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Efficacy of Oxygen Treatment Using Home Oxygen Concentrators for the Treatment of Cluster Headaches: A Randomized, Crossover, Multicenter Study

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Background and Purpose Oxygen treatment is the first-line acute treatment for cluster headaches (CHs), but this can be impeded by insurance coverage and oxygen-tank maintenance. Oxygen concentrators filter nitrogen from ambient air to produce oxygen-rich gas, and can therefore be an alternative to conventional oxygen therapy using a tank. We investigated the effectiveness and safety of using two home oxygen concentrators and compared them with using oral zolmitriptan for the acute treatment of CHs.

Methods Forty patients with episodic CHs in an active cluster period were enrolled in this randomized, crossover, multicenter study. Two attacks during the cluster period were treated using oxygen delivered by connecting two home oxygen concentrators, whereas the other two attacks were treated using oral zolmitriptan (5 mg) in a random sequence. The primary endpoint was substantial pain reduction (0 or 1 on a five-point rating scale from 0 to 4 points) at 15 min after treatment.

Results In total, 125 attacks among 32 patients were randomized and treated (63 attacks using oxygen and 62 using zolmitriptan) according to the study protocol. More attacks treated using oxygen reached the primary endpoint than did those treated using zolmitriptan (31.7% [20/63] vs. 12.9% [8/62], p=0.013). After 30 min, 57.1% of the patients who received oxygen and 38.7% who received zolmitriptan reported pain relief (p=0.082). All patients treated using oxygen reported an improvement in pain, and 61.3% preferred oxygen while only 9.7% preferred zolmitriptan. No adverse events occurred during the oxygen treatment.

Conclusions Oxygen treatment administered using two home oxygen concentrators resulted in better pain relief than oral zolmitriptan in patients with episodic CHs. Our results suggest that home oxygen concentrators are capable of efficiently supplying oxygen in a similar manner to using an oxygen tank.

Keywords cluster headache; oxygen; home oxygen concentrator; acute treatment.

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INTRODUCTION

Cluster headache (CH) is a severe neurological disorder characterized by recurrent episodes of excruciating pain, often accompanied by autonomic symptoms.[1] Severe pain often lasts for 15−180 min in the active period of CH at a frequency from one to eight times per day every other day.[1,2] The burden of CH can lead to functional impairments that significantly affect the patients.[2] Rapid-acting treatment is therefore necessary to quickly relieve severe pain and the associated symptoms.

Oxygen treatment is the first-line acute treatment for CHs, backed up by level A evidence from European and American guidelines.[3,4] Oxygen has several advantages over triptans which are often used to treat CH, including lower cost, fewer side effects, and suit-

able for use in triptan-contraindicated patients such as those with coronary artery disease. It can also be used during pregnancy and lactation, with it reducing the risk of medication overuse. A high-flow oxygen regimen is recommended for acute treatment by inhaling 100% oxygen at a 6–12 L/min flow rate via a nonrebreather facemask for 15 min after the onset of pain.[5,6]

However, oxygen treatment might not be feasible in some countries due to the difficulty in accessing and prescribing oxygen tanks. Limitations in insurance coverage may also restrict the use of oxygen tanks for treating CHs;[7] the responses to a previous survey indicated that oxygen treatment was only reimbursed in 50% of countries worldwide.[8] Oxygen treatment is unfortunately not covered by insurance for patients with CH in South Korea, and the coverage mostly comprises concentrators that can only produce oxygen at a maximum flow rate of 5 L/min. Oxygen concentrators filter nitrogen from ambient air to produce oxygen-rich gas. Compared with oxygen tanks, oxygen concentrators have the benefit of not needing to be refilled; however, typical concentrators have limitations in maximum oxygen concentration (≤98%) and flow rate (≤5 L/min). Our previous exploratory study found that oxygen treatment using two connected home concentrators to provide high-flow oxygen was effective in reducing or ceasing CH pain.[9]

In this randomized, crossover, multicenter study, we aimed to determine the effectiveness and safety of oxygen using two home oxygen concentrators compared with zolmitriptan in the acute treatment of episodic CHs.

METHODS

Patients

This prospective study included adults aged 18–65 years with episodic CHs from headache clinics at eight hospitals in South Korea between November 2021 and November 2022. CH was diagnosed based on the third edition of the International Classification of Headache Disorders.[1] All patients were interviewed by experienced neurologists specializing in headache disorders and were primarily evaluated using brain imaging to confirm the CH diagnosis. To minimize intertreatment effects, the study included patients who met the following criteria: 1) experiencing at least 3 days of CH attacks within 1 week, 2) agreeing to a minimum interval of 1 day between oxygen and zolmitriptan for acute treatment, and 3) agreeing to maintain current preventive medication until the study protocol was completed. Patients were excluded if they had a coexisting migraine or tension-type headache that could not be differentiated from CH or other primary headaches, had chronic obstructive pulmonary disease, or had previously received oxygen treatment using a concentrator. Patients who received previous treatment with an oxygen tank or a 5-$HT_{1B/1D}$ receptor agonist were included.

Study setting

The study protocol was explained to the patients who provided informed consents to participate. The research protocol was approved by the Ethics Committee of the Dongtan Sacred Heart Hospital (IRB No. 2021-08-018). This study was approved by the IRB of each participating hospital.

The patients received oxygen or zolmitriptan for four CH attacks as a crossover trial. Each patient received an oxygen treatment session for two CH attacks and two zolmitriptan treatment sessions for two other attacks, with a minimum 1-day washout period between each treatment. The order of each treatment session sequence for each patient was generated randomly and assigned by the study coordinator using the R program ver. 2022.02.0+443; R Studio, Boston, MA, USA (Fig. 1). Both treatments were administered only in cases with moderate or severe pain (score of 3 or higher on a scale from 0 to 4). Zolmitriptan (5 mg) was used as a treatment through oral administration. For oxygen treatment, two stationary oxygen concentrators (Everflo, Philips Respironics, Murrysville, PA, USA) were connected to obtain a 10 L/min

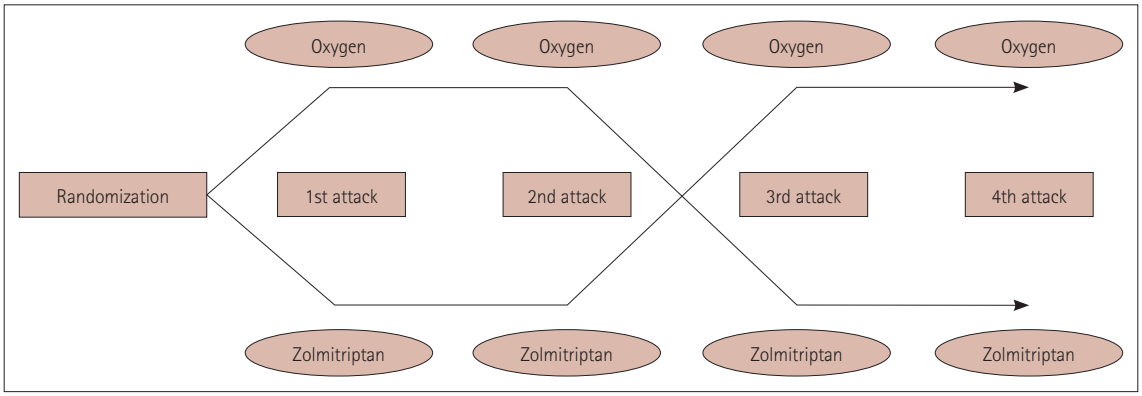

Fig. 1. Schematic of the crossover design in the study.

flow rate through a nonrebreather face mask. Any attacks other than those assessed in the study were treated using oxygen or zolmitriptan based on the choice of the patient, and information about those treatments was not collected. Each patient completed a structured questionnaire before and after each treatment, and pain severity was assessed at the beginning and 15, 30, 60, and 120 min after treatment. Rescue medication was administered 30 min after treatment initiation. The possible options for rescue medication included triptans, non-steroidal anti-inflammatory drugs, and other analgesics, with no restrictions imposed.

Clinical evaluation and endpoints

Patients were interviewed by the investigators and completed a structured questionnaire on headache characteristics. Demographic data and clinical information were collected, including CH characteristics during the current bout (attack frequency and duration), diurnal rhythmicity, use of preventive medication for CH, presence of coexisting migraines, smoking status, and alcohol consumption.

Pain severity was rated on a five-point scale from 0 to 4: 0 for pain free 1 for mild pain, 2 for moderate pain, 3 for severe pain, and 4 for very severe pain.[10] The primary endpoint was pain relief, defined as a pain score of less than 2 points (i.e., 0 or 1) at 15 min. The secondary endpoints included pain-relief and pain-free statuses at each time point (15, 30, 60, and 120 min), the need for rescue medication, attack duration, pain severity over time, treatment effectiveness, and patient preferences. The patients recorded the date and time of the attack, the time of treatment and rescue medication administration, and the end of the attack during the treatment session. The effects of treatment on controlling pain and accompanying symptoms (autonomic symptoms or restlessness) were assessed on the following five-point rating scale: ineffective, low effectiveness, moderate effectiveness, highly effective, and very highly effective, with "highly effective" and "very highly effective" considered good treatment effects.

Statistical analysis

The required sample size was calculated using a statistical power of 0.80 and a type I error rate of 0.05 based on the results of our previous exploratory study.[9] A dropout rate of 33.3% was assumed, which yielded a sample size of 38. We selected 40 patients as the size of each group considering the risk of a slightly higher dropout rate in a randomized clinical trial.

Data were presented as numbers with percentages or medians with interquartile ranges (IQRs). The Kolmogorov–Smirnov test was used to determine whether variables conformed to a normal distribution. Comparisons of within-subject response rates between the oxygen and zolmitriptan treatments were performed using the McNemar test for paired proportions. The correlation between pain relief at 15 min after treatment and the regimen (oxygen or zolmitriptan) was analyzed using logistic regression with the generalized estimating equations (GEEs) methodology to account for intrasubject correlations, after adjusting for age and sex. Attack durations were compared using the Wilcoxon signed-rank test. Pain severities over time were compared using repeated-measures analysis of variance. If the curves were found to differ significantly, a Bonferroni-correction post-hoc analysis was used to compare pairs at the same time point. Statistical analyses were conducted using IBM SPSS software (version 22.0, IBM Corp., Armonk, NY, USA). Significance was set at a two-tailed probability value of $p<0.05$.

RESULTS

Patients

A flowchart of the study is shown in Fig. 2. During the study period, 40 patients with episodic CHs were recruited and randomly assigned to receive either oxygen-then-zolmitriptan (n=20) or zolmitriptan-then-oxygen (n=20) treatment. After excluding 8 patients for the reasons listed in Fig. 1, 32 completed the study. Among them, 31 patients underwent 2 oxygen and 2 zolmitriptan treatments for 4 CH attacks in addition to 1 patient who received 1 oxygen treatment for 1 CH attack due to not having experienced more attacks. The demographics and CH characteristics did not differ significantly between the treatment groups (Supplementary Table 1 in the online-only Data Supplement). Finally, 125 attacks were treated (63 using oxygen and 62 using zolmitriptan) among the 32 included patients.

Table 1 lists the demographics and characteristics of the included patients (n=40) and those who were actually treated (n=32). The median age of the patients who were treated was 40.0 years (IQR, 31.0–44.8 years), with males predominating (87.5%). The median age at CH onset was 25.0 years (IQR, 22.0–32.0 years). Coexisting migraine presented in 25% of the patients, and 62.5% had diurnal rhythmicity. Preventive medication was maintained in 56.3% (n=18) of the patients, in which steroids, verapamil, and lithium were used by 37.5%, 46.9%, and 12.5%, respectively. No significant differences were observed between included patients with CH and those who were treated (Table 1).

Primary and secondary endpoints

Table 2 and Fig. 3 present the proportions of patients who achieved pain relief and pain free after treatment. Signifi-

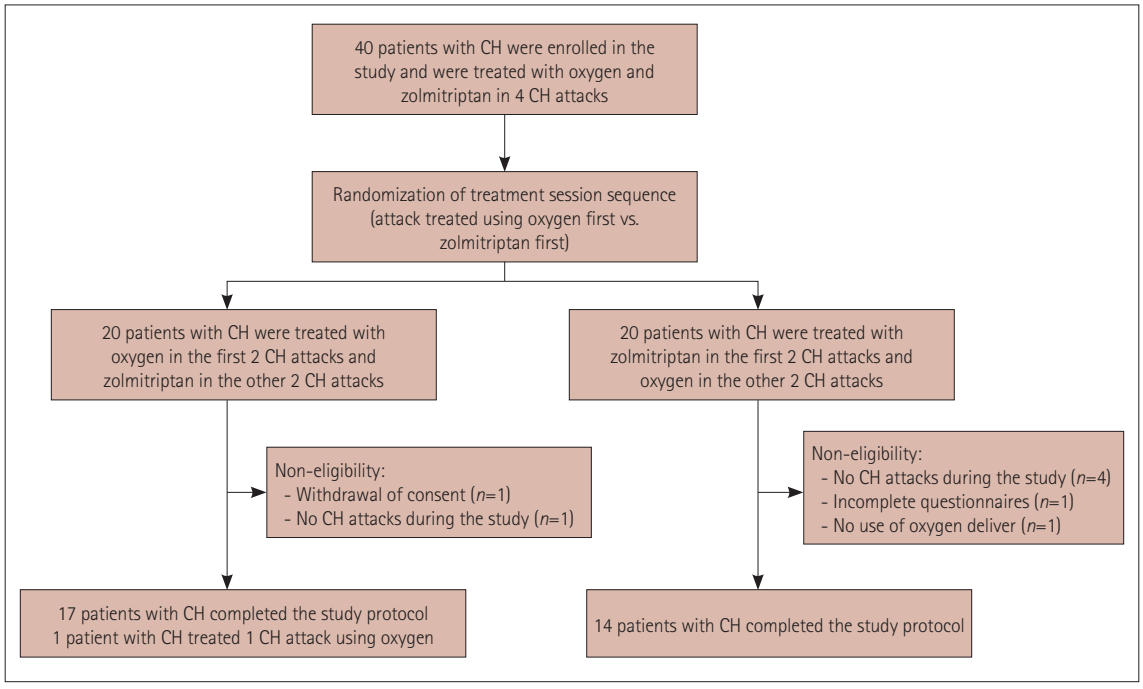

Fig. 2. Flow diagram of the study. CH, cluster headache.

Table 1. Patient demographics and characteristics

	Included (*n*=40)	Treated (*n*=32)
Age, years	38.5 [31.0–44.0]	40.0 [31.0–44.8]
Sex, male	35 (87.5)	28 (87.5)
Body mass index, kg/m^2	24.1 [21.0–25.5]	23.8 [21.0–25.8]
Education		
High-school graduation	4 (10.0)	3 (9.4)
College graduation	36 (90.0)	29 (90.6)
Smoking	17 (42.5)	13 (40.6)
Alcohol consumption	20 (50.0)	15 (46.9)
Coexisting migraine	10 (25.0)	8 (25.0)
Age at CH onset, years	25.0 [22.0–31.5]	25.0 [22.0–32.0]
Diurnal rhythmicity	24 (60.0)	20 (62.5)
Attack frequency during the current bout	1.0 [1.0–1.5]	1.0 [1.0–1.5]
Attack duration during the current bout	90.0 [52.5–120.0]	90.0 [60.0–120.0]
Preventive medication for CH		
None	18 (45.0)	14 (43.8)
Steroid	15 (37.5)	12 (37.5)
Verapamil	17 (42.5)	15 (46.9)
Lithium	4 (10.0)	4 (12.5)

Data are median [interquartile range] or number (%) values.
CH, cluster headache.

cantly more attacks achieved pain relief after an attack at 15 min after treatment using oxygen inhalation than using zolmitriptan (*n*=20/63 [31.7%] vs. *n*=8/62 [12.9%], *p*=0.013).

Table 2. Efficacy endpoint results

	Oxygen	Zolmitriptan	*p*
No. of attacks treated	63	62	
Pain-relief status			
15 min	20 (31.7)	8 (12.9)	0.013
30 min	36 (57.1)	24 (38.7)	0.082
60 min	55 (87.3)	42 (67.7)	0.011
120 min	58 (92.1)	54 (87.1)	0.508
Pain-free status			
15 min	8 (12.7)	5 (8.1)	0.254
30 min	20 (31.7)	9 (14.5)	0.021
60 min	42 (66.7)	27 (43.5)	0.018
120 min	51 (81.0)	44 (71.0)	0.180
Need for rescue medication	11 (17.5)	14 (22.6)	0.194
Attack duration, min	50 [30–60]	70 [40–120]	0.003

Data are median [interquartile range] values for the attack duration or number (%) values for the number of attacks.

Pain relief at 15 min after treatment using oxygen inhalation was superior to that when using zolmitriptan in the GEE analysis (*p*=0.012). More attacks achieved pain-free states at 30 min after treatment through oxygen inhalation than through zolmitriptan (*n*=20/63 [31.7%] vs. *n*=9/62 [14.5%], *p*=0.021). The median attack duration was significantly shorter for oxygen than for zolmitriptan treatment (50 min [IQR, 30.0–60.0] vs. 70 min [IQR, 40.0–120.0 min], *p*=0.003). There was no significant difference between the groups in rescue medication use; this was required for 17.5% of the attacks in the oxygen group and for 22.6% of those in the zolmitriptan

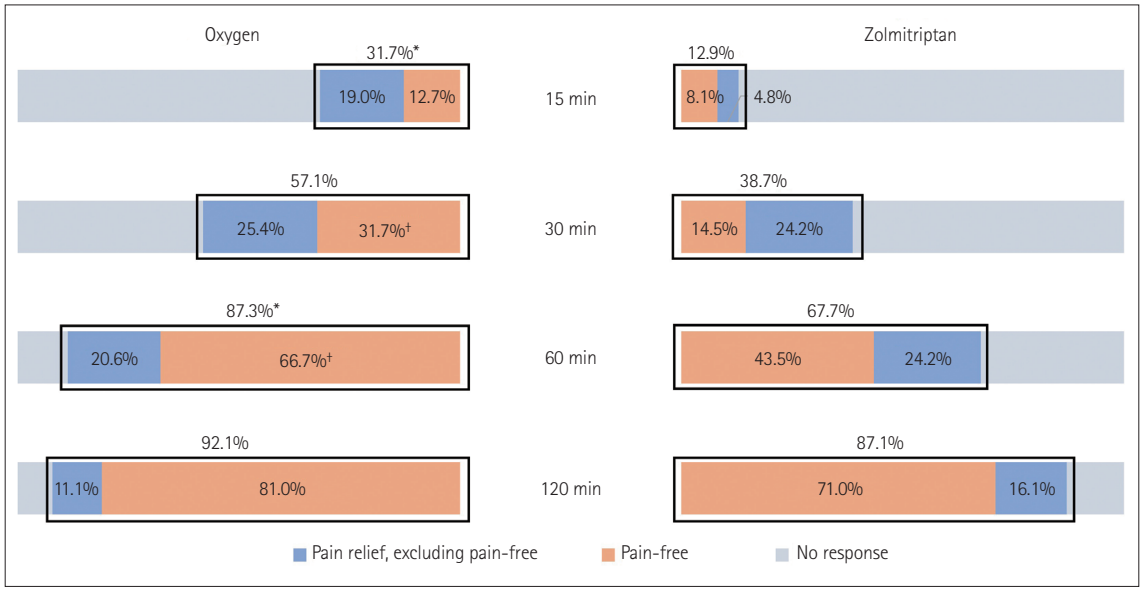

Fig. 3. Comparison of pain-relief and pain-free rates between oxygen and zolmitriptan treatments. *Significant differences in the pain-relief rate between the two treatments at one time point; †Significant differences in the pain-free rate, between the two treatments at one time point.

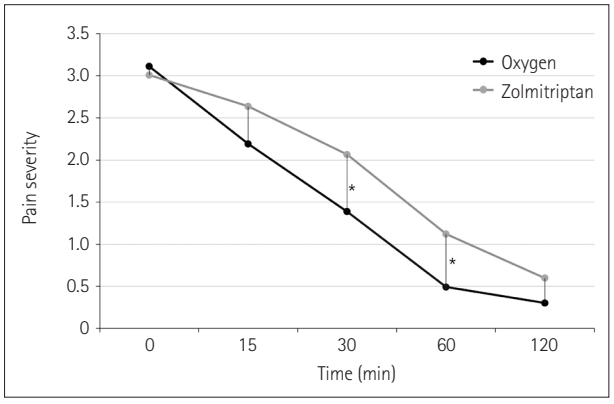

Fig. 4. Comparison of the effect on pain severity between oxygen and zolmitriptan. An asterisk indicates a significant difference (p<0.01) at one time point in a post-hoc repeated-measures ANOVA with Bonferroni correction.

Table 3. Patient satisfaction with the treatment effect

	Oxygen	Zolmitriptan
Effect on pain control		
Ineffective	0 (0)	2 (6.5)
Low effectiveness	3 (9.7)	6 (19.4)
Moderate effectiveness	2 (6.5)	6 (19.4)
Highly effective	13 (41.9)	14 (45.2)
Very highly effective	13 (41.9)	3 (9.7)
Effect on accompanying-symptoms control		
Ineffective	0 (0.0)	3 (9.7)
Low effectiveness	3 (9.7)	5 (16.1)
Moderate effectiveness	6 (19.4)	9 (29.0)
Highly effective	11 (35.5)	13 (41.9)
Very highly effective	11 (35.5)	1 (3.2)

Data are number (%) values (n=31, one patient did not complete the questionnaire).

group (p=0.194). The median time between onset and taking rescue medication did not differ significantly between the two groups, at 50.0 min (IQR, 33.0–70.0 min) and 67.5 min (IQR, 33.0–114.8 min) for the oxygen and zolmitriptan groups, respectively (p=0.547).

Fig. 4 shows the temporal course of pain severity according to treatment group. Comparing the time curves reveals a significant difference between the oxygen and zolmitriptan groups over time (p<0.001). In the post-hoc analysis performed to determine significance at individual time points, oxygen induced more significant pain improvement at 30 and 60 min after treatment than did zolmitriptan (p=0.009 and p=0.007, respectively).

Table 3 lists patient reports of satisfaction with the treatment effect. Thirty-one patients completed the questionnaires after participating in the entire study protocol. All patients reported that oxygen affected pain control and relief of the accompanying symptoms, whereas 6.5% and 9.7%, respectively, reported that zolmitriptan was ineffective. Regarding pain control, 83.8% of the patients reported good treatment effects from oxygen compared with 54.9% from zolmitriptan (p=0.022). For accompanying-symptoms control, there was no significant difference in the prevalence of good treatment effect reports between the two groups (71.0% vs. 45.1%, p=0.057). Nineteen patients (61.3%) expressed a preference for oxygen, three (9.7%) preferred zolmitriptan, and nine (29.0%) had no preference.

Safety of oxygen

No adverse events were observed from oxygen treatment, while four patients reported side effects from the zolmitriptan treatment: muscle heaviness (n=1), nausea (n=2), and bradycardia (n=1). One patient reported difficulty using oxygen treatment at home but still preferred it over zolmitriptan.

DISCUSSION

Our key findings were as follows: 1) for the primary endpoint, treatment using two home oxygen concentrators provided more-effective pain relief from CH attacks at 15 min after treatment than did using zolmitriptan, 2) more attacks were pain-free at 30 min after oxygen treatment than after zolmitriptan treatment, and the pain severity was also significantly improved at this time point following oxygen treatment, and 3) all patients reported that oxygen treatment had an effect on pain control and most were satisfied with this treatment effect.

Approximately one-third of the attacks in our study achieved pain relief at 15 min after oxygen treatment, which was more effective than after zolmitriptan treatment. Previous crossover trials have yielded the proportion of participants who responded to oxygen treatment administration versus controls.[5,6,11,12] Fogan[6] compared the effectiveness of oxygen at a 6 L/min flow rate relative to atmospheric air. They evaluated pain severity on a scale from 0 to 3 and found that 56% (n=9/16) of the participants experienced complete or substantial relief (score of 2 or 3) from oxygen treatment in at least 80% of their attacks. In contrast, only 7% (n=1/14) of the participants responded similarly to the placebo treatment. Cohen et al.[5] similarly investigated the effectiveness of acute oxygen treatment at a 12 L/min flow rate, and found a significant difference in the proportion of attacks successfully treated using oxygen versus high-flow air. Specifically, receiving oxygen resulted in a pain-free or adequate-pain-relief status at 15 min in 117 of 150 attacks (78%), whereas this was achieved in only 30 of 148 attacks (20%) treated using high-flow air. A recent study conducted at a tertiary headache center failed to demonstrate the efficacy of oxygen treatment among demand valve oxygen mask, O2ptimask, and a simple mask at flow rates of 15 L/min.[12] That study compared the treatments with a placebo delivered via a demand valve oxygen mask over 15 min. The pain-relief rate for oxygen treatment in our study (31.7%) was comparable to that obtained by Petersen et al.[12] (29% using a simple mask); however, it was lower than the rates obtained in previous studies (56%–82%). The reason for these discrepancies may be differences in study conditions, such as primary endpoint assessments and preventive medication use. We assessed pain relief as mild or no pain on a five-point rating scale, which was stricter than that used in some previous studies. Indeed, zolmitriptan also achieved a lower pain-relief rate at 15 min in our study (12.9%) compared with a previous study that assessed the effects of zolmitriptan at 10 mg and 5 mg (22.8% and 22.9%, respectively) using improvements of 2 points or greater on a five-point rating scale.[13] In addition, the proportion of patients who received preventive medication in our study was much higher than that in the previous trial, which might have led to differences in the efficacy of the oxygen and zolmitriptan treatments.[5] The demographic features in our study encompassed patients from a tertiary headache center with a median CH duration of 15 years. These patients may be more challenging to treat, which may have contributed to the relatively low pain-relief rate.

In addition to the positive primary endpoints, we observed that oxygen treatment had a tendency toward greater improvement in pain severity over time, reduced attack duration, and greater patient satisfaction than zolmitriptan. The cumulative frequency of pain relief was as high as 57% after 30 min of oxygen treatment, with 31.7% of the patients reporting no pain. In one previous study, oxygen treatment achieved pain relief or a pain-free status at 30 min in 72% of attacks,[5] whereas 63.3% and 54.2% of patients treated using zolmitriptan at 10 and 5 mg, respectively, achieved pain relief at the same time point.[13] As mentioned above, demographic and methodological differences may have influenced these differences. Regarding patient satisfaction, oxygen treatment achieved a good pain-control effect in our study (83.8%), which was higher than the rate achieved in previous studies.[5,14] However, it was difficult to establish exact criteria for comparison. Cohen et al.[5] observed a treatment effect in 60% of CH attacks, whereas Pearson et al.[14] observed complete effectiveness in 13% and very effective treatment in 41% of their patients. These secondary endpoints further support the effectiveness of the oxygen treatment method.

In this study we achieved a high flow rate for oxygen by connecting two home oxygen concentrators. Connecting two oxygen concentrators can deliver high oxygen concentrations in military or limited oxygen resources.[15] This method was intended to make it feasible for patients with CHs to cost-effectively receive oxygen treatment because the Korean National Health Insurance service does not cover the oxygen-tank regimen as recommended by the guidelines.[3,4] Oxygen concentrators offer several advantages over traditional oxygen tanks.[16] They do not require regular tank refilling or replacement and provide a continuous oxygen supply, thus eliminating the need for frequent tank changes. Regarding safety, no adverse events were observed in patients treated using oxygen in our study. Based on the positive results ob-

tained when using the oxygen concentrators in our study, we suggest that these devices are a viable treatment option for patients with CH in countries that face medical-insurance- or cost-related challenges. However, further research is necessary to confirm the efficacy of this treatment.

A major strength of our study was the determination of the efficacy of oxygen concentrators for acute treatment of CHs using a randomized, crossover, multicenter trial. We also calculated the required sample size while also considering the dropout rate, and recruited an adequate number of patients to obtain statistically significant results. To the best of our knowledge, this was the first randomized trial involving Asian patients with CH. However, this study had some limitations. First, it did not include a placebo or blinding process. However, our results may be less biased because we used an active control group that received zolmitriptan, which has been demonstrated to be superior to placebo in previous trials.[10] Second, we could not recruit a large sample due to the low prevalence of CH and the difficulty in enrolling patients with active CH. Third, the low dose of zolmitriptan used in our study may have resulted in an inadequate comparisons of treatment efficacy. A previous study found that oral zolmitriptan at doses of 5 and 10 mg was effective in the acute treatment of CH compared with a placebo.[13] We assumed that the dosage was significant since more than half of the patients in our study reported a good treatment effect from zolmitriptan.

In conclusion, based on our findings, oxygen using two home oxygen concentrators can provide better pain relief than oral zolmitriptan for the acute treatment of episodic CH. We suggest that treatment using a home oxygen concentrator may be an alternative option for the acute treatment of CH.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2023.0103.

Availability of Data and Material

All data generated or analyzed during the study are included in this published article (and its supplementary information files).

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Conflicts of Interest

Byung-Kun Kim and Min Kyung Chu, contributing editors of the Journal of Clinical Neurology, were not involved in the editorial evaluation or decision to publish this article.

Soo-Jin Cho has been the site investigator for a multicenter trial sponsored by Novartis, Allergan, Abbvie Pharma, Ildong Pharma, and Hyundai Pharma. She received honoraria as a speaker or moderator from Teva, Lilly Korea Ltd., Lundbeck, SK Chemical Pharm, Yuyu Pharma, Shinpoong Pharma, and Pfizer and the grant from JW Pharma. Byung-Kun Kim served on Lundbeck's Advisory Board. He received honoraria as a moderator and speaker from Lundbeck, AbbVie, Pfizer, Eli Lilly, Teva, Yuyu Pharm, and SK Pharm. He has been the principal investigator of clinical trials sponsored by Eli-Lilly, Novartis, Lundbeck, Teva, AbbVie, and Ildong Pharm.

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REFERENCES

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* 2018;38:1-211.
2. Rozen TD, Fishman RS. Cluster headache in the United States of America: demographics, clinical characteristics, triggers, suicidality, and personal burden. *Headache* 2012;52:99-113.
3. May A, Leone M, Afra J, Linde M, Sándor PS, Evers S, et al. EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias. *Eur J Neurol* 2006;13:1066-1077.
4. Robbins MS, Starling AJ, Pringsheim TM, Becker WJ, Schwedt TJ. Treatment of cluster headache: the American Headache Society evidence-based guidelines. *Headache* 2016;56:1093-1106.
5. Cohen AS, Burns B, Goadsby PJ. High-flow oxygen for treatment of cluster headache: a randomized trial. *JAMA* 2009;302:2451-2457.
6. Fogan L. Treatment of cluster headache. A double-blind comparison of oxygen v air inhalation. *Arch Neurol* 1985;42:362-363.
7. Mo H, Chung SJ, Rozen TD, Cho SJ. Oxygen therapy in cluster headache, migraine, and other headache disorders. *J Clin Neurol* 2022;18:271-279.
8. Evers S, Rapoport A; International Headache Society. The use of oxygen in cluster headache treatment worldwide - a survey of the International Headache Society (IHS). *Cephalalgia* 2017;37:396-398.
9. Hong Y, Cho SJ, Bae DW, Chung PW, Moon HS, Chu MK, et al. Exploratory study of the effectiveness of oxygen therapy using home ox-

ygen concentrators for cluster headache. *J Korean Neurol Assoc* 2020;38:29-32.
10. Schoenen J, Snoer AH, Brandt RB, Fronczek R, Wei DY, Chung CS, et al. Guidelines of the International Headache Society for controlled clinical trials in cluster headache. *Cephalalgia* 2022;42:1450-1466.
11. Kudrow L. Response of cluster headache attacks to oxygen inhalation. *Headache* 1981;21:1-4.
12. Petersen AS, Barloese MC, Lund NL, Jensen RH. Oxygen therapy for cluster headache. A mask comparison trial. A single-blinded, placebo-controlled, crossover study. *Cephalalgia* 2017;37:214-224.
13. Bahra A, Gawel MJ, Hardebo JE, Millson D, Breen SA, Goadsby PJ. Oral zolmitriptan is effective in the acute treatment of cluster headache. *Neurology* 2000;54:1832-1839.
14. Pearson SM, Burish MJ, Shapiro RE, Yan Y, Schor LI. Effectiveness of oxygen and other acute treatments for cluster headache: results from the cluster headache questionnaire, an international survey. *Headache* 2019;59:235-249.
15. Cheah PK, Steven EM, Ng KK, Hashim MI, Abdul Kadir MH, Roder NP. The use of dual oxygen concentrator system for mechanical ventilation during COVID-19 pandemic in Sabah, Malaysia. *Int J Emerg Med* 2021;14:30.
16. Hardavella G, Karampinis I, Frille A, Sreter K, Rousalova I. Oxygen devices and delivery systems. *Breathe (Sheff)* 2019;15:e108-e116.