

The Effect of Hyperbaric Oxygen Therapy on Reducing Blood Cortisol Levels in Individuals with Anxiety Disorders

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ARTICLE INFO

Keywords: Cortisol, HBO, Oxygen Hyperbaric, Anxiety disorders, Therapy

Received : 12, September

Revised : 15, October

Accepted: 28, November

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ABSTRACT

This research pertains to developmental advancements in the health and maritime sectors, specifically focusing on diving and hyperbaric oxygen therapy's (HBO) application. The study holds the potential to enhance comprehension regarding the Effects of Hyperbaric Oxygen Therapy (HBO) in addressing anxiety disorders, thus contributing significantly to the realms of health and maritime industries. Hyperbaric oxygen therapy involves subjecting patients to heightened pressure environments while administering pure oxygen at levels exceeding atmospheric pressure, with a minimum clinical threshold of 1.4 ATA. (HBO) interventions, utilized for countering hypoxia and cortisol reduction, exhibit promise in mitigating anxiety disorders. The research methodology commences with a systematic screening procedure employing an anxiety disorders questionnaire, ensuring the acquisition of a well-defined, credible, consistent, and unbiased participant pool. Employing a quasi-experimental design featuring a randomized pre-post control group arrangement, the study targets males aged 25-40 with anxiety disorders, drawn from Dr. Ramelan Surabaya's psychiatric clinic.

INTRODUCTION

Sleep disorders are a common clinical problem, underscoring the importance of adequate, high-quality sleep for body recovery and optimal daily functioning. Insufficient or inadequate sleep can disrupt physical, mental, social, emotional well-being and anxiety, which ultimately affects overall health and quality of life (1), (2). The prevalence of such anxiety disorders varies between 10% and 30% within the general population, influenced by factors like ethnicity, sociodemographic characteristics, health status, lifestyle, familial structure, and work environment (1).

Sleep disturbances often accompany depression and other stress- and anxiety-related disorders, characterized by elevated cortisol levels, altered norepinephrine (NE), and malfunctions in the hypothalamic-pituitary-adrenal (HPA) axis. Excessive HPA axis activity adversely affects sleep, leading to irregular sleep patterns, decreased deep slow wave sleep, and shorter sleep duration. Stress triggers activation of the HPA axis through the hypothalamus, which causes the release of corticotropin-releasing hormone (CRH). This then stimulates the production of adrenocorticotrophic hormone (ACTH), activating the adrenal glands to release cortisol, especially in situations involving increased levels of pro-inflammatory molecules such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor- α (TNF- α), commonly observed in inflammatory conditions. This surge in cortisol levels significantly contributes to sleep disturbances. Sleep issues may also involve heightened nervous system metabolism to maintain neural electrical potentials, demanding substantial oxygen consumption and resulting in notable oxidative production (3).

Hyperbaric oxygen (HBO) therapy involves immersing patients in a pressurized environment and administering 100% oxygen at levels exceeding atmospheric pressure (4). Initially utilized for maritime purposes, particularly in diving and hyperbaric contexts, HBO therapy has expanded for use as an adjunctive treatment in various clinical pathologies, notably those linked to hypoxia or ischemia, including anxiety disorders. HBO interventions, aimed at addressing hypoxia, inflammation, normalizing HPA axis irregularities, reducing nocturnal CRH hyperactivity, and lowering cortisol levels, hold potential in ameliorating sleep disruptions. Hence, comprehensive investigation into HBO's effect on sleep disturbances through cortisol reduction is warranted. This study exclusively enlists patients from the psychiatric polyclinic at RSPAL Dr. Ramelan and excludes student participation.

Based on the description that has been stated in the background above, the researchers formulated the problem, namely "How can HBO have an effect on reducing blood cortisol levels in patients with anxiety disorders?".

LITERATURE REVIEW

Hyperbaric Oxygen (HBO)

Hyperbaric oxygen therapy or hyperbaric oxygen (HBO) is a therapy that places the patient's entire body in an environment of increased pressure and the patient breathes 100% oxygen. The minimum pressure normally accepted for clinical care is 1.4 atmospheres absolute or 1.4 ATA. Absolute atmosphere is a scale that incorporates the total pressure exerted on a body regardless of where

the body is, i.e. at sea level or in a pressure chamber. 1.4 ATA can be simplified to think of as 1.4 times the usual environmental stress felt by the physiology of each patient at ideal sea level (4).

The main mechanism of hyperbaric oxygen is to increase the amount of dissolved oxygen and re-oxygenate tissue that has impaired circulation and decreased oxygen supply. HBO helps provide abundant dissolved oxygen, which not only helps survive without haemoglobin but also stimulates tissue metabolism by activating respiration at the cellular level. The physiological effects of HBO fall into 3 categories: increasing the partial pressure of oxygen, exerting a direct effect on blood vessels by vasoconstriction or increasing physical stress. The increase in the partial pressure of oxygen in the circulating blood is brought about by the condition that the partial pressure of oxygen increases during breathing in conditions of impaired alveolar function. HBO increases the diffusion of oxygen from the alveolar space to the capillaries surrounding the alveoli. And increase the amount of dissolved oxygen in the pulmonary veins and will be distributed to the peripheral arteries after being pumped by the heart. Increased oxygen pressure or dissolved oxygen in the blood or excessive oxygenation results in tissue oxygenation and increases oxygen supply and causes tissue damage, which will cause various disease sequences (5).

Anxiety disorders

Inadequate or inadequate recovery during sleep can disrupt regular physical, mental, social, emotional and anxiety functioning, thereby Effecting overall health and quality of life (1), (2). Sleep is believed to be regulated by two main types of mechanisms: mechanisms that regulate sleep timing, such as the circadian system, and mechanisms that regulate sleep duration, referred to as sleep homeostatic mechanisms. Although the molecular mechanisms that regulate circadian rhythms are well understood, the mechanisms that regulate sleep homeostasis, which most likely involve neurons, have not been clearly elucidated. Typical sleep patterns involve alternating cycles of light sleep, deeper slow wave sleep, and rapid eye movement (REM) sleep (6).

Research studies show that prolonged sleep deprivation or shorter sleep duration in humans is associated with metabolic disorders, cardiovascular problems, inflammation, mental health conditions, anxiety and premature death. Sleep disturbances, increased cortisol, altered NE levels, and HPA axis dysfunction are also associated with depression and stress- and anxiety-related disorders. Interestingly, persistent insomnia without depression is associated with increased cortisol levels, especially at night and in the early phases of sleep. This increase in cortisol is likely a major factor contributing to sleep problems. Additionally, increased cortisol levels may serve as an indicator of increased CRH and central nervous system norepinephrine activity (6).

In certain anxiety disorders, dysfunctional HPA axis activity may be a contributing factor. Conversely, in other situations, HPA axis dysfunction is a consequence of sleep disruptions, as evident in obstructive sleep apnea. Overactivity of the HPA axis can cause fragmented sleep, reduced slow wave sleep, and abbreviated sleep duration. Sleep problems can worsen HPA axis

dysfunction, creating a reinforcing cycle. Insomnia and obstructive sleep apnea are anxiety disorders distinctly linked to HPA dysfunction (7).

Cortisol

Cortisol, a glucocorticoid steroid hormone, is produced by cells in the fasciculata zone of the adrenal glands when stimulated by ACTH hormone secretion from the pituitary gland (8). In humans, cortisol is the final product of the HPA-Axis, functioning as both a stress hormone and a potent natural immunosuppressant. It plays a vital role in regulating functions like glucose metabolism, insulin release, arterial pressure, immunity, and inflammatory responses (9).

The HPA axis governs the secretion of glucocorticoids, including cortisol. Signals from the suprachiasmatic nucleus trigger the release of corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) from the hypothalamus' paraventricular nucleus. The hormone acts on the anterior pituitary where corticotropin cells are active and secrete adrenocorticotropin hormone (ACTH) and will circulate throughout the body. ACTH acts on the adrenal cortex and stimulates the synthesis of glucocorticoid release. Upon release, cortisol influences various physiological functions within target tissues, Effecting metabolism, immune response, skeletal development, cardiovascular health, reproduction, and cognitive abilities. The HPA axis employs a negative feedback mechanism using glucocorticoids to regulate this system. Glucocorticoids inhibit the release of ACTH and CRH by acting on the anterior pituitary and the hypothalamus, with the primary site of negative feedback being the hypothalamus. Factors like stress, physical activity, and low blood sugar levels can heighten the secretion of corticotropin releasing hormone (CRH), while proinflammatory cytokines such as IL-1, IL-6, and TNF α also promote ACTH release (10).

HBO Research Road Map with Cortisol

In a prior research conducted by Lund V et al in 1999, it was noted that professional divers experienced a notable decrease in cortisol levels ($p = 0.001$) when undergoing hyperbaric oxygen (HBO) treatment, involving inhalation of 100% oxygen for 60 minutes at 2.5 ATA. However, the mechanism behind this effect was not elucidated (11). Another study by Oyaizu et al. clarified that HBO treatment inhibits the increase of circulating macrophages during the acute phase and then accelerates macrophages in muscle tissue and increases the number of proliferation and differentiation of satellite cells and a number of muscles fibers.

(12)'s study explained that serum levels of IL-6 and creatinine kinase (CK) significantly decreased after HBO therapy. So that when inflammation decreases due to HBO, stress due to inflammation will decrease and adrenal stimulation to secrete glucocorticoids (cortisol) will decrease (13).

METHODOLOGY

The study employed a quasi-experimental research design. The research design was a randomized pre-post control group design. 9 people with anxiety disorders in the psychiatric polyclinic of RSPAL Dr. Ramelan Surabaya, male, aged 25-40 years. Subjects were divided into 3 groups, the control group without HBO (K1) and the treatment group with HBOT breathing 100% oxygen 2.4 ATA for 3x30 minutes intervals of 5 minutes breathing ordinary air for 5 consecutive days (K2). Cortisol hormone examination using the enzyme-linked immunosorbent assay (ELISA) method 1 day before the 1st HBO session and 1 day after the 5th HBOT session.

Data Retrieval or Collection Procedures

Fill out a questionnaire to collect information so that the sample is close to homogeneous. Research participants filled out a statement willing to follow, obey and carry out the research provisions until completion. Participants were also given knowledge about the rights and obligations of participants. The research ethical due diligence was carried out prior to treatment at Lakesla Surabaya.

Preparation of Research Subjects

Patients with anxiety disorders in the psychiatric polyclinic of RSPAL Dr. Ramelan Surabaya which meets the inclusion and exclusion criteria. Participants are in good health, do not do strenuous physical activity for at least 24 hours before the test and get enough sleep at night. Avoiding eating a large meal, drinking coffee or smoking for 2-3 hours before the test. Then HBO therapy was carried out at Lakesla Drs. med. R Rijadi Sastroepanoela, Phys Surabaya.

Implementation of the HBO Treatment

The HBO treatment uses a dose of 9 US Navy, namely the administration of oxygen with a higher level than ordinary air in a high-pressure chamber (RBT) made of steel (hyperbaric chamber) at room temperature 28oC and 50% humidity. In this case it is inhaling 100% O₂ 2.4 ATA for 3 x 30-minute intervals 2x 5 minutes breathing ordinary air 5 days in a row.

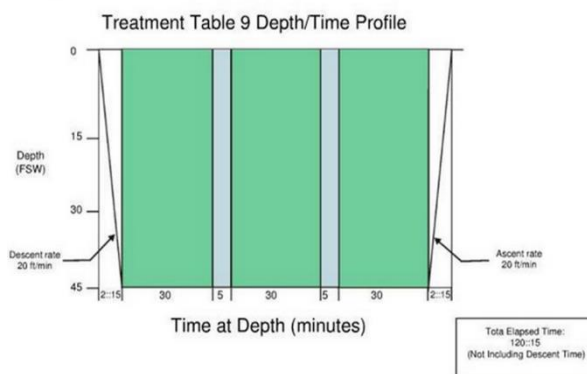


Figure 1. HBO Dosage Table 9 US Navy

Data analysis

The data obtained from this study will then be processed statistically using the Statistical Product and Solution (SPSS) version 22 program. The dependent

variable tested in this study is a numerical scale, so before determining a parametric or non-parametric test it is necessary to do a descriptive analysis test first. In the descriptive analysis test, the data will be tested for normality using the Shapiro-Wilk test to find out whether the data is normally distributed or not. If the data is normally distributed, then it will be continued with the Levene homogeneity test to find out whether the sample variance is different or not. If the data has a homogeneous variation then it is continued with the Pair-T Test and if it is not homogeneous it is continued with a non-parametric test, namely the Wilcoxon test.

RESEARCH RESULT

Cortisol Examination Results

The research variable that is suspected to be affected by HBO therapy in patients with anxiety disorders is cortisol levels. Examination of cortisol levels with ELISA was carried out in patients without anxiety disorders and patients with anxiety disorders before HBO therapy and after the 10th day of completion of HBO therapy. All blood samples were taken through a vein in the manner described in the research method.

Table 1. Cortisol levels in patients with anxiety disorders before and after HBO therapy

	Cortisol level (ng/ml)	
	Before HBO therapy	After HBO therapy
mean	79.09	76.38
SD	59.87959	26.50992
Min	9.94	41.73
Max	205	123.1

The results showed that the average cortisol level in anxiety disorders patients before HBO therapy was 79.09 ng/ml and after HBO therapy was 76.38 ng/ml. or can be presented in the graph as follows:

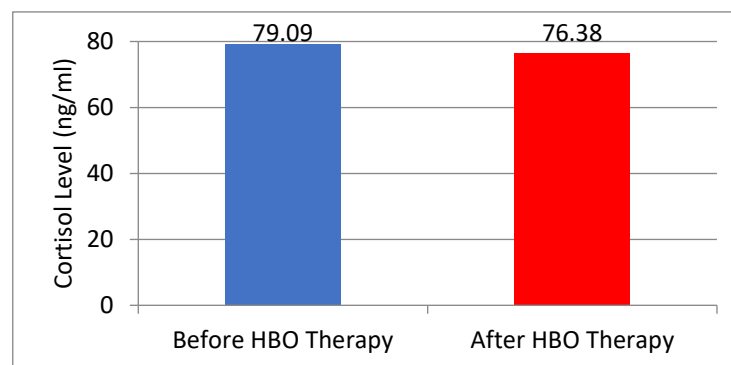


Figure 2. Cortisol levels of anxiety disorders patients before and after HBO therapy

The picture above shows that the average cortisol level in anxiety disorders patients after HBO therapy is lower than before HBO therapy.

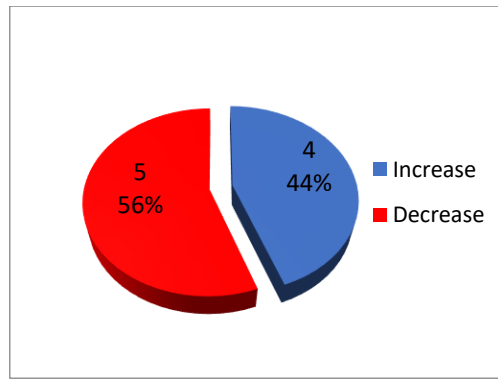


Figure 3. Description of cortisol levels in anxiety disorders patients after HBO therapy

Figure 3 above shows that most of the anxiety disorders patients experienced decreased cortisol levels after undergoing HBO therapy by 5 people (56%) while those who experienced increased cortisol levels after HBO therapy were 4 people (44%).

Statistical Analysis of Cortisol Examination Results

All cortisol examination results using ELISA were tested for normality using the Shapiro-Wilk test.

Table 2. Normality Test

Cortisol before HBO therapy	0.178	9	0.200	0.923	9	0.418
Cortisol level after HBO therapy	0.207	9	0.200	0.945	9	0.634

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

The normality test results for cortisol level data before HBO therapy yielded a significant value of 0.418 ($p > 0.05$), and after HBO therapy, it was 0.634 ($p > 0.05$). This indicates that both sets of data follow a normal distribution. Subsequent data testing using the Lavender homogeneity test.

Table 3. Test of Homogeneity of Variance

		Levene Statistic	df1	df2	Sig.
Cortisol level	Based on Mean	2.928	1	16	0.106
	Based on Median	2.341	1	16	0.146
	Based on Median and with adjusted df	2.341	1	10.893	0.155
	Based on trimmed mean	2.657	1	16	0.123

The Lavene homogeneity test yielded a significant value of 0.106 (p value > 0.05), indicating that the data exhibits homogeneity. Given the normal

distribution and homogeneity of the collected data, the Paired T Test was performed.

Table 4. Paired T Test

Pair	Cortisol level before HBO	Paired Differences			95% Confidence Interval of the Difference		t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper			
1	Cortisol level after HBO	2.712	65.69660	21.89887	-47.78666	53.21110	.124	8	0.904

The paired t-test analysis of the data produced a significant p-value of 0.904 ($p > 0.05$), indicating that there is no notable difference in cortisol levels among anxiety disorders patients before and after HBO therapy. In other words, HBO therapy does not appear to affect cortisol levels in patients with sleep disorders.

DISCUSSION

This study describes the effect of HBO therapy on the hormone cortisol in patients with anxiety disorders. Several studies explain that cortisol levels and the condition of Anxiety disorders have a reciprocal relationship with each other. The study by (14) found that high daily cortisol levels were associated with sleep disorder. However, a study conducted by (15) found no relationship between increased cortisol levels and the incidence of Sleep Disorder. The study by (16) also stated the opposite. Their study found that the incidence of insomnia was associated with low cortisol levels during the day. Nevertheless, our research revealed that individuals with sleep disorders exhibited a higher mean cortisol level. This discovery is intriguing and presents novel evidence indicating elevated average cortisol levels in patients with sleep disorders. This aligns with a study carried out by (17), which stated that participants with anxiety disorders had an average daily level of the hormone cortisol which tended to be high.

The results showed that the average cortisol level in anxiety disorders patients before HBO therapy was 79.09 ng/ml and after HBO therapy was 76.38 ng/ml or decreased after HBO therapy. The results showed that most of the patients (56%) experienced a decrease in cortisol levels after HBO therapy. The results of this study are in line with a study conducted by (12) explaining that HBO therapy will reduce the inflammatory response which in turn will reduce stress due to inflammation and adrenal stimulation to secrete glucocorticoids (cortisol) will also decrease. In this study, the results showed that after HBO therapy, the average cortisol level decreased in the majority of patients.

The data analysis results indicated that there was no noteworthy disparity in cortisol levels among patients with sleep disorders before and after HBO therapy. Likewise, HBO therapy did not have a discernible Effect on cortisol levels in these patients. The reason for this lack of effect of HBO therapy on cortisol levels in anxiety disorders patients is attributed to the varied body responses seen in these patients undergoing HBO therapy, specifically concerning cortisol levels. This observation is depicted in Figure 3. Based on this study it shows that HBO therapy at a pressure of 2.4 ATA cannot induce a hormonal stress reaction or affect cortisol levels in general which can reduce cortisol levels in anxiety disorders patients

CONCLUSIONS AND RECOMMENDATIONS

From this study, it can be concluded that:

1. The average cortisol level in anxiety disorders patients before HBO therapy was 79.09 ng/ml and after HBO therapy was 76.38 ng/ml
2. Most anxiety disorders patients experienced a decrease in cortisol levels after undergoing HBO therapy as many as 5 people (56%)
3. There is no effect of HBO therapy on cortisol levels in anxiety disorders patients

Researchers hope that further studies will explain further about the mechanism of the process of reducing cortisol levels after HBO therapy. Researchers also hope that this study can become a reference for further studies regarding the efficacy of HBO therapy on cortisol levels and explain further about the relationship between the two variables.

ADVANCED RESEARCH

Each study has limitations; thus, you can describe it here and briefly provide suggestions for further research.

ACKNOWLEDGMENT

Thanks to Hang Tuah University Surabaya, Indonesia and the Marine Health Institute of the Indonesian Navy for the permission and location for this research

Source of Funding: Hang Tuah University, Surabaya, Indonesia

Conflict of Interest: The authors declare no conflict of interest.

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