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Treatment of Migraine with Hyperbaric Oxygen

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Fife WP, Fife CE, Treatment of migraine with hyperbaric oxygen. J Hyper Med 1989; 4(1):7–15—The pathophysiology of migraine headache includes focal cerebral hypoxia and vasodilatation. Hyperbaric oxygen (HBO) has been demonstrated to cause cerebral vasoconstriction while increasing tissue oxygen levels. Twenty-six patients with migraine headache pain were treated with HBO between 1.3 and 2.4 ATA. All but one obtained complete relief of migraine symptoms within minutes of exposure, including 2 patients with facial hemiparesis, and none had adverse effects from treatment. This preliminary trial suggests that HBO may be a useful treatment for patients with severe migraine symptoms.

hyperbaric oxygen, HBO, migraine, headache

Introduction

Headache pain can be classified into categories based on pain mechanisms (1, 2). It is estimated that approximately 90% of headaches are secondary to muscle tension, whereas vascular headaches (including both cluster and migraine) comprise 8%, and inflammatory headaches comprise approximately 2% (3). Vascular headaches usually begin before the age of 30 yr (4) and often may be associated with tension headaches (5). Although representing a small percentage of all types of headaches, vascular headaches are associated with considerable morbidity and may be the most common type of headache pain requiring medical intervention.

The cause or causes of migraine headache are not clearly understood, although a number of triggering mechanisms have been described such as neurogenic reflexes or impulses (3). The sequence of events leading to the headache may begin with cerebral vasoconstriction. During the prodrome phase of classic migraine, cerebral blood flow may be reduced in focal areas by an average of 36% (6), and neurologic deficits appropriate to the area of vasoconstriction may be manifested (7). The resultant hypoxia and acidosis cause the release of vasoactive substances, followed by massive vasodilatation of the intracranial arteries. This results in a further release of vasoactive substances and perhaps local tissue injury and edema (8). It is at this time that pain and other migraine symptoms appear.

An ideal therapeutic agent for the treatment of migraine might be one capable of causing vasoconstriction while correcting hypoxia. The vasoconstrictive effect of oxygen has been known for many years. However, the results of surface oxygen for the treatment of migraine were disappointing. In one study where 100% O_2 was breathed at 10 liters · min^{-1} for 5 min, only 4 of 15 patients obtained relief from pain. Furthermore, some migraine patients in this study were found to have a paradoxical vasodilatory response to surface oxygen, as measured by thermography (9).

Hyperbaric oxygen, however, has an intense vasoconstrictive effect (10–12). It has been shown that cerebral edema may be reduced by as much as 50% after breathing pure oxygen for as little as 5 min at an inspired partial pressure of oxygen equal to two atmospheres absolute (ATA) (13–15). This elevated inspired partial pressure of oxygen greatly increases arterial oxygen partial pressure and results in an elevated partial pressure of oxygen in the tissues, even though perfusion may be locally reduced due to vasoconstriction.

The ability of hyperbaric oxygen (HBO) to reduce cerebral blood flow while increasing tissue P_{O_2} raised the question as to whether hyperbaric oxygen therapy might reduce or abort migraine symptoms. We have been studying this problem for the past 10 yr, during which time 36 treatments were administered to 26 patients with diagnosed migraine, 10 patients being treated on more than one occasion.

Methods

The project as well as the specific protocols were approved by the Texas A&M University Institutional Review Board.

Subjects were selected by various physicians who determined that the diagnosed disease was migraine headache and that there was no evidence of meningitis, tumors, or other CNS pathology. The 26 referred subjects (6 males and 20 females) whose physical examinations revealed no contraindications to HBO therapy, such as pulmonary abnormalities, were accepted.

No effort was made to match genders or select on the basis of age or underlying diseases, except that patients with pulmonary abnormalities were excluded from the study. The cohort in this study was predominantly female, which was not surprising because the incidence of migraine is approximately 3 times greater among females than among males (5).

All patients were referred during the pain phase of migraine, pain having often been present for several days and poorly responsive to various oral medications. Two patients experienced facial hemiparesis routinely during attacks and presented for treatment with neurologic deficits.

All patients were treated in one of two double-lock, multiplace chambers. In some instances an oxygen mask (aviators or double-lip Scott type) was employed whereas in others a plastic hood was used (both the Duke hood and the Sea-Long), both equipped with over-board dump. The patient reclined

on a gurney with the head and back comfortably elevated. The chamber was compressed with air while the patients were carefully observed by the inside attendant. None of the subjects failed to reach proper pressure because of ear or sinus dysbarism. Since some were in great pain secondary to headache and could not perform the Valsalva maneuver, compression often was very slow.

During treatment, no medication was given to patients other than an oxymetazoline hydrochloride nasal inhalant (such as Afrin) if there was a possible difficulty in equalizing pressure in the sinuses or ears. In most instances, patients already had been on one or more of the standard migraine medications before entering the chamber, some of them for several weeks.

Initially, oxygen therapy was begun after reaching 1.6 ATA. This is equivalent to a pressure equal to 20 feet of sea water (fsw). However, as patients often required very slow compression, oxygen inhalation was routinely begun at 10 fsw. Slow compression was then continued to desired depth. To assess the relative efficacy of different inspired partial pressures of oxygen, treatments were done at several ambient pressures. These ranged from 1.3 to 2.6 ATA of oxygen.

Special care was taken to keep the subject calm and quiet. No loud talking was permitted, and chamber lighting was dimmed to ease eye discomfort.

When complete relief was achieved, oxygen treatment was continued for an additional 10 min. The mask or hood then was removed and the patient was allowed to rest quietly for several minutes while breathing chamber air. In the two instances in which mild symptoms returned after discontinuing oxygen, oxygen breathing was reinstituted for a few minutes until symptoms were again completely resolved. When no symptoms returned after 10 min of air breathing, the patient was slowly decompressed at a rate of 0.5–1 ATA $\cdot$ min^{-1}. If there was any concern over the possibility of pulmonary air trapping, decompression was even slower.

Results

The results of the varied inspired partial pressures of oxygen are shown in Table 1. It seemed that relief began to occur at any pressure greater than 1.3 ATA, although in 5 patients it was not complete until reaching 2.4 ATA.

The results were remarkable for their reproducibility. Of the 26 patients who were treated, all but 2 obtained complete relief within 27 min. In most instances, complete relief from nausea, if it was present, came within the first 5 min after oxygen breathing was begun, and complete relief from pain and photophobia came within 12 to 16 min. Both patients with facial hemiparesis had resolution of their neurologic deficit during treatment.

One patient who did not obtain complete relief (JV) was determined to have a persistent underlying tension headache, and although the severe pain of migraine was eliminated, her posttreatment medical examination revealed that she still suffered from a tension headache focused in the nuchal area. No

Table 1: Varied Inspired Partial Pressure of Oxygen

Patient	Gender	Complete Relief, min	Pressure of First Relief, ATA
LH	M	19	2.4
MH	F	14	1.6
SH	F	13	2.4
ED	M	18	1.4
WS	M	16	2.4
LW	F	7	1.6
KM	F	15	2.4
LW	F	6	1.6
SV	F	14	1.6
SH[a]	F	16	1.6
MB	F	20	1.6
CS	F	26	1.6
LW	F	31	1.6
JS	F	16	1.6
PY	F	27	2.4
BB	F	10	1.6
MD	F	8	1.3
PT	F	22	1.6
BG	M	15	1.6
EF	F	14	1.6
JP	F	18	1.6
CG	F	14	1.6
PW	F	11	1.3
CF	F	20	1.6
DS	F	13	1.6
ES	M	—	No relief
CF[a]	F	8	1.3
CF	F	16	1.6
JV[b]	F	25	1.6
LR	F	10	1.3
CM	F	16	1.3
TH	M	20	1.6
MC	F	13	1.3
AG	F	23	1.6
MG	F	23	1.6
JP	F	16	1.6

[a]Slight return of headache several hours later. [b]Tension headache remained after treatment.

patient obtaining complete relief from therapy experienced a return of pain upon leaving the chamber. Several hours after finishing treatment, 2 patients (SH, CF) had return of mild headache pain, which was responsive to acetaminophen. One patient (ES) obtained no relief from HBO therapy, despite treatment at 2.4 ATA for 45 min.

Discussion

Differences may exist between the initial events in the development of common vs. classic migraine. It is unclear whether initial vasoconstriction occurs in common migraine (16), but vasodilatation and probably hypoxia ultimately occur in both common and classic migraine (8). No distinction was made in this study between patients with common and classic migraine; both types of patients obtained relief with HBO.

Data gathered from studies of cerebral blood flow using xenon washout or thermography indicate that both cluster and migraine involve abnormalities of cerebrovascular reactivity, although their etiology and pathophysiology are quite different (7, 17, 18). Sakai and Meyer (17) have demonstrated that this excessive cerebrovascular reactivity is secondary to an "unstable" autonomic nervous system and abnormal responses of cerebrovascular receptor sites. In both common and classic migraine there may be an increase in sympathetic activity, which not only affects the vasculature but may activate cerebral metabolism and increase oxygen demands, thus worsening local hypoxia (8). No such vascular or metabolic changes have been observed in patients with tension headache (17).

Pharmacologic treatments for migraine such as beta blockers and calcium channel blockers have achieved some success in headache prophylaxis. Presumably they act by preventing vasodilatation, although the exact mechanism is not clear (19, 20). Ergot derivatives have been thought to alleviate migraine pain by causing vasoconstriction. However, one study of cerebral blood flow during migraine did not show a decrease in cerebral perfusion with ergotamine despite an improvement in pain (21). It may instead act by redistributing cerebral blood flow (8). Various antiinflammatory, antidepressant, or narcotic analgesic medications are also used for acute migraine pain. In addition to side effects, drug therapy is complicated because the efficacy of these medications vary between individuals and within the same individual at different times.

Wolff (22) was the first to use oxygen in the treatment of migraine. During the prodrome of classic migraine, patients breathing 10% carbon dioxide (CO_2) in oxygen were able to abort headache pain and obtain long-lasting relief. Presumably the CO_2 counteracted the vasospasm of the prodromal phase (as well as the vasoconstrictive effect of the oxygen), while the improved oxygen delivery corrected metabolic abnormalities. This observation was not put into clinical use.

The exact mechanism by which HBO effected relief from migraine pain in this study is not clear. Presumably the effects are the result of cerebral vasoconstriction and correction of hypoxia. How hyperbaric oxygen causes vasoconstriction is not fully understood. At one time this effect was thought to be secondary to decreased arterial carbon dioxide concentrations. It is now

accepted that oxygen has direct vasoconstrictive effects, possibly by increasing sympathetic vascular tone (23). In vitro studies have demonstrated that hyperoxia enhances arterial vasoconstrictive reactions to catecholaminergic drugs (24). Enhancement of the effect of catecholamines may be the mechanism of the intense vasoconstriction seen with hyperbaric doses of oxygen. It is not entirely clear whether the pain of migraine is the direct result of vasodilatation or the result of substances produced in response to the hypoxia. The resolution of pain with HBO therapy might also be the result of the correction of the associated local hypoxia and acidosis. The patients had been on a variety of medications before receiving HBO. What interactions these medications had, if any, with hyperoxia is not known.

Perhaps the most remarkable observation in this study was the speed with which very severe pain was relieved. Within minutes of instituting oxygen breathing, facial expressions of pain were observed to gradually disappear, and patients with photophobia were able to open their eyes. In one instance, after the pain subsided, the patient (JP) complained of claustrophobia and wanted to leave the chamber as soon as possible, complete relief having been obtained after 18 min. Claustrophobia did not prevent her from returning several months later when another migraine episode developed, again she asked to leave after 16 min, her pain having resolved.

It is probably not necessary to hold the patient in the chamber under pressure for 10 min after the pain is gone. However, there has been some concern that when 100% oxygen breathing is discontinued there might be a rebound effect resulting in a recurrence of cerebral vasodilatation. Slight pain did recur in 2 patients (MG, JP) while they were in the chamber after discontinuing oxygen. After a few more minutes of oxygen breathing, the final outcome was a complete cessation of pain even in those 2 cases.

Most treatments require no more than 30–45 min of chamber operation from the time the patient enters until he or she leaves. Occasional difficulty in equalizing pressure in the sinuses or ears may extend this time due to the need for slower compression. In this study, no treatments had to be discontinued due to ear or sinus problems.

It may be noticed that there are relatively few repeated treatments among these patients. This is because most of them are students who are not permanent in the area.

Inasmuch as the use of HBO therapy is usually more benign than the use of many drugs, it may be a viable alternative to some pain medications. It does not have the side effects of most of the medications presently used for acute migraine pain such as gastrointestinal upsets, increased blood pressure, dependency, or addiction. Further, it may be used on a daily basis, although in our experience such frequent treatments were not necessary.

Although HBO therapy now is used on several hundreds of patients each day with rare adverse effects, it should not be administered by unqualified or inexperienced personnel. Although it is possible that air trapping in the lungs

may be a problem in patients with certain pulmonary abnormalities, this can be minimized by careful patient selection and cautious decompression. At pressures between 1.3 and 1.6 ATA, which were adequate for alleviating migraine pain in most of these patients, the risk of convulsions due to CNS oxygen toxicity is extremely low. There are some indications that a recent injection of insulin may increase the risk of oxygen convulsions. Several of the patients in this study were insulin-dependent diabetics, but none had recently taken insulin. We ask all of our diabetic patients to come for treatment soon after eating.

No female included in this study was pregnant, although migraines often occur during pregnancy. The use of HBO on pregnant women continues to be controversial. Studies on pregnant female sheep, in which daily oxygen treatments were given during the last 40 days of pregnancy, failed to show any recognizable abnormalities of the newborn (Fife WP, unpublished data), and no teratogenic effects have been seen in human females who have required HBO for other reasons. Although not presently recommended, pregnancy may not be a contraindication to HBO therapy.

Although the incidence of migraine decreases with advancing age, elderly patients can experience migraines. Inasmuch as studies using surface oxygen have also shown significant decreases in oxygen-induced vasoconstriction with advancing age (7, 23, 25), it is possible that HBO may be less efficacious in elderly migraine sufferers.

The question may be raised as to the potential usefulness of oxygen in cluster headache patients. Sakai and Meyer (17) demonstrated an even greater vasoconstrictive response to surface oxygen in cluster headache patients than in normal individuals or those without migraine. Studies using surface oxygen by mask at varying flow rates demonstrated improvement in more than half of the participants (26–29). One double-blind, crossover study of oxygen vs. air among 19 cluster patients showed headache relief 20 to 100% of the time using surface oxygen at 6 liter $\cdot$ min^{-1} via nonrebreathing face mask (30). Thus, one can postulate that hyperbaric oxygen could be of considerable benefit to these patients.

A final question is whether our results were due to HBO or to a placebo effect. This question was raised by Schuler and her associates (20) in connection with the use of migraine treatment drugs. They suggested that to be assured of the effectiveness of a drug, a therapeutic response rate of 50% must be elicited from migraine drug trials because there may be a 20–40% therapeutic effect from placebo response. In this study there was a positive response rate of 96.8%. Although double-blind studies are recognized as the most reliable experimental evidence, the results of this preliminary study indicate that the resolution of migraine pain was due to the effects of HBO.

The conclusion from this series of studies is that in an overwhelming number of cases, HBO will quickly provide complete relief of migraine symptoms. There is no evidence from this study that HBO acts as a prophylactic

treatment for migraine or that it cures the underlying causes of migraine. HBO has no effect on muscle tension headache; its possible benefit in the treatment of cluster headache has not been determined.

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