



Oxygen Therapy in Cluster Headache, Migraine, and Other Headache Disorders

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Oxygen therapy (OT) can relieve head pain in certain primary headache disorders, including cluster headache (CH). The exact underlying mechanism is currently uncertain, but suggested mechanisms include inhibition of the trigeminoautonomic reflex, modulation of neurotransmitters, and cerebral vasoconstriction. OT is the standard for acute treatment of CH, but patients with CH often experience considerable difficulties accessing home OT due to problems with insurance coverage. Inhalation of 100% oxygen at 6–12 L/min for 15–30 min using a non-rebreather face mask is one of the most effective acute therapies for CH, but several trials have indicated the superiority of higher oxygen flow rates of up to 15 L/min and/or using a demand-valve oxygen mask that can produce very high flow rates. Two randomized controlled trials have demonstrated the efficacy of OT in migraine, but obtaining reliable evidence is considered difficult because of different inhalation protocols, varying outcome measures, and small samples. There are some reports on the efficacy of OT as an adjuvant therapy in hypnic headache, primary headache in the emergency department, and even postdural puncture headache. The goal of this review article is to expand the knowledge regarding the use of oxygen in the treatment of headache disorders.

Keywords cluster headache; demand-valve oxygen; masks; migraine disorders; oxygen inhalation therapy; trigeminal autonomic cephalalgias.

BACKGROUND

Oxygen therapy (OT) is an effective medical treatment for low blood oxygen levels and carbon monoxide toxicity.¹⁻³ Inhaled oxygen is also a very effective abortive treatment for cluster headache (CH), which is also called “suicide headache.” Oxygen inhalation was suggested as an acute therapy for CH following several clinical trials performed since 1981.⁴⁻⁶ OT is now recognized as the standard of care for the acute treatment of CH according to the guidelines of the European Federation of Neurological Society and the American Headache Society.^{7,8} However, the low prevalence of CH, delayed diagnosis due to poor public and physician awareness, difficulty in accessing a home oxygen system,^{9,10} and problems with insurance coverage inhibit the widespread use of OT for CH. Moreover, a few clinical studies have produced contradictory findings regarding the efficacy of OT in other primary headaches, such as migraine.¹¹

This review investigated the concept and classification of OT, and here we summarize the efficacy of OT in primary headache disorders. Overall, OT is a safe and accessible treatment, and so the efficacy, appropriate protocol, and putative mechanisms of OT in primary headache disorders need to be recognized by the entire medical community. Such an awareness can contribute to improving the accessibility of OT for patients with CH.

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SEARCH STRATEGY

We identified articles on the association between OT and headache using a systematic search of the PubMed (incorporating MEDLINE) database. Searches including full papers and abstracts were performed on March 9, 2021 using the following search string: (“high-flow oxygen therapy” OR “home oxygen therapy”) AND (“headache” OR “migraine”). Search strings were entered into the database as free text with no restrictions in order to minimize the possibility of omitting relevant records, except for the exclusion of articles published in languages other than English. Hypoxia-related headache such as high-altitude headache and headache associated with carbon monoxide intoxication and hyperbaric OT (placing a patient’s entire body in an increased-pressure environment, usually 2–3 atmospheres of absolute pressure) were not evaluated.

The search retrieved 192 records from the PubMed database. A review of these records for relevance resulted in the deletion of 19 non-English articles and 134 articles that were insufficiently relevant, and so 39 records were selected for inclusion. Additional searches performed with relevant search terms identified another 22 articles, and so 34 original articles and 27 review articles were finally included in this review (Fig. 1).

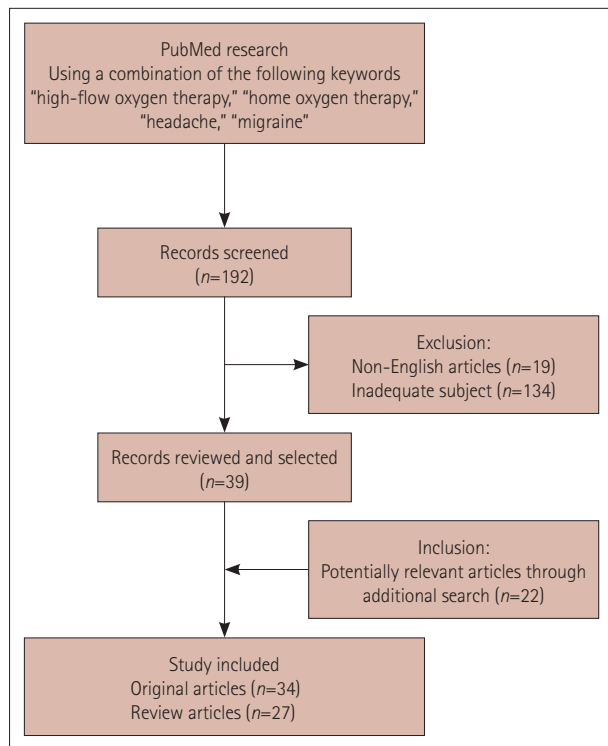


Fig. 1. Flow chart of the study selection.

HISTORY OF OXYGEN THERAPY

OT was recognized as an effective treatment for pneumonia with hypoxia by Barach in 1920, and was developed for the treatment of migraine by Alvarez and Mason in 1940.¹² OT was first used to treat CH in 1952 by Horton.^{13,14} Long-term OT (LTOT) began to be recognized as an important treatment because it increased survival rates in patients with chronic obstructive pulmonary disease in the Nocturnal Oxygen Therapy Trial and British Medical Research Council Domiciliary studies conducted during the 1980s.¹⁵

Kudrow⁴ reported the effectiveness of oxygen inhalation in 52 patients with CH in 1981, and the first placebo-controlled trial of OT for CH in 2009 clearly demonstrated its efficacy.⁵ OT has been evaluated as an intervention for migraine and tension-type headache, but these investigations have produced contradictory results.^{16,17}

CLASSIFICATION OF OXYGEN THERAPY AND DELIVERY SYSTEMS

OT is classified according to the flow rate and modality of oxygen delivery.¹⁸ A “low-flow system” is defined as an oxygen flow rate that is lower than a patient’s inspiratory flow (<30 L/min). The fraction of inspired oxygen (FiO₂) is dependent on the inspiratory flow. For example, when receiving 100% oxygen at 10 L/min via a face mask, the calculated FiO₂ will be 0.37, 0.47, and 0.60 for peak inspiratory flow rates of 50, 30, and 20 L/min, respectively, when the surrounding air flow has an FiO₂ of 0.21 {FiO₂=[(air flow (L/min)×0.21 + oxygen flow (L/min))] / total flow}. In contrast, a “high-flow system” provides higher oxygen flow than a nasal cannula or simple face mask, and FiO₂ is hardly affected by the inspiratory flow in this setting (Table 1).

OT is also classified according to the continuity of oxygen supply. Persistent LTOT is mainly administered in chronic

Table 1. Classification of types of oxygen therapy

Flow system	Modality	Flow rate (L/min)	Expected FiO ₂
Low	Nasal cannula	1–6	0.24–0.44
	SM	5–12	0.20–0.50
Intermediate	Mask with reservoir bag (NRM)	10–15	0.55–0.95
High	DVO	40–160	0.40–1.00
	Venturi mask*	40–50	0.40–0.50
	High-flow nasal cannula [†]	40–60	0.40–1.00 [†]

*Reliable as a high-flow system when FiO₂ exceeds 0.4; [†]High-flow nasal cannula can produce an FiO₂ of 1.00 when using a humidifier to make the gas mixture saturated and warmed (31°C–37°C). DVO, demand-valve oxygen mask; FiO₂, fraction of inspired oxygen; NRM, non-rebreather face mask; SM, simple face mask.

medical cardiopulmonary diseases with hypoxemia, such as congestive heart failure, cor pulmonale, and severe emphysema. Intermittent LTOT is applied in less-severe medical conditions such as hypoxemia or obstructive sleep apnea. LTOT is also called “home OT” because oxygen concentrators, liquid oxygen, and compressed oxygen cylinders are mainly located at patients’ homes. Each modality has its strengths and weaknesses, but an oxygen concentrator is generally used due to it being stable and safe.¹⁹

OT in the context of headache disorders comprises a variation of intermittent LTOT, and various OT systems have been applied in CH.^{1,18,20} FiO_2 is affected by the concentration of oxygen in the inhaled gas, supply systems such as the ventilator, and the mask or cannula (Fig. 2). The expected FiO_2 of OT using a simple face mask or nasal cannula is lower than the concentration of the supplied oxygen due to mixing with room air.

When a mask is used with a reservoir bag, there is a one-way valve between the mask and reservoir bag to prevent the patient from inhaling their own exhaled air. This provides a higher oxygen concentration, and is called a “non-rebreather face mask” (NRM). Although no mask modality can change low flow into high flow, this type of OT with oxygen flow rates of 6–15 L/min has been designated as “high-flow OT” in several papers written by neurologists and emergency department (ED) physicians.^{1,5} We classified such a system as “intermediate” flow in this paper to avoid confusion with high-flow OT using the high-flow system.

Furthermore, there is also a periodic oxygen delivery meth-

od, termed demand-valve OT, which is commonly used in scuba diving. In this method, a valve delivers oxygen depending on the individual’s breathing, and so the oxygen supply is controlled by the respiratory rate and tidal volume. The valve shuts off when the user breathes out, thereby preventing them from inhaling their own exhaled air. When the user inspires more deeply, more oxygen will be administered. The benefit of demand-valve systems over other systems for delivering inhaled continuous oxygen is that it provides 100% undiluted oxygen (no ambient air is mixed in) and supports hyperventilation to allow for hyperoxia, which in turn may be important for the efficacy of acute headache treatment. The various OT methods are classified according to modality, flow rate, and expected FiO_2 in Table 1.²¹

MECHANISM OF OXYGEN THERAPY IN HEADACHE DISORDERS

The exact mechanism underlying the effects of OT in headache disorders is uncertain. Suggested mechanisms include inhibition of the cranial parasympathetic pathway or trigeminoautonomic reflex, modulation of neurotransmitters or neuropeptides such as calcitonin-gene-related peptide suppression of neurogenic plasma protein extravasation, and cerebral artery vasoconstriction.²²⁻²⁴ Experimental recordings of the trigeminocervical complex revealed that 100% oxygen inhalation inhibited the effect of superior salivary nucleus stimulation, suppressed neuronal firing in the trigeminocervical complex, and reduced increases in blood flow in the corneal

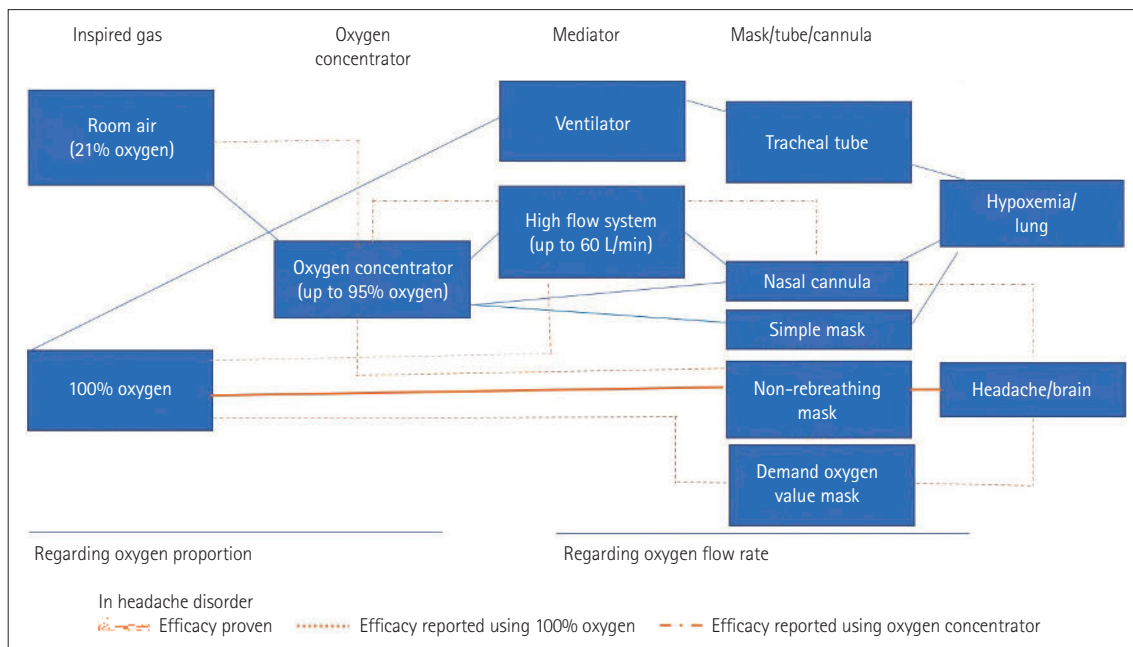


Fig. 2. Process of inhalation of oxygen via different routes to the lung and brain, multiple factors affecting the fraction of inspired oxygen, and efficacy of oxygen therapy.

and lacrimal sac. However, meningeal vasodilation and activation of the trigeminocervical complex by dural electrical stimulation was not affected by oxygen inhalation, and so OT might not be effective at the trigeminal afferents or in typical migraine. Hyperoxia via 100% oxygen administration causes vasoconstriction, and the cooling effect of the inhaled oxygen might attenuate activation of the trigeminovascular system, which would be beneficial in treating CH and migraine.²⁵

Cortical spreading depression involves a slowly moving wave of neuronal inactivation through brain tissue, and is known to be associated with the pathophysiology of brain hypoxia, seizure, and the aura of migraine.^{26,27} Hyperoxia was found to suppress cortical spreading depression, reduce brain injury, and possibly promote oxygen utilization, suggesting that it could be effective in alleviating migraine.¹⁷

CLUSTER HEADACHE

CH is a cyclic headache disorder that is marked by short-duration, severe headaches with associated cranial autonomic symptoms, and agitation. The pain is so severe that sufferers might contemplate or sometimes even commit suicide, resulting in it also being called suicide headache. Patients may experience multiple attacks per day and are completely disabled by each attack. For such a severe pain syndrome, it is fascinating that OT can be so effective whereas opiates, for example, are ineffective. OT is a first-line acute abortive therapy for CH, and >70% of patients are likely to respond to OT.²⁰ There is level-A evidence for the efficacy of OT, and is reported to be as effective as triptan injections.

Two trials have demonstrated the efficacy of OT over placebo (room air), but they used different volumes of oxygen, ranging from 6 to 12 L/min (Table 2).^{5,6} The preference of patients with CH for oxygen was evident in both trials,¹⁷ and 78% of them were pain-free at 15 min after OT, whereas only 20% were pain-free after inhaling room air.

The most effective combination of mask type and oxygen flow rate for CH remains controversial. Various types of oxygen masks can be used in headache disorders.^{21,28} Several open trials have suggested the superiority of a high flow rate up to 15 L/min or a demand-valve oxygen mask (DVO) that can deliver flow rates up to 160 L/min. Two double-blinded clinical trials found no differences in primary outcome according to oxygen flow rate or type of mask.^{29,30} However, the per-protocol study population of each arm was too small to draw concrete conclusions, and patients preferred high-flow oxygen masks or DVOs over other options.

Oxygen concentrators, which take in ambient air and filter out nitrogen to produce an oxygen-enriched gas, can be an alternative to using an oxygen tank as the source of oxygen

when treating CH.¹⁹ Oxygen concentrators have the advantage of not requiring refilling, but the average machine has some limitations regarding the maximum oxygen concentration ($\leq 98\%$) and flow rate (≤ 5 L/min). Connecting two oxygen concentrators is reportedly effective in treating CH when higher oxygen concentrations and flow rates are required.²⁸

Surveys have found that the subjective efficacy of OT was complete or very effective in 29%–54% of patients.^{31–33} Regarding the time taken to achieve complete pain relief, 51% and 27% of responders stated that it was ≤ 20 and >40 min, respectively. Patient surveys suggest that a combination of oxygen and other abortive medications has often been used with improved efficacy. Approximately 20% of patients with CH did not respond to OT, with the various reported predictors of a poor response including being a nonsmoker, longer CH attack duration, accompanying photophobia or phonophobia, nausea/vomiting, restlessness, chronic CH, and the presence of interictal headache.^{34–36} These data were based on patient surveys, some of which were simple comparisons without covariables, and racial differences were unknown, which means that the validity of the results is questionable. The benefit of OT over triptans lies in its cardiovascular safety profile, especially in a population that includes a relatively high proportion of chronic heavy smokers and alcohol overconsumers.

OT is not prohibitively expensive, with the annual cost of OT for CH reportedly being $< \$1,000$ for episodic CH and $< \$5,000$ for chronic CH.³⁷ However, its rate of use is approximately 10% lower in countries where insurance is not provided (e.g., South Korea).^{38,39}

MEDICAL INSURANCE COVERAGE FOR CLUSTER HEADACHE

OT for CH is not uniformly covered by medical insurance worldwide. A survey published in 2017 found that both oxygen and devices are reimbursed in only eight countries, including the United Kingdom, Canada, and China.⁴⁰ Insurance coverage for OT was implemented in Japan in 2018⁴¹ and in the United States in 2021.⁴² According to Dr. B. Jenkins (personal communication on August 2, 2021), patients with CH in Australia cannot obtain oxygen prescriptions in the public healthcare system, and so they rely on individual private health insurance companies. In South Korea, oxygen is classified as a prescription drug, but CH is not included in the clinical code for OT, and so patients with CH seek OT at their own expense without a prescription or public/private insurance coverage.⁴³

The lack of insurance coverage for OT can cause many issues for patients with CH. Some patients with CH lose employment partly due to their headache disorders, resulting in

Table 2. The protocols and efficacy of oxygen therapy for CH and migraine in clinical trials

Study	Per-protocol population	Design	Intervention	Mask/cannula	Measures	Results
Fogan ⁶	19 CH (males aged 20–50 years)	Double blind, randomized, placebo-controlled crossover (after 6 attacks)	6 L/min oxygen vs. air inhalation for 15 min (no preventives)	NRM	Relief score (from 0 for none to 3 for complete)	1.93±0.22 (mean±SD) for oxygen, 0.77±0.23 for air ($p<0.01$)
Cohen et al. ⁵	57 ECH & 9 CCH (mean age 39 years, 12 females), 150 attacks	Double blind, randomized, placebo-controlled crossover (after 2 attacks)	12 L/min oxygen vs. air inhalation for 15 min (withdrawal of preventives in ECH, stable dosage in CCH)	NRM	Pain rating (from 0 for pain-free to 3 for severe), positive in 1 category less than the start	Pain-free 78% for oxygen vs. 20% for air ($p<0.001$)
Petersen et al. ²⁹	30 ECH & 27 CCH (mean age 45 years, 15 females), 102 attacks	Single blind, placebo-controlled, crossover	15 L/min for 15 min under 4 settings: 100% oxygen or room air ($n=11$) using DVO ($n=31$), oxygen using OM ($n=32$) or SM ($n=28$)	DVO, OM, or SM	2-point decrease in pain on a 5-point rating scale	No difference in efficacy 52% for DVO, 44% for OM, 40% for SM, 44% for DVO-air (placebo)
Dirkx et al. ³⁰	70 CH, 604 attacks	Double blind, randomized, placebo-controlled crossover (after 2 attacks)	7 vs. 12 L/min oxygen inhalation for 15 min	NRM	Pain-free after 15 min during first 2 days of the study	No difference 29.2% for 12 L/min vs. 36.2% for 7 L/min
Singhal et al. ¹⁶	20 episodic migraineurs, 64 attacks* (planned 40 patients, early termination due to funding limitation)	Double blind, randomized with 4 E-cylinders (2 with oxygen, 2 with room air)	10–15 L/min for 30 min	SM	Pain rating (0–10), nausea, visual symptoms	No difference in pain score at 15 min, better score (0–1) at 60 min for pain (45% vs. 23%) and visual symptoms (36% vs. 6%)
Shah et al. ¹⁷	51 episodic migraineurs (mean age 48 years, 92% females), 51 attacks	Single blind, randomized	15 L/min for 15 min under 4 settings: dry oxygen, dry air, humidified oxygen, or humidified air (control) [†]	High-flow nasal cannula	Pain rating (0–10), nausea, photosensitivity, sound sensitivity at 2 h	Significant reduction in pain scores and photosensitivity in 3 active arms. Reduction in nausea and sound sensitivity in humidified-oxygen arm

*14 treated, 4 attacks; 1 treated, 3 attacks; 2 treated, 2 attacks; 3 treated, 1 attack; [†]Vapotherm® device.

CCH, chronic cluster headache; CH, cluster headache; DVO, demand-valve oxygen mask; ECH, episodic cluster headache; NRM, non-rebreather face mask; OM, O₂ptimask; SM, simple face mask.

them being unable to afford the cost of home oxygen, which could reduce their headache-related disability.⁴⁴ The United States Cluster Headache Survey noted that 16% of patients with CH reported that oxygen was unaffordable, and that 12% actually purchased welder (nonmedical) grade oxygen to treat their headaches since it was an economically feasible alternative.⁴⁵ One concern with non-medical-grade oxygen is that the tanks may have been previously filled with harmful/toxic gases, leading to the contamination of oxygen with trace amounts of these gases.

MIGRAINE

Several small non-placebo-controlled studies have found that inhaled oxygen is not effective as an acute treatment for migraine. While two randomized controlled trials have evaluated the efficacy of OT in migraine, the use of different methods of oxygen inhalation, various outcome measures, and small samples make it difficult to draw concrete conclusions from these studies (Table 2).^{16,17}

One study found that applying OT at 10–15 L/min for 30 min via a simple face mask did not yield any difference in

pain scores at 15 min compared with room air.¹⁶ However, the proportion of patients with a pain intensity of 1 or lower after 60 min was higher in the OT group than the room-air group (45% vs. 23%), and migrainous visual symptoms (photophobia, blurred vision, and scotomata) were also decreased (35% vs. 6%). Another study evaluated three conditions of oxygen delivery using a high-flow nasal cannula at 15 L/min for 15 min (dry oxygen, dry air, and humidified oxygen, with humidified air as the control), and found efficacy in terms of the pain scores at 2 h relative to the control using a linear regression model of -1.6, -1.7, and -2.3 for dry oxygen, dry air, and humidified oxygen, respectively.¹⁷

Taking the above findings together, it might be concluded that migraine headache with “cluster features” (cranial autonomic symptoms) will respond better to OT than will migraine without these associated symptoms. In one case, a migraineur with ipsilateral autonomic symptoms and an initial pain-free status underwent 15 min of inhalation of 100% oxygen, and experienced a recurrence of headache 30 min after the discontinuation of OT.¹¹ Considering that migraine attacks last longer than CH attacks, the optimal duration of OT and the proper timing of treatment initiation remain uncertain.

Normobaric OT was reported to be inferior to hyperbaric OT in relieving migraine symptoms in the setting of a hyperbaric chamber.²⁰ However, investigating this was beyond the scope of the present review. Moreover, patients with CH or migraine might be unwilling to enter a hyperbaric chamber, and also their availability is extremely restricted.

OTHER PRIMARY HEADACHE DISORDERS

The efficacy of OT has not been well evaluated in other headache disorders, but there are a few case summaries and randomized controlled trials regarding the use of OT and headache. It might seem intuitive that OT would be effective against other trigeminal autonomic cephalalgias apart from CH, but this does not appear to be the case except for one published case of partial efficacy in chronic paroxysmal hemicrania.⁴⁶⁻⁴⁸

For tension-type headache, one randomized controlled trial identified the usefulness of OT. That study evaluated 204 patients with headaches (including 96 with tension-type headaches and 56 with migraine) during 60 min after inhalation of 100% oxygen via NRM at 15 L/min for 15 min in the ED. The headache duration was approximately 3 h and 78%–80% of the patients were taking a medication for headache at baseline. Recommended outcome measures, such as the 100% or 50% responder rate, were not evaluated, but there was a significant improvement in the pain scores on a visual analog scale among patients receiving OT compared with those re-

ceiving room air. The mean score improved from 77 to 54 (out of 100) with OT and 72 to 60 with placebo at 15 min, and the rate of needing rescue analgesics at 30 min was 72.5% in OT and 86.3% in placebo. These results indicated the efficacy of OT as an adjuvant therapy for headache in the ED rather than the sole efficacy of OT. This is a promising finding given that identifying nonopioid treatment options for headache in the ED is crucial. However, the diagnostic accuracy was not validated, and the results were not controlled for the duration of headache and type of medication before arriving at the ED.

Hypnic headache is a rare primary headache disorder that develops only during sleep, and caffeine intake during the evening is surprisingly the choice of treatment. In a survey of 20 German patients with hypnic headache, 4 patients used 100% oxygen inhalation as abortive therapy, which was effective in only 1 patient.⁴⁹

The use of OT daily (every hour for 3 min) for the treatment of withdrawal headache in patients with medication-overuse headache reportedly relieved headache due to the expected vasoconstrictive effect.⁵⁰ This was reported by Horton, who was also the first to investigate the efficacy of oxygen for CH.

While it falls outside the scope of this review, OT has been tested with intravenous metoclopramide as an adjuvant therapy for patients with postdural puncture headache who refused or who had contraindications for an epidural blood patch. Ten out of 12 patients who received inhaled oxygen at 12 L/min via an NRM reported improvement in headache intensity even prior to receiving metoclopramide.⁵¹ OT is inexpensive and available in most hospital settings, and so its efficacy as a sole or adjuvant analgesic for postdural puncture headache needs to be properly evaluated.

SEX DIFFERENCES IN OXYGEN TREATMENT RESPONSE FOR HEADACHE

In the pivotal CH study of Kudrow,⁴ inhaling oxygen at 7 L/min had the same efficacy in male and female patients. In the United States Cluster Headache survey, approximately equal numbers of male and female patients with CH stated that oxygen was an effective therapy, but with the response being slower in females than in males.⁵² This sex-related difference might have been due to the applied oxygen flow rates, since 51% of females were treated at flow rates of 7–10 L/min whereas 45% of males were treated at flow rates of ≥ 13 L/min. In another study, the efficacy of OT in 246 patients with CH was higher in females than males, but the difference was not statistically significant.³⁴ There are insufficient data for identify any sex-related differences with respect to OT in primary

Table 3. Comparison of OT role in cardiopulmonary disease and headache disorder

	Cardiopulmonary disease	Headache disorder
Oxygen state	Hypoxemia	Normoxemia
Suggested pathophysiology	Metabolite such as lactate is generated by anaerobic metabolism, resulting in tissue damage and tissue death	Neurological inflammation, activation of specific neuropeptide and trigeminovascular system
Aim of OT	Change from hypoxemia to normoxemia	Change from normoxemia to hyperoxemia, relieve severe headache, improve quality of life
Pathomechanism of OT	Prevention of tissue damage by hypoxemia	Hyperoxemia, parasynthetic system activation, anti-inflammatory effect in dura, superior salivatory nucleus stimulus, inhibition of vasodilatation
Side effect	Oxygen toxicity and tissue damage could occur, especially when $FiO_2 > 0.50$	Little risk of oxygen damage because OT duration is < 1 h

FiO_2 , fraction of inspired oxygen; OT, oxygen therapy.

headache disorders.

RISK OF OXYGEN TOXICITY AND FIRE-RELATED RISK

Home OT has a potential risk of oxygen toxicity. The production of oxygen free radicals such as superoxide anion, hydrogen peroxide, and hydroxyl radical causes tissue destruction. When inhaling oxygen at a flow rate higher than an FiO_2 of 0.50, it is recommended to minimize the duration to less than 48 h.^{53,54} Regarding headache disorders, the exposure time to high-dose oxygen is short, within the range of 15–60 min, and there should be little risk of oxygen toxicity (Table 3).

OT and smoking can increase the risk of fire, and CH is associated with cigarette smoking.⁵⁵ Patients with CH should therefore be given appropriate information about not smoking during OT.

CONCLUSION

OT is an effective and relatively safe option for the acute treatment of CH and other primary headache disorders. Establishing the optimal flow rate and mode of oxygen delivery is essential to the widespread use of OT for headache disorders. The overall safety profile of OT makes it a very attractive treatment option for use at the homes of patient as well as in the ED.

Availability of Data and Material

All data generated or analyzed during the study are included in this published article.

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Conflicts of Interest

Dr. Mo was involved as a site investigator of multicenter trial sponsored Biohaven Asia Pacific Ltd. Dr. Cho was involved as a site investigator of multicenter trial sponsored Otsuka Korea, Allergan, Ildong Pharmaceutical Co., LTD, Novartis International AG, Eli Lilly and Company, Hyundai-pharm. Co. Ltd., Biohaven Asia Pacific Ltd, H. Lundbeck A/S (Lundbeck), and Parexel Korea Co., Ltd., and received lecture honoraria from Allergan Korea, WhanIn Pharm Co., LTD, Shinpoong Pharma. Co., Ltd, and SK chemicals in the past 24 months. Dr. Chung reported no conflict of interest. Dr. Rozen nothing to disclose, no conflict of interest.

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