Further application of hyperbaric oxygen in prostate cancer

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Abstract

Hyperbaric oxygen therapy (HBOT) has been used as an adjuvant treatment for multiple pathological states, which involves hypoxic conditions. Over the past 50 years, HBOT has been recommended and used in a wide variety of medical conditions, clinically in the treatment of ischemic or nonhealing wounds and radiation-injured tissue, and in the treatment of malignancy. The mechanism of this treatment is providing oxygen under pressure which is higher than the atmosphere thus increasing tissue oxygen concentration. When cells get enough oxygen in the microenvironment, they become active and replicate effectively. Prostate cancer is the second most common cancer and the fifth leading cause of cancer death among male around the world. It is estimated that more than 29,000 men died from metastatic prostate cancer in 2014. With the development of the prostate-specific antigen-based screening technology, prostate cancer incidence has increased markedly over time. According to the survey, the morbidity and mortality of prostate cancer have surpassed bladder cancer and renal carcinoma, becoming the most common cancer in urology in Chinese adults. Nowadays, the main solution to deal with prostate cancer is still the surgical ways, including laparoscopic radical prostatectomy and robot-assisted radical prostatectomy. Nevertheless, the complications of the surgical treatment have not been completely avoided. HBOT has gained great clinical recognition over the decade. It has been demonstrated that HBOT has considerable effects on carcinoma, especially on decreasing complications and improving mortality. So, it is important to combine the HBOT with patients who suffer from prostate cancer. This review illuminates the effect and underlying mechanism of the HBOT in prostate cancer for further clinical application.

Key words: hyperbaric oxygen therapy; prostate cancer; carcinostasis; experimental research; underlying mechanism; clinical research; therapeutic implications

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INTRODUCTION

Hyperbaric oxygen therapy (HBOT) proves to be the most significant medical technique to have treated many diseases over the past 50 years, including malignant cancer. The accrual era of hyperbaric medicine began in 1961, when Brummelkamp et al. studied the first series of patients who are affected by clostridium myonecrosis (gaseous gangrene) with very positive results. The first reports of studies on the physiological effects of hyperbaric oxygen were done at Harvard in the 1930s. It is primarily used in acute and chronic wound conditions in America currently. In China, HBOT began in the 1960s and developed rapidly after political reform and opening-up. Normally, hyperbaric oxygen was invented for conditions related with gas bubble, such as cerebral air embolism and decompression sickness, leading to the earliest medical research on this kind of treatment. The impact of hyperbaric oxygen on cancer cells was not clearly defined, and the results of early studies were controversial at first. One study demonstrated that HBOT restrained the development of oral carcinoma when it began to occur; Nevertheless, HBOT has the possibility to accelerate tumor growth during the proliferation phase. Similar conclusions were achieved in the last few years, and one research concluded that hyperbaric oxygenation may expedite cancer cell proliferation and then promote cell carcinogenesis. However, modern knowledge almost clearly illuminates that HBOT will have no advantage on cancer development, and it might reduce the main tumor mass. Recently, several reviews which describe HBOT in cancer treatment have been published. Tumor mass often exists in some areas where hypoxia appears, it has been reported that hypoxia promotes malignant cell proliferation and makes cancer cells adapt to the environment, which again induces cancer growth. HBOT can help physicians surmount this matter. The mechanism of HBOT is making use of 100% oxygen which is higher than normal atmospheric pressure. This kind of oxygen elevates the amount of dissolved oxygen in the plasma, thus increasing oxygen content in hemoglobin. It will induce organic ischemic tolerance and hypoxia with the use of hyperbaric chamber. Therefore, the concentration of oxygen in cancer tissue increases significantly during hyperbaric oxygen exposure. The standard procedure for HBOT claims that patients breathe pure oxygen under pressure between 1.5 and 2.5 atmospheres absolute inside the hyperbaric chamber, and it allows the body’s natural healing process to take place and repair winding tissue is repaired. We conclude that the administration of HBOT can provide many clinical benefits in the treatment of tumors. Prostate cancer is the most common male malignant tumor in Europe and the United States and is also the second-highest mortality rate cancer among male malignant carcinomas. The mortality of prostate cancer presents an obvious ascending tendency. In
Europe, prostate cancer is the most common carcinoma, with an incidence rate of 214 cases per 1000 men, surpassing lung cancer and colorectal cancer.26 As in Europe, prostate cancer is also becoming a major public health issue in China. According to the National Central Cancer Registry of China 2015 Annual Report, the overall incidence rate of prostate cancer was 7.1/10^5 populations in 2011.21 This data rose up to ninth in the highest rate cancer in male. Some differences occur in prostate cancer morbidity and mortality. Prostate cancer incidences were 10.06/10^5 in urban area, and with a lower rate of 4.79/10^5 in rural area. Prostate cancer mortality rates were 2.98/10^5 for the whole population, 3.95/10^5 in urban area and 1.97/10^5 in rural area, respectively.22 It creates an enormous significant social and economic burden for our society. The primary treatment of prostate cancer including active surveillance, radical prostatectomy, radiotherapy and hormonal treatment.29 However, treatment-related complications of prostate cancers are still the obstacle faced by urologists. Some patients are unwilling to suffer from the complications when they choose the treatments. Hence we consider if there is a way to do little harm on the patients, such as HBOT. Local hypoxia which happens in the central tumor areas is one of the major issues and it gives rise to ineffective medical treatment of prostate cancer. HBOT may help overcome this problem.1 In order to explore the practicability of the efficiency of HBOT in prostate cancer, we will discuss the effect of HBOT on prostate cancer and the potential mechanisms of HBOT on the basis of experimental and clinical studies in this article.

**Experimental Studies of Hyperbaric Oxygen in Prostate Cancer**

As is well known, animal experiments are the foundation of basic medical and preclinical research and both of them are established to discover the mechanism of HBOT on prostate cancer. Consequently, we have found several studies which conclude HBOT as stand-alone treatment of prostate cancer. Chong et al.23 detected that HBOT does not accelerate the growth of indolent prostate cancer. During the HBOT, they found that there were no differences in both groups, including tumor microvessel density, proliferative index, differentiation and apoptosis markers. The other research was fair to find any change in active tumor growth after HBOT.24 No differences were observed in tumor microvessel density, proliferative index, or apoptosis markers compared with the non-HBOT group in the study. The conclusions of these studies all indicated that HBOT will not promote the growth of cancer cells. However, all of them were not able to detect anti-cancer function of HBOT, and we think this is due to different experimental conditions and methods. We will analyze several recent experimental studies related to this treatment for prostate cancer treatment in this paper (Table 1), and then summarize the outcomes. As for in vitro model, we have found several articles with beneficial results. It has been reported that HBOT can decrease the rate of growth, and increase sensitivity to anticancer agents.25 Also, it demonstrated that HBOT may potentiate cancer chemotherapeutic agents that cause damage to DNA during DNA synthesis or HBOT may inhibit cell division causing accumulation in G0/M.26 The effect of HBOT on LNCaP cells indicated that HBOT was an efficacious way to restrain the growth of prostate cancer. It suggested that HBOT may increase the efficacy of radical prostatectomy or chemotherapy by inducing partial synchronization or cell cycle accumulation. This kind of valuable therapy could be useful in treatment of malignant carcinoma, particularly like poorly vascularized tumors which embrace a significant hypoxic cell fraction. HBOT could be further examined as a potential gas for prostate cancer in the clinical setting, which we believe it would succeed.

| Author | Model | Main results |
|--------|-------|--------------|
| Tang et al.20 | Mice | Hyperbaric oxygen did not promote the growth of indolent prostate cancer, nor did it have any significant effect on the new vessels. |
| Chong et al.21 | Mice | HBOT did not accelerate the growth of indolent prostate cancer in a murine model |
| Tang et al.24 | Mice | HBOT did not have a tumor stimulatory effect on prostate cancer and could potentially be used safely in conjunction with other therapeutic modalities. |
| Kalns et al.25 | LNCaP cells | HBOT could decrease the rate of growth, and increase sensitivity to anticancer agents, however, the effects were cell line dependent. |
| Kalns et al.26 | LNCaP cells | HBOT may potentiate cancer chemotherapeutic agents that cause damage to DNA during DNA synthesis or HBOT may inhibit cell division causing accumulation in G0/M. |

Note: HBOT: Hyperbaric oxygen therapy.

**Mechanism of Hyperbaric Oxygen in Curing Prostate Cancer**

The mechanism of hyperbaric oxygen in treating prostate cancer has not been fully illustrated. However, several literatures have shown the DNA lesions induced by oxygen-derived species in microenvironment.27,28 Recently, numerous studies have been used to demonstrate the changes in the intracellular microenvironment.29 There are two possible explanations to elucidate this carcinostasis phenomenon. Firstly, the damage caused by HBOT is owing to •OH radical formation.30 In a hyperbaric oxygen environment, metal ions could be released within the cell actively due to oxidative stress. The concentration of iron and copper ions intracellular will be extremely high. As a result of cellular respiration, a great diversity of enzymatic reactions happens with oxidase enzymes, and these processes produce plenty of electrons. When electrons are transferred between the complexes of the mitochondrial electron-transport chain, some of them are captured by molecular oxygen to form the O2•. Other major sources of O2• include the enzymes xanthine oxidase and the membrane bound enzyme nicotinamide adenine dinucleotide phosphate oxidase.31 O2• will be transformed to hydrogen peroxide by the superoxide dismutase enzymes. Hydrogen peroxide will react with ions of iron or copper to form •OH.32 When •OH is formed, it will penetrate the nuclear membrane and then bind...
to the DNA. As the result of this reaction, •OH will make the composition a target for HBOT damage. Another explanation of the DNA damage is that hyperbaric oxygen leads to a series of metabolic events inside the cell. It motivates the activation of nuclease enzymes, which cleave the DNA and make it an isolated one. It is also suggested that high pressure oxygen causes the rise of free Ca²⁺ in intracellular, which can fragment DNA by activating Ca²⁺-dependent endonucleases. It works like apoptosis, which means programmed cell death, an example of apoptosis is the killing of immature thymocytes by glucocorticoid hormones, which activate a self-destructive process that apparently involves Ca²⁺-dependent DNA fragmentation. Meanwhile, when it comes to cell level, HBOT has the ability to recruit cells into the G₀/M of the cell cycle. The experiment of exposure to oxygen (3 atm; 1 atm = 1.01 × 10⁵ kPa) found that the percentage of putative senescent cells decreased and that G₀/M increased. It means increased oxygen pressure makes senescent cells to enter the cell cycle. The increased number of cells which gather in the G₀/M population implies that a high pressure oxygen is successful to create a DNA damage checkpoint at G₀/M period. At the same time, cells finish replicating DNA and are trapped at G₀/M period. This period is rather important because many treatments depend on DNA damage, cell cycle checkpoint arrest, and subsequent apoptosis. The failures of many therapeutic approaches to cancer arise from the emergence of a highly resistant core of previously hypoxic cells after initial rounds of treatment. In the way of recruiting more cells into G₀/M periods, curative effect of other therapies which aim at eliminating tumor will be increased and hence survival time of patients will be lengthened. The protective effect of HBOT on curing the prostate cancer is exhibited in the Figures 1 and 2.

Figure 1: HBOT damages cellular DNA by activating metal ion channels.
Note: In a HBO environment, metal ions were activated. The concentration of iron and copper ions intracellular was increased. Through respiratory chain complex O₂⁻• was formed. O₂⁻• will be transformed to hydrogen peroxide by the SOD enzymes. H₂O₂ reacts with iron or copper to form •OH. •OH penetrates the nuclear membrane and binds to the DNA. Nuclease enzymes activated, cleave the DNA and make it an isolated one. Free Ca²⁺ rises in intracellular, it activates Ca²⁺-dependent endonucleases and fragments DNA. SOD: Superoxide dismutase; HBO: hyperbaric oxygen; HBOT: hyperbaric oxygen therapy.

Figure 2: HBOT causes cells trap at G₀/M period and discontinue replicating DNA.
Note: HBO makes cells to enter the cell cycle of G₀/M period. At the same time, cells finish replicating DNA and are trapped at G₀/M period. HBO: Hyperbaric oxygen; HBOT: hyperbaric oxygen therapy.

CONCLUSION AND PROSPECTS
So far, we have found studies on the possible treatment of prostate cancer with HBOT, confirming that HBOT for curing prostate cancer is clinically significant. It works primarily through two mechanisms: Firstly, hydrogen peroxide reacts with ions of iron or copper to form •OH, making the DNA an isolated one. Secondly, it makes cells finish replicating DNA and is trapped at G₀/M period. However, this treatment is rarely used clinically. We believe that this treatment is meaningful, so there should be further research on the application of HBOT in prostate cancer.

The ability of HBOT to alleviate brain injury is admitted by public and it has been applied in many diseases of neurosurgery. Patients need to lie down their bodies and breathe pure oxygen in a treatment chamber, which is set 2 to 3 times higher than atmospheric pressure, and finally the oxygen is distributed around infected areas. The treatment can reduce brain injury of cerebral ischemia and hemorrhage. HBOT could be considered as the alternative of red blood cell transfusion which is intended to increase oxygen delivery in anemic patients after subarachnoid hemorrhage. It has also been commonly applied in the treatment of stroke since 1960s and has proved to be a safe and beneficial treatment strategy. Although HBOT is still not a preferred way to resist urology cancer in current medicine, it is making gradual strides for use in genitourinary medicine due to its low risk and likelihood to achieve favorable results. Radiation therapy is widely used in urology to treat prostate cancer as a main therapy, or as an adjuvant therapy after a radical prostatectomy. HBOT is effectively dealing with radiation-induced hemorrhagic cystitis can appear during radiotherapy or a long time after therapy. HBOT is effectively dealing with radiation-induced hemorrhagic cystitis. Its overall effectiveness in various pathologies has been manifested in...
many clinical studies and trials.\cite{47,48} According to the above experiments, it is shown that hyperbaric oxygen can effectively inhibit the growth of tumor cells, but the effect is not good when the HBOT is used in vitro experiments only. We suppose that the concentration of hyperbaric oxygen is high when it acts on a single tumor cell, but when it acts on local or the whole body, hyperbaric oxygen cannot achieve the concentration of tumor cell growth inhibition, thus affecting the therapeutic effect. Therefore, we surmise if it is possible to combine the HBOT with the ultrasound guided transrectal prostate puncture, which can be placed around the tumor mass, and the hyperbaric oxygen is sent through the probe to create the hyperbaric oxygen environment around the tumor mass, thus achieving the therapeutic effect. We hope that there will be further research or experiments in the future that can be used in the treatment of hyperbaric oxygen in vitro, to reduce the growth of tumor cells and to achieve the purpose of treatment.

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