hours. The change in serum bilirubin levels also indicates that early HBOT could be responsible for maintaining hepatic metabolism without energy insufficiency since it is known that the excretion of bile pigments in the canalicular space occurs against a considerable concentration gradient and is dependent on ATP.[4,8,9]

In cases of hepatocellular carcinoma (HCC), it has been found that HBOT can overcome deficiencies in systemic and hepatic O_2 supply and subsequently reduce postoperative complications. Furthermore, HBOT improved postoperative Immune Response and long-term survival after liver section in patients with HCC.[4,9]

Lower systemic O_2 content is associated with impaired functional recovery of the graft after LTx. The hepatic flow circulation consists of a dual blood supply in which 75% of the blood flow comes from the portal vein, and 25% comes from the hepatic artery. In hepatic O_2 supply, 50% of oxygenation is supplied by the portal vein and 50% by the hepatic artery. O_2 availability is a fundamental aspect of the cellular microenvironment and is related to functional and metabolic balance. In particular, highly metabolic organs, such as the liver, require adequate O_2 supply for parenchymal durability. Due to the hepatic anatomical structure, the O_2 concentration progressively decreases through the sinusoids, from the periportal zone to the perivenous zone. Lower O_2 supply in the perivenous zone is associated with greater vulnerability to hypoxia-induced hepatocyte injury. Therefore, a deficient amount of systemic O_2 may impair the achievement of an adequate O_2 level to meet the metabolic demand of the graft, eventually affecting the functional recovery of the post-transplant graft in patients undergoing LTx. 2

Patients with postoperative APD have lower O2 content immediately before and continuously after graft reperfusion compared to patients without postoperative APD. After the pre-anhepatic phase, O2 content decreased in the DPA group but increased in the non-APD group. The analysis revealed that oxygen content during the anhepatic phase and higher preoperative C-reactive protein (CRP) levels were factors independently associated with the occurrence of APD. Postoperatively, patients with APD had a longer duration of hospitalization, a higher incidence of acute kidney injury and infection, and higher mortality rates compared to patients without APD.[2]

Improved oxygenation of the transplanted liver allows recipient factors such as wound healing and infection control to be enhanced. When tissue O_2 tensions fall below 30mmHg, neovascularization stops, and fibroblast ceases to function. Neutrophils also become ineffective in fighting infection at this PaO_2 because they can no longer destroy bacteria oxidatively, as they lose the ability to generate toxic radicals. HBO also helps to improve the delivery of O_2 to tissues, reducing edema through vasoconstriction. Furthermore, it protects against reperfusion injury that may occur after hepatic artery recanalization. HBO therapy inhibits cell membrane lipid peroxidation by antagonizing interactions between toxic oxygen radicals and cell membrane lipids. HBOT also inhibits the leukocyte-dependent conversion of xanthine dehydrogenase to oxidase, thereby stopping the generation of oxygen radicals by xanthine oxidase. These radicals influenced the result of lipid peroxidation.[10]

The use of HBOT also plays a role in treating post-transplant complications. TAH after LTx causes hypoxic injury to the liver, which, consequently, can lead to gangrene and liver failure. If the hepatic artery is recanalized, the liver may suffer additional damage due to

I/R injury. HBOT can provide sufficient O_2 to the liver through the portal system or through the hepatic artery to prevent hepatocytes from dying in the early post-thrombotic period. During HBO treatments at 2 ATA in 100% O_2, the O_2 content in the blood is increased by 125%, and this is not possible with supplemental O_2 at sea level only. The O_2 content in blood is the combination of O_2 transported by hemoglobin and dissolved in plasma. These same studies have shown that O_2 tension increases by a factor of 10 in plasma and other tissue fluids. This effect of increased O_2 content in blood and plasma can counteract the decreased O2 supply due to TAH[8,10]

It is also worth mentioning that, in a study, the use of HBOT was verified in an adult recipient of an orthotopic liver transplant who developed TAH. The patient, in this case, underwent 30 HBOT treatments at 2.5 ATA for 1 hour each. This patient was monitored for 8 months, and during this period, his liver function normalized, allowing him to be discharged from the hospital without retransplantation.[11]

Central pontine myelinolysis (CPM) is the most serious neurological complication of LTx and can increase early mortality. In one study, HBO therapy was applied to a male patient with CPM who underwent LTx from a living donor after moderate coma, increased autonomic activities, improved limb muscle tension and elevated Glasgow-Pittsburgh score.[12]

FINAL CONSIDERATIONS

The antioxidant, anti-inflammatory and antiapoptotic effects of HBO were active mechanisms in hepatic I/R injury. From this, it was possible to verify that HBOT is a beneficial therapy for preserving the liver, as it helps to maintain liver function, prolong liver preservation time and improve the results of LTx. Furthermore, it can be used not only in the maintenance of the donor and the donated organ but mainly in patients who will undergo transplantation.

The lower concentration of arterial O_2 may negatively affect the recovery of graft function after LTx, despite the preservation of the hepatic vascular flow. Before graft reperfusion, levels of O_2 content components such as hemoglobin content, PaO_2, and $SatO_2$ must be regularly assessed and carefully maintained to ensure adequate O_2 supply to transplanted liver grafts. Since the allogeneic blood transfusion appears to have detrimental complications, rescue blood autotransfusion, such as using a cell protection device, is a potentially safe and effective option for maintaining hemoglobin homeostasis during surgery.

Therefore, the use of acute postoperative HBOT to reduce the need for blood transfusions can be used to overcome deficiencies in systemic O_2 supply, thus reducing postoperative complications. Finally, as a secondary effect, this therapy can promote the postoperative benefit for the control of HCC.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Silva HRS, Lima MI e Fonseca Neto OCL; **Conception and design:** Schwambach BS, Braga MELS, Ferreira LA, Andrade SV, Vieira CAFF, Oliveira LCMC, Batista MCS, Souza BMN, Lima MI e Fonseca Neto OCL; **Data analysis and interpretation:** Schwambach BS, Braga MELS, Ferreira LA, Andrade SV, Vieira CAFF, Oliveira LCMC, Batista MCS, Souza BMN; **Article writing:** Schwambach BS, Braga MELS, Ferreira LA, Andrade SV, Vieira CAFF, Oliveira LCMC, Batista MCS, Souza BMN; **Critical revision:** Lima MI e Fonseca Neto OCL; **Final approval:** Fonseca Neto OCL.

DATA AVAILABILITY STATEMENT

All dataset were generated or analyzed in the current study.

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