The Potential of Hyperbaric Oxygen Therapy Against Codeine Addiction Reduction

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ABSTRACT

Excessive opioid usage such as codeine can lead to anxiety, dose dependency, and addiction. Furthermore, drug addiction induce intoxication and in some case death. Several approach can be done to treat codein abuse. Hyberbaric oxygen is one of the therapy choices, considered that it can be used as main and supporting management. Related studies said increasing level of Nitric Oxide (NO) and Dopaminergic, main substances in drug addiction, can be inhibited by hyperbaric oxygen therapy thus it has the potential value to reduce narcotic addiction such as codeine. However, the review papers of previous research is rare. Therefore, this article discussed codeine, hyperbaric oxygen therapy (HBO), and its relation to decrease level of codein addiction, based on scientific literatures. In conclusion, HBO treatment has a potential correlation to minimize the effects of opioid withdrawal, since it can induce nitric oxide and involves the control of monoaminergic neurotransmitters that reduce withdrawal effects.

Keywords : Hyperbaric Oxygen Therapy; Drug Addiction; Codeine.

1. INTRODUCTION

Narcotics definition by Law number (No). 35 of 2009 is substances or drugs derived from plants or non-plants, both synthetic and semi-synthetic, which can cause decreases or changes in consciousness, loss of taste, reduce to eliminate pain, and dependence, that divided into three groups. First group is papaver somniferum derivate such as opium (raw or processed), cocaine, weed, heroine, amphetamine, etc. Second group are fentanyl, methadone, morphine, levometorphan, etc. Third group such as codeine, propiram, buprenorphine, etc. First group of narcotics has a high addictive level, cannot be used as medical substances, and only for developing of science development that also has strict regulations and punishments. Whereas second and third groups has lower addiction compared to first group (I > II > III), on these group can be used as medical preferences and has less punishment compared to group I [1].

Codeine contained as alkaloid in opioum estimated as 0.7-2.5% and opioid estimated as 0.3-3.0%. Codeine commonly forms in codeine phosphate for medication usage. Codeine is used to relieve mild to moderate pain, cough, and mild acute diarrhea for a short duration. Combination of antipyretic analgesic with codeine such as paracetamol or aspirin (pain management) and kaoline within anti-diarrhea [2–4]. Accidental usage often found such as codeine-based cough syrup. Lack of distribution regulation compared to other opioid such as morphine and oxycontin influence codeine abuse and long-term drug effect. Although codeine has less potent effect, but there are exerts effects similar to morphine such as euphoria, apathy, staggering and relaxation. Codeine as an opioid has a high risk for its users to develop tolerance and eventually become addicted [5].

Number of opiod user in the world estimated around 33 million each year. In America, about 4.7 million people use non-medical painkillers including codeine. In the UK increased fivefold number between 1991 and 2002, indicate with rising harmful risk of opioids such as dependence and addiction. In UK depict an increasing number of deaths caused by codeine from 131 cases in 2016 to 156 within 2017. Global number of opioid addictions vary across countries. In the United States, 8-12% are addicted [5,6].

Codeine addiction may also lead to intoxication, interactions between foreign chemicals (toxins) and biological systems result in damaging living organisms. In general, poisoning is more concerned with the acute effects of the toxin relate to death and the clinical toxicity appearance [7]. Several sign such as pupil constriction, comma, and breathing distress. Opioid intoxication diagnosed by intravenous injection of naloxone resulting in rapid improvement within addicted person [8]. The main clinical management of opioid poisoning or intoxication is intravenous administration of naloxone [9]. Opioid addiction can be treated in several ways. According to WHO, therapy for opioid addiction is through a series of pharmacological and psychosocial interventions aimed at reducing or discontinuing opioid use, preventing future harm associated with opioid use, and improving the quality of life and well-being of opioid dependent patients [10].

In recent years, Hyperbaric Oxygen Therapy has been developed. Hyperbaric oxygen therapy according to the Undersea and Hyperbaric Medical Society (UHMS) is an intervention therapy that the person will inhale oxygen close to 100% intermittently while in a hyperbaric chamber with greater pressure than sea level pressure, which is 1 ATA. For clinical purposes, the pressure in the hyperbaric chamber should equal or exceed 1.4 ATA when breathing close to 100% oxygen. In certain circumstances hyperbaric oxygen therapy is a temporary primary treatment modality and an adjunct to surgical or pharmacological intervention [11]. Furthormore, we wanted to investigate the effect of hyperbaric oxygen therapy on codeine addiction.

2. CODEINE

Codeine is an alkaloid contained in opium 0.7-2.5%, besides that codeine alkaloids are also found in opioids 0.3-3.0%. Codeine is an analgesic drug used in the management of mild to moderate pain, cough, and persistent diarrhea and belongs to a class of opioid drugs that are often used by health practitioners but long-term use can cause dependence or addiction. In addition to analgesic drugs, codeine is also a type of depressant drug that can suppress the functional activity system of the Central Nervous System (CNS) which works by suppressing the center of consciousness, pain, heart rate, and breathing [2,3].

There are 3 main opioid receptors, G-protein receptors μ (mu), δ (delta) and κ (kappa). When opioids interact with these receptors, several mechanisms of intracellular action occur, resulting in a decrease in intracellular cAMP, cell hyperpolarization, and a decrease in neurotransmitters. Meanwhile, mu receptors in the midbrain are the dominant type of receptors for analgesic mechanisms. Mechanism of action in codeine is to bind to mu-opioid receptors which will lead to the transmission of pain throughout the body and the central nervous system [3].

Codeine is distributed in the form of tablets or syrup and will be absorbed through the gastrointestinal tract around 70-80% will be metabolized in the liver by conjugation of glucuronic acid to codeine-6 glucuronide (C6G) and by O-demethylation to morphine (5-10%) and N-demethylation to norcodeine (10%). Cytochrome P450 2D6 is the main enzyme responsible for the transformation of codeine to morphine and P450 3A4 is the main enzyme that mediates the conversion of codeine to norcodeine. Morphine and norcodeine are then further metabolized by conjugation with glucuronic acid. The glucuronide metabolites of morphine are morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Morphine and M6G have been shown to have analgesic activity in humans [12].

In general, endogenous opioids have various functions as an analgesic, anti-nociceptive effect, especially in peripheral injured tissues. Circulating leukocytes containing opioid peptides will extravasate upon activation of adhesion molecules and chemotaxis by chemokines. Furthermore, there is stimulation of the release of opioid peptides through several factors, including corticotropin (CRF), interleukin-1β (IL-1) and noradrenaline. These opioids (both endogenous and exogenous) bind to opioid receptors (OR) synthesized in the dorsal root ganglia and transported along intra-axon microtubules to the peripheral (and central) terminals of sensory neurons. Subsequent inhibition of ion channels (eg, TRPV1, Ca++) and release of substance P (sP) results in an anti-nociceptive effect [12].

3. ADDICTION

Addiction is a complex chronic condition caused by genes, environment, and a person's life experiences that involve complex interactions between cells in the brain. The formation of an addiction is caused by an obsession, euphoria, or comfort when using a substance [13]. In conditions of addiction, there is an urge to desire, get, and the emergence of a drug withdrawal syndrome. In the case of addiction, users associate substance use with personal feelings that can lead to a sense of obsession and compulsive behavior but ignoring the negative side effects that can occur [14]. Peoplo who abused drugs are some of them senior students, almost 70% of high school students will have tried, alcohol, 50% will have taken an illegal drug, nearly 40% will have smoked a cigarette, and more than 20% will have misused a prescription drug for a nonmedical purpose [15]. Consumption of a chemical substance causes feeling of addiction, which generated in a series of events in the brain through the stages of pre-occupation/anticipation, intoxication/binge, and withdrawal/negative effects. These processes are related to each other, and gradually will be intense and lead to a pathological condition called as addiction. This addiction caused by dopamine receptor signaling in the nucleus accumbens, which is the part of the brain that responds when there are consecutive stimuli from the amygdala (limbic pathway) and prefrontal cortical areas where their functions are interrelated between responding to emotions (limbic) and thinking logically in making decisions (prefrontal cortex) [16]. Chronic exposure and easy access to drugs make individuals prone to addiction, this is due to glutamatergic mediation in the striato-thalamo-cortical pathway that can affect cognitive and logical thinking areas in the prefrontal lobe. Addictive drugs, such as opioids, bind to pre-synaptic GABA receptors and activate mu and inhibitory gaba inhibitors in the VTA (Ventral Tegmented Area), leading to increased dopamine release in the nucleus accumbens. Acute exposure will cause a stress relief effect, but chronic exposure can cause a dependence effect on drug doses. First stage, the patient will feel pleasure, but over time there will be a tolerance effect from drugs, high dosage demand needed and lead to drug seeking behavior. The emergence of this addiction will increase over time, where initially the person is user then gradually becomes an abuser and finally addicted [17].

4. CODEINE ADDICTION

Globally, there has been increasing number with 27% in codeine consumption in the last few decades. Lack of public knowledge about the side effects, excessive use and intentional abuse make codeine has considerable health consequences. In some countries, codeine preparations can be purchased without a prescription. In addition, codeine products are also available in combination preparations (paracetamol, ibuprofen, or aspirin) [18]. Excessive use of opioids, including codeine, in addition to causing addiction can also cause death. In the population of patients who have medical indications for the use of codeine, there will be an increase in the dose needed for codeine which correlates with dependency [3].

Repeated administration of codeine class of drugs can cause a decrease (tolerance) or an increase (sensitization) in the effects of behavior and use. Sensitization is usually a major problem and plays an important role in the abuse of opioid drugs. Specifically, this class of drugs works by releasing nitric oxide (NO). Nitric oxide is a powerful neuromodulator produced by nitric oxide synthase (NOS) [19].

5. MECHANISM OF OPIOID

In several studies, it was found that opioid drugs reduce inhibitory GABAergic synaptic transmission (LTPGABA) via the guanylate cyclase (sGC) and nitric oxide (NO) pathways. This drug will then bind to opioid receptors and block the binding between NO and sGC which ultimately results in LTPGABA not being produced. In the end, addiction will occur [20]. Binding of endogenous (endo-morphine molecule) or exogenous (morphine molecule) ligands to opioid receptors leads to activation of Go or Gi proteins. Furthermore, phosphorylation will occur by a family of kinases called G protein-coupled receptor kinases (GRKs), the process will induce molecular changes in the cell, including arrestin binding. G protein consists of three subunits (alpha, beta, and gamma). The binding of the ligand to the receptor results in the activation of the opioid receptor by binding of the GTP to the subunit, whereas the GTP complex dissociates from the dimeric subunit. Both complexes, GTP and dimers, participate in intracellular signal transduction. This results in inhibition of adenylate cyclase activity, reduced levels of cyclic adenosine monophosphate (cAMP) in cells, and suppression of protein kinase A activity. GTP also activates the phospholipase-C (PLC) and mitogen-activated protein (MAP) kinase pathways. PLC hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP2) to inositol 1,4,5-

trisphosphate (IP3) and diacylglycerol (DAG). IP3 increases calcium release from the endoplasmic reticulum which activates calcium-dependent signaling. Activation of potassium channels causes an increase in cell hyperpolarization, indirectly reducing cell excitability. Dimers directly block calcium channels (P/Q-type, N-type, and L-type channels) and reduce calcium concentrations in cells, causing suppression of other neurotransmitters. The stimulatory effect of opioid receptors on potassium and calcium channel activity has been repeatedly confirmed in various brain areas (hippocampus, nucleus locus coeruleus, abdominal lid area, etc.), and this mechanism has been considered a key effect for opioid receptor stimulation (ultimately leading to addiction) [21].

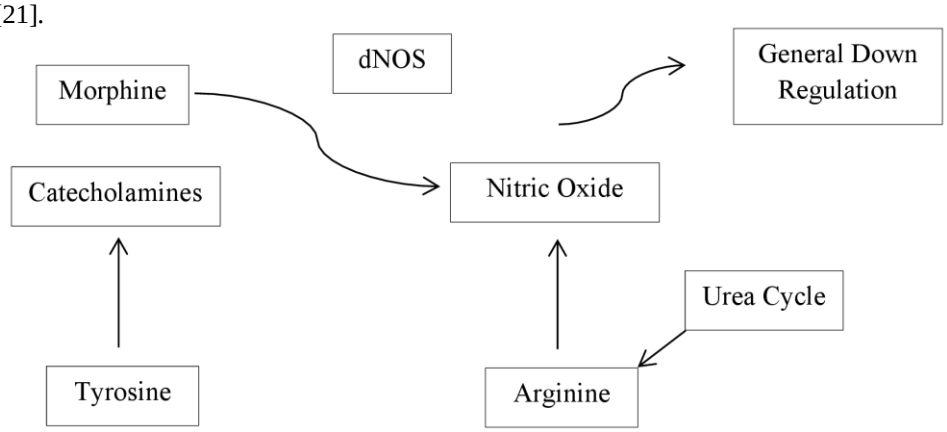

Figure 1 Morphine Induction Mechanism of Nitric Oxide

6. MECHANISM OF MORPHINE INDUCTION OF NITRIC OXIDE

On chronic exposure, morphine induces phosphorylation of opioid receptors by GRK. This phosphorylation prepares opioid receptors for arrestin binding. Arrestin binding blocks further G protein-mediated signaling, thereby, inducing desensitization of opioid receptors [21]. After going through the krebs cycle, the secondary products will go to the urea cycle. The urea cycle produces arginine, which is the main source of nitric oxide. This cycle then continues and produces a guanide group as the main carrier of free ammonia. In general, the release of NO from cNOS results in free radical scavenging, antiviral and bacterial action, downregulation of immune responses, vascular, and nervous tissue and stabilizes the effects of excitatory microenvironments in addition to functioning as chemical messengers. In addition, morphine has the ability to release NO, which is very useful as a form of free radical scavenger [22].

7. HYPERBARIC OXYGEN THERAPY

Hyperbaric oxygen therapy (TOHB) is a therapy based on hyperbaric medical science. Hyperbaric health is a branch of science that studies the administration of therapy in a high-pressure air chamber, where the patient will breathe 100% oxygen in a room or commonly called a chamber with a pressure of more than 1 ATA (atmosphere absolute). Initially, TOHB was only limited to diving case diseases and as science progressed it could be used on non-dive diseases [23]. Hyperbaric oxygen therapy according to the Undersea and Hyperbaric Medical Society (UHMS) is an intervention therapy in which a person will inhale oxygen close to 100% intermittently while in a hyperbaric chamber with a pressure greater than sea level pressure of 1 ATA [11,24].

Hyperbaric Oxygen Therapy works in the human body based on gas laws and the effects of the body's biochemistry through Boyle, Dalton, and Henry's laws in conditions of increased oxygen levels in the blood (hyperoxemia) and tissues (hyperoxia). Boyle's law states that for a constant temperature, the volume of a gas is inversely proportional to the absolute pressure. As the volume of a gas decreases with increasing ambient pressure, its density (mass/volume) increases. Combined with the central redistribution of blood due to diving,

as well as the respiratory apparatus itself (demand valve, flow resistance, dead space), the work of breathing will be increased compared to inhaling the same gas at the surface [25]. Dalton's law states that in a gas mixture each element exerts a pressure proportional to its fraction of the total volume (partial pressure). Henry's law states that the amount of dissolved gas in a fluid or tissue is directly proportional to the partial pressure of the gas in contact with the fluid or tissue. Refers to the fact that the amount of gas that will dissolve in a liquid is directly proportional to the partial pressure of the gas above the liquid. An increase in environmental pressure (and thus partial pressure) results in more gas dissolving into the liquid portion of the blood and tissues. This is the theoretical basis for increasing tissue oxygen tension with HBO treatment. HBO operators play important role for decompression therapy because inert gases such as nitrogen will evelate.

Body mechanism called ventilation and diffusion is used to distribute oxygen. Diffusion is the process of transferring oxygen homeostasis between the alveoli and the bloodstream, whereas ventilation is the process of gas inspired from outside the body to the bronchial branches of the lungs. Diffusion happens when the partial pressure of oxygen (PO2) is lower than the partial pressure of carbon dioxide (CO2), and gas exchange takes place. In erythrocytes, blood oxygen is linked to hemoglobin (Hb), and only a small percentage is dissolved and transported systemically. Gas flow from arterioles and venules to different bodily tissues continues the diffusion process; this gas exchange is regulated by changes in oxygen partial pressure and oxygen saturation of Hb (SO2), as well as other variables such as temperature, PCO2, and pH [26].

Increased angiogenesis is a benefit of hyperbaric oxygen therapy, as it elevates NO production, which leads to upregulation of Nrf2 and growth factors like epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and endothelin-1. TNF- α, matrix metallopeptidase 9 (MMP-9) and tissue inhibitor of metalloproteinase-1 (TIMP-1) all increased as well [27].

8. Hyperbaric Oxygen Therapy Mechanism as a Potential Choice to Reduce Codeine Addiction

In various studies, hyperbaric oxygen therapy (HBOT) has been proven to reduce the effect of opioid addiction. This is due to HBOT's anti-nociceptive mechanism, which increases the release of opioid peptide neurons, resulting in an increase in the amount of peptides, which lowers the effects of addiction. According to previous studies, HBOT increases the levels of Nitric Oxide (NO) products in rat's brains, enhances the expression of Nitric Oxide Synase (NOS), and stimulates NO production in brain tissue. This indicates that the HBOT method causes anti-nociception by increasing opioid peptide release in neurons. Whereas a rise in opioid peptides aids in the reduction of addiction [28].

Other studies suggest that HBOT causes an increase in NOS activity, despite the fact that NO is a component involved in the development of codeine addiction. On the other hand, it was discovered that HBOT therapy inhibited NOS, which resulted in the suppression of addiction symptoms although the nociceptive effects remained. This difference could imply that the effect of NO on the emergence of addiction is balanced, similar to the role of NO-induced pro-nociception and anti-nociception, anxiogenic and anxiolytic effects, and their involvement in neurotoxicity and neuroprotection [29]. Another study found that administering HBO decreases withdrawal effects in the rat brain through regulating monoaminergic neurotransmitters and the NO-cGMP signaling pathway, suggesting that HBO could be used as a therapeutic alternative for opioid addiction [28].

While NO is a component responsible for the development of codeine intoxication, there is additional evidence suggesting that HBOT stimulates increased NOS activity. However, on the other hand, it was found that HBOT therapy suppresses NOS, which leads to suppression of addictive effects while sustaining nociceptive effects. This difference balances the effects of NO on the development of addiction and is significant with their involvement in NO-induced nociception and anti-nociception, anxiogenic and anxiolytic functions, and neurotoxicity and neuroprotection. May suggest that it does not differ [29]. Another study suggests that administration of HBO involves the regulation of monoamine neurotransmitters and NOcGMP signaling pathways that suppress withdrawal symptoms in rat brain and may be a therapeutic option for opioid addiction [28].

In individuals with discouraged psychosocial conditions and a compelling impulse to get moment delight and states of constant openness to drugs that can expand dopamine, one of them is the utilization of codeine. Codeine has structures in hack medication and analgesics. The utilization of narcotic subordinates causes an increment in monoaminergic receptors, in particular dopamine and norepinephrine. From the beginning, the client will feel a feeling of quiet for quite some time of utilization, however as the portion builds, it causes an ongoing response in the cortical striato-thalamus, to be specific the impact of resilience and expanding the portion with the goal that the satisfaction of dopamine is satisfied to make up for the sensation of stress alleviation. Narcotic medications will lessen inhibitory GABAergic synaptic transmission (LTP-GABA) and lead to habit. The job of TOHB is NOS decrease and nitric oxide restraint, which at first causes depolarization of excitatory GABA driving forces through narcotic receptors. This is relied upon to change the excitation of the motivation and stifle the reaction that at first makes desensitization an increment in adequate portion sharpening and a decrease in the adverse consequences that can happen.

In people with depressed psychosocial conditions and a strong urge to get instant pleasure and conditions of chronic exposure to drugs that can increase dopamine, is term of using codeine. Codeine has forms in cough medicine and analgesics. The use of opioid derivatives causes an increase in monoaminergic receptors, namely dopamine and norepinephrine [28]. Addictive drugs, such as opioids, bind to pre-synaptic GABA receptors and activate mu and inhibitory gaba inhibitors in the VTA (Ventral Tegmented Area), causing increased dopamine release in the nucleus accumbens [17]. At first the user will feel a sense of calm for several times of use, but with increasing doses it causes a chronic reaction in the cortical striato-thalamus, namely a tolerance effect and a withdrawal syndrome occur, a sense of obsession and compulsive behavior occurs but ignores the negative side effects [13].

Morphine chronic exposure induces phosphorylation of opioid receptors by GHGs. This phosphorylation prepares opioid receptors for arrestin binding. Arrestin binding blocks further G protein-mediated signaling, thereby, inducing desensitization of opioid receptors [21]. With persistent morphine exposure coincident with nociception-driven surges in NO, regulatory events including activation of guanylate cyclase (GuCy) and protein kinase G (PKG), as well as increased NO-based reactive oxygen species (ROS) availability, interfere with the morphine-mediated signaling cascade. Morphine binds to adenyl cyclase inhibitory receptors, increasing of adenly cyclase causes an increase in protein kinase which will activate the nmda receptor to bind to glutamate. Continuous exposure will lead to calcium bind with calmodulin and activates calmodulin kinase thus NO upregulation is not well tolerated, and the cycle remains unchanged [30]

.In some cases where the effect of tolerance increases, it will lead to addiction. HBOT has a role in suppressing addiction to codeine needs through several mechanisms, mainly by monoaminergic receptor [28]. When HBOT is performed, the oxygen concentration in the body will increase and produce a cellular response, the response will produce two effects, namely an increase in endogenous opoids and an increase in nitric oxide (NO). An increase in NO will stimulate a further increase in GHG and NO synthase (NOS). GHG has a role in decreasing GABA, while NOS stimulates an increase in NO production [30]. The increase in NO and the effect of HBOT on decreasing GABA will cause an increase in dopamine in the body, this will cause depolarization of cells and ultimately cause a stimulant effect. It is interesting that the HBOT-modulated stimulatory effect and NO increase have an inverse effect on codeine requirements. So that with increasing levels of dopamine in the body due to the effects of HBOT will reduce dependence on codeine

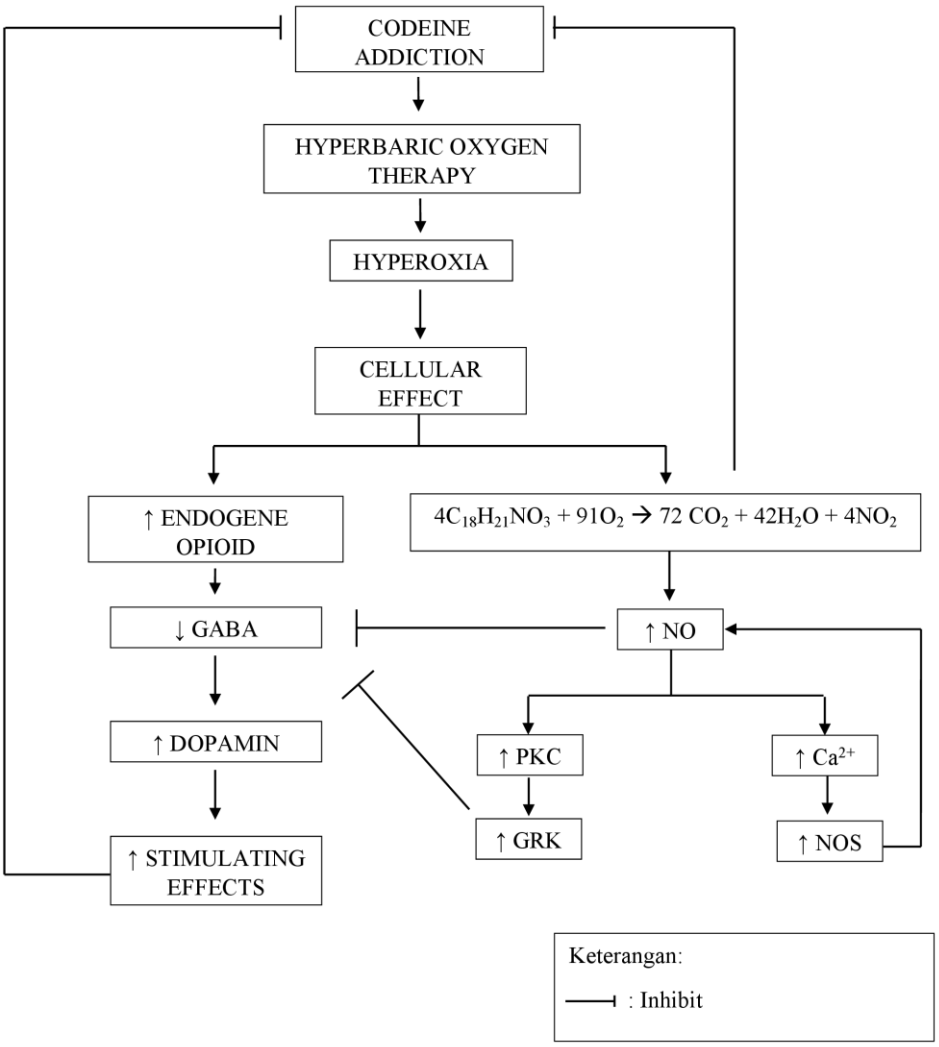

Figure 2 Mechanism of Hyperbaric Oxygen Therapy to Codeine Addiction

9.CONCLUSION

HBO treatment has a correlation to minimize the effects of opioid withdrawal in animal models. It is a potential choice as an addiction therapy option since it can induce nitric oxide and involves the control of monoaminergic neurotransmitters that reduce withdrawal effects. There is a paucity of research, particularly on the effects of hyperbaric oxygen therapy on codeine addiction and studies involving human populations. The use of HBO as a treatment alternative for reducing withdrawal symptoms necessitates the continuing of non-pharmacological approaches to drug access and patient habituality control. However, further research is needed to figure out the correlation between nitric oxide and HBO treatment, as well as its adverse effects and benefits for withdrawal in human. It is also important to look at the biomolecular and the physiological mechanism of nerve structures and functions, to get satisfactory helpful outcomes for narcotic addiction, besides pharmacological and psychosocial treatments.

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