



Online article and related content
current as of December 13, 2009.

High-Flow Oxygen for Treatment of Cluster Headache: A Randomized Trial

Anna S. Cohen; Brian Burns; Peter J. Goadsby

JAMA. 2009;302(22):2451-2457 (doi:10.1001/jama.2009.1855)

<http://jama.ama-assn.org/cgi/content/full/302/22/2451>

Supplementary material

eFigure

<http://jama.ama-assn.org/cgi/content/full/302/22/2451/DC1>

Correction

[Contact me if this article is corrected.](#)

Citations

[Contact me when this article is cited.](#)

Topic collections

Neurology; Headache; Migraine; Randomized Controlled Trial; Drug Therapy; Drug Therapy, Other

[Contact me when new articles are published in these topic areas.](#)

Related Articles published in
the same issue

Cluster Headache

Huan J. Chang et al. *JAMA*. 2009;302(22):2502.

Subscribe

<http://jama.com/subscribe>

Permissions

permissions@ama-assn.org

<http://pubs.ama-assn.org/misc/permissions.dtl>

Email Alerts

<http://jamaarchives.com/alerts>

Reprints/E-prints

reprints@ama-assn.org

High-Flow Oxygen for Treatment of Cluster Headache

A Randomized Trial

Anna S. Cohen, PhD, MRCP

Brian Burns, MD, MRCP

Peter J. Goadsby, MD, PhD, DSc, FRACP, FRCP

CLUSTER HEADACHE IS A STEREOTYPICAL primary headache syndrome characterized by attacks of unilateral excruciating pain usually in the eye, periorbital region, and temple with associated cranial autonomic symptoms such as conjunctival injection, lacrimation, nasal blockage, rhinorrhea, ptosis, and eyelid edema. During attacks patients are often restless, agitated, or both. Attacks typically last for 15 to 180 minutes untreated and have a frequency of 1 every other day for up to 8 attacks a day.¹

Attacks usually occur in bouts, or *clusters*, lasting for weeks or months, separated by remissions lasting months or years. Episodic cluster headache is defined as bouts of attacks lasting 7 days up to a year with breaks of 1 month or more between bouts. Bouts are usually circannual, occurring once a year, with a mean bout duration of 8 weeks.² *Chronic cluster headache* is defined as occurring for more than a year without remission or with remissions lasting less than a month. Cluster headache attacks may also occur with clocklike regularity during the day and may be precipitated by sleep,³ usually occurring 90 minutes after the onset of

See also Patient Page.

Context Cluster headache is an excruciatingly painful primary headache syndrome, with attacks of unilateral pain and cranial autonomic symptoms. The current licensed treatment for acute attacks is subcutaneous sumatriptan.

Objective To ascertain whether high-flow inhaled oxygen was superior to placebo in the acute treatment of cluster headache.

Design, Setting, and Patients A double-blind, randomized, placebo-controlled crossover trial of 109 adults (aged 18-70 years) with cluster headache as defined by the International Headache Society. Patients treated 4 headache episodes with high-flow inhaled oxygen or placebo, alternately. Patients were randomized to the order in which they received the active treatment or placebo. Patients were recruited and followed up between 2002 and 2007 at the National Hospital for Neurology and Neurosurgery, London, England.

Intervention Inhaled oxygen at 100%, 12 L/min, delivered by face mask, for 15 minutes at the start of an attack of cluster headache or high-flow air placebo delivered alternately for 4 attacks.

Main Outcome Measures The primary end point was to render the patient pain free, or in the absence of a diary to have adequate relief, at 15 minutes. Secondary end points included rendering the patient pain free at 30 minutes, reduction in pain up to 60 minutes, need for rescue medication 15 minutes after treatment, overall response to the treatment and overall functional disability, and effect on associated symptoms.

Results Fifty-seven patients with episodic cluster headache and 19 with chronic cluster headache were available for the analysis. For the primary end point the difference between oxygen, 78% (95% confidence interval, 71%-85% for 150 attacks) and air, 20% (95% confidence interval, 14%-26%; for 148 attacks) was significant (Wald test, $\chi^2=66.7$, $P<.001$). There were no important adverse events.

Conclusion Treatment of patients with cluster headache at symptom onset using inhaled high-flow oxygen compared with placebo was more likely to result in being pain-free at 15 minutes.

Trial Registration isrctn.org Identifier: ISRCTN94092997

JAMA. 2009;302(22):2451-2457

www.jama.com

sleep. Cluster headache affects more men than women (male-female ratio of 2.5:1) and has an estimated prevalence of 0.3% in the general population.⁴ Cluster headache is probably the most severe pain known to humans. Most female patients describe each attack as worse than childbirth.

Author Affiliations: Headache Group, Institute of Neurology, The National Hospital for Neurology and Neurosurgery, Queen Square London, England (Drs Cohen, Burns, and Goadsby); and Department of Neurology, University of California, San Francisco, San Francisco (Dr Goadsby).

Corresponding Author: Peter J. Goadsby, MD, PhD, DSc, FRACP, FRCP, Headache Group, Department of Neurology, University of California, San Francisco, 1701 Divisadero St, San Francisco CA 94115 (pgoadsby@headache.ucsf.edu).

Treatment for cluster headache relies on therapy to abort the individual attack, and prophylactic therapy aims to prevent or suppress attacks during the cluster bout.⁵ Acute attack therapy must be fast-acting, be easily bioavailable, and provide effective relief from the symptoms. A low adverse-effect profile is also desirable. The most effective treatment of acute cluster headache attack is the serotonin, 5-hydroxytryptamine (5-HT)_{1B/1D} receptor agonist sumatriptan, administered by injection. Sumatriptan 6 mg subcutaneous injections have been shown to be effective in double-blind, placebo-controlled trials as early as 15 minutes after administration.^{6,7} Sumatriptan 20 mg by nasal spray is effective at 30 minutes after dosing.⁸ Zolmitriptan 10 mg orally are effective at 30 minutes after dosing in episodic cluster headache only,⁹ while intranasal zolmitriptan 5 and 10 mg are effective in both forms 30 minutes after dosing.^{10,11} The drawbacks of the triptan agents include limitations on daily usage. Current practice is to limit sumatriptan usage to 2 subcutaneous injections or 3 nasal sprays a day in order to prevent tachyphylaxis and rebound.¹² Triptan agents are contraindicated in patients with a vascular risk, such as ischemic heart disease.¹³

The other first choice for acute cluster headache attacks is the inhalation of high-dose, high-flow oxygen. The great advantage of oxygen is that it has no established adverse effects, can be readily combined with other treatments, and can be used several times daily. Inhaled oxygen at 100% for 15 minutes at the start of the attack has been observed to be safe and effective in aborting a cluster headache attack,¹⁴ as has been confirmed in a small controlled study of 15 patients,¹⁵ and is recommended in standard guidelines.^{16,17} It is not clear how common the use of oxygen is, but it is almost certain that the lack of a good quality controlled trial limits its application. Herein we report a randomized, double-blind, placebo-controlled crossover study of high-flow oxygen in the acute attack of

cluster headache to try to settle this quarter-century old question so that, if effective, its use can be promoted. The data were presented in preliminary format at the XIVth International Headache Congress in Stockholm in June 2007.¹⁸

METHODS

A phase 3, single referral center, randomized, placebo-controlled double-blind crossover study compared oxygen at 100% and air delivered at 12 L/min for 15 minutes from the early part of an attack. The target population included patients aged 18-70 years, with either episodic cluster headache or chronic cluster headache. They remained in the study for as long as it took to treat 4 attacks. The total duration of the study was to be 5 years.

Patients

Patients were screened from clinics at the National Hospital for Neurology and Neurosurgery, London, and identified via patient support groups, particularly the Organisation for Understanding Cluster Headache-UK (OUCH-UK). Patients were thus drawn widely from across the United Kingdom. Patients were recruited and followed up between 2002 and 2007.

Patients were included in the study if they had (1) episodic cluster headache or chronic cluster headache that was classified using the first edition of the *International Classification of Headache Disorders*,¹⁹ although all patients fulfilled the second edition criteria¹; (2) experienced between 1 attack every other day to 5 a day (the duration of the attacks was between 45 minutes and 3 hours); (3) were between the ages of 18 and 70 years.

Patients were excluded if they (1) had chronic migraine; however, patients with both migraine or other episodic headaches were included if they could distinguish these episodes from cluster headaches; (2) were pregnant and lactating, and to ensure that they were not pregnant, all women of childbearing age underwent a pregnancy test; (3) had moderate to severe chronic ob-

structive pulmonary disease because the high-dose, high-flow oxygen might affect their hypoxic respiratory drive; (4) could not tolerate the oxygen mask in the correct fitting; or (5) had previously tried oxygen at doses of 4 L/min and higher.

Patients with episodic cluster headache were required to withdraw prophylactic medication at least 1 week before the study began. Those with chronic cluster headache whose attacks continued while taking medication were required to continue taking a stable dose of prophylactic medication for 2 weeks before starting the study. Ergot derivatives were not allowed within 24 hours before treatment with study medication nor were other treatments within 6 hours before the treatment with study medication.

Conduct of the Study

Medical and smoking histories were taken at the initial visit. After the study was explained, patients gave written informed consent, underwent a brief medical and general neurological examination, were taught how to use a compressed air cylinder identical to the type they would use at home, and received diary cards to record treatment effect at 5, 10, 15, 30, and 60 minutes. Patients were free to withdraw from the study, which was conducted in their homes, at any time. A face mask (Intersurgical, Wokingham, Berkshire, England) and 2 standard CD-sized, 2-liter cylinders (BOC, now Linde Gases, Priestley Road, Guildford, Surrey, England) with integral valve, regulator, flowmeter, and operating instructions were delivered to each patient's home: one labeled "treatment 1"; the other, "treatment 2": one with 100% oxygen; the other, air.

Patients were instructed to administer a single treatment for any attack using the "treatment 1" cylinder at 12 L/min for 15 minutes through a firm plastic nonbreathing facial mask (intersurgical high-concentration nonbreathing masks) and use the "treatment 2" cylinder at the same rate and

duration for the next attack and switching again for the remaining 2 attacks, thus alternating the gases in a cross-over fashion.

If after 15 minutes of treatment patients experienced no relief, they could take any rescue medication they needed. Patients were asked not to take more medication for 4 hours.

Randomization of study-eligible patients was performed using opaque sealed envelopes, inside of which was a card labeled "A" or "B," which determined the order the patient received active treatment or placebo. The physician contacted the manufacturer with the address of the patient and respective randomization for home delivery. Copies of the randomization code were locked in the office of the principal investigator (P.J.G.) and the manufacturer, where they remained unbroken until the end of the trial.

Ethical Considerations and Sponsorship

The study was approved by the National Hospital for Neurology and Neurosurgery and Institute of Neurology Joint Research Ethics Committee. The trial was jointly sponsored by University College London and BOC Limited, which supplied the cylinders and the masks.

The primary end point for effectiveness of the treatment was to render the patient pain free in 15 minutes or in the absence of a diary to have patient adjudged adequate relief at 15 minutes.

Secondary end points included (1) rendering the patient pain free at 30 minutes; (2) reduction in pain scale at 15, 30, 45, and 60 minutes; (3) need for rescue medication from 15 minutes after treatment; (4) overall response to the treatment and overall functional disability; and (5) effect on associated symptoms.

Pain was rated as 0 for pain free, 1 for mild, 2 for moderate, 3 for severe, and 4 for very severe pain. A reduction in the pain scale was considered positive if the pain scale at each time point was at least 1 category less severe than the start of the headache.

Global response to treatment was considered positive if the patient indicated "good" or "excellent" and negative if "no effect" or "moderate." Associated symptoms, lacrimation, conjunctival injection, ptosis, periorbital swelling, miosis, blocked or running nose, facial sweating, nausea, photophobia, phonophobia, and restlessness were counted before and after treatment. Functional ability was assessed by the patients as being able to function normally, able to sit and converse, restless but able to interact with others, or very restless, including crying, pacing, and not being able to interact with others.

Patients recorded the date and time of the attack and the time the treatment was started. They also stated whether they felt adequate relief at 15 minutes. The need for rescue medication after 15 minutes was recorded. Adverse events were recorded up to 24 hours after each attack, as well as the time to the next attack, and their relationship to the treatment considered by the authors prior to unblinding the study.

Once the patients had treated 4 attacks, they returned the diaries to the investigators and called the gas supplier to collect the cylinders from their homes. Patients who did not respond were contacted by telephone, mail, or email to encourage return. For some patients whose diary was lost, it was possible to collect the data from telephone interview, email, or at further clinic follow-up visits (9 patients, 8% of the randomized population, 12% of completed results). This involved only the primary end point of being "pain free or adequate relief at fifteen minutes."

Data were collated on a Microsoft Excel spreadsheet. To eliminate observer bias, the patient diaries were not entered into the database until all patients had completed the study and the randomization code was not revealed until all data had been entered and quality checked by a second observer.

Patients who withdrew before finishing the study had data from their available attacks analyzed, while sub-

sequent untreated attacks were not considered. Missing data from those patients for whom there was primary end point data only were analyzed for the primary end point only. Patients took a rescue medication after 15 minutes of the study treatment were not included in subsequent data analysis because this would have invalidated the assessment of efficacy of the trial treatments. For incomplete diary data for secondary data points, we used the last observation carried forward approach.

Statistical Analysis

Based on outcomes from intranasal⁸ and subcutaneous⁶ sumatriptan in cluster headache, we considered that a 25% difference between placebo and active treatment would be clinically significant. We estimated that 55 patients were needed for a power of 80% and an α of 5%. A drop-out rate of 15% was allowed, and therefore 70 patients were to be recruited. Outcome data were treated as binary. Our planned analysis specifically allowed for the dichotomous outcome and used a generalized linear model and logistic regression approach to determine the effect of active treatment and treatment order, sex, and cluster headache type, ie, episodic vs chronic cluster headache.¹ Considering that the attacks are not strictly independent because the patients remain the same, a multilevel multivariate analysis²⁰ was performed (P.J.G.) using the software that has been developed by the Multilevel Project,²¹ MlwiN (version 2.0, University of Bristol, Bristol, England). From our initial protocol that aimed to avoid multiple comparisons, we did not test the secondary end points, preferring to report the numerical outcome. Significance was assessed at the .05 level.

RESULTS

A total of 334 patients were assessed for eligibility and 109 were randomized between March 2003 and April 2007. The FIGURE and eFigure (available at <http://www.jama.com>) shows the flow of patients through the trial and includes rea-

sons for exclusion or noncompletion being shown. The flowchart in the Figure accounts for all the patients screened, enrolled, randomized, treated, completed, withdrawn, and lost to follow-up. The reasons for doing so are included.

The blind was not broken for any patient during the study. The study population was comparable with the total recruited population (TABLE 1).

Fifty-seven patients with episodic cluster headache and 19 with chronic cluster

headache were available for the intention-to-treat analysis (Figure, Table 1). Fifty-five patients with episodic cluster headache and 18 with chronic cluster headache received all 4 treatments, 1 patient with episodic cluster headache received the first 3 treatments and another received the first treatment only. Among those with chronic cluster headache, 1 patient received the first 2 treatments only (Figure).

The difference between oxygen, 78% (95% confidence interval, 71%-85% for

150 attacks) and air, 20% (95% confidence interval, 14%-26% for 148 attacks) was statistically significant (Wald test, $\chi^2_5=66.7$, $P < .001$; TABLE 2).

In the logistic model, the terms for sex, cluster headache type, and attack order were not significant.

All secondary end points are reported numerically in Table 2. At all time points, oxygen was superior to air numerically. Similarly for the disability measures, use of rescue medication, and reduced in associated symptoms, oxygen was numerically superior to air.

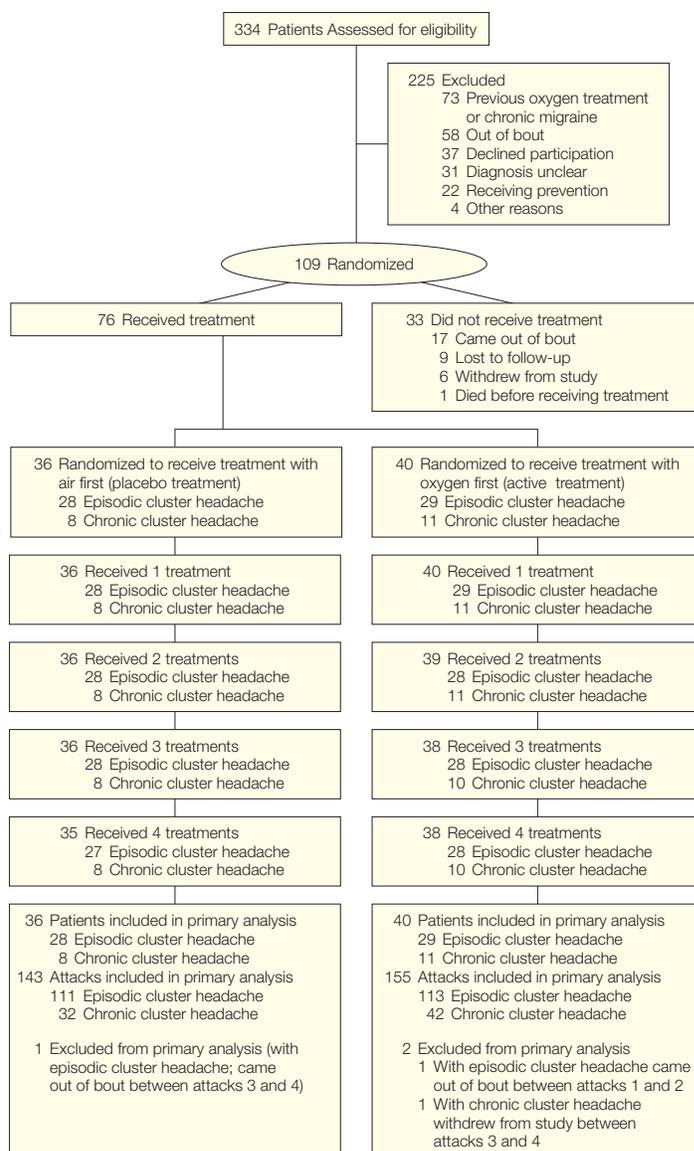
There were no serious adverse events related to the treatments. Of the patients who reported adverse events, the majority did not require any further action to be taken. One patient was admitted to the hospital with gallstones and gastritis that were unrelated to his cluster headache or the treatments. His medications were changed, and he resumed the trial. This change in medication was thought not to be significant for the trial because none of the medications were used as preventives for his cluster headache attacks and none would interact with the trial treatments. The rest of the adverse events are shown in TABLE 3.

There were few protocol violations, but in each case the patients were included in the analysis on an intention-to-treat basis. The protocol violations are shown in TABLE 4.

COMMENT

This trial provides strong evidence for the efficacy of high-flow-rate inhaled oxygen for the acute attack treatment of acute cluster headache compared with placebo. The primary end point of "pain free at 15 minutes" or "patient reported adequate relief at 15 minutes" was met. In addition for each of the secondary end points, oxygen was numerically superior to air. There were no serious adverse events related to the trial medications, which is as expected because oxygen has no known adverse effects at this dose for such short durations of inhalation. To our knowledge, this is the first adequately powered trial

Figure. Disposition of Patients From Screening to Study Completion



of high-flow oxygen compared with placebo, and it confirms clinical experience and current guidelines that inhaled oxygen can be used as an acute attack therapy for episodic and chronic cluster headache.¹⁶ Along with the recent development of an animal model of components of the disorder that has begun to provide insights into its potential mechanism of action,²² these data should provide impetus for the study of oxygen in cluster headache.

This randomized, crossover, placebo-controlled study was thought to be the best approach because patients, and their physicians, would ideally like to know whether a particular treatment was better for them as opposed to better generally for any group of their peers. The crossover design has been used successfully in trials of other acute attack medications in cluster headache and migraine.^{10,23} Moreover, recruitment considerations in a relatively rare condition make a crossover study pragmatic. Given the time to complete the study, a parallel group study may simply not be feasible in this group. A further advantage of a crossover study is there can be no imbalance between treated and control groups, since they are the same.

However, crossover designs add a level of complexity since 1 patient contributes at least 2 observations that are then not strictly independent. Regression analysis assumes that data points are independent. Therefore a multilevel multivariate analysis was performed²⁰ to take account of that issue. A strength of this crossover study came from the extraordinary commitment of the patients, which led to a very low drop-out rate in the treating patients and thus further supported the crossover design. Only 1 patient withdrew who could have completed further treatments and 2 stopped because their bout stopped; taken against a cohort of 76 at the start, this is a very good retention rate.

Conducting the study from the patients' homes was a study limitation that may have contributed to many patients either withdrawing or being lost

Table 1. Characteristics of Patients

	No. (%) of Patients	
	Randomized (n = 109)	Completed Study (n = 76)
Age, mean (SD), y	39 (9)	39 (10)
Sex		
Male	89 (82)	64 (84)
Female	20 (18)	12 (16)
Type of cluster headache		
Episodic	81 (74)	57 (75)
Chronic	28 (26)	19 (25)
Attack duration, mean (SD), min	83 (31)	83 (31)
	(n = 81)	(n = 57)
Average bout duration, mean (SD)/ episodic cluster headache per wk	11 (16)	12 (17)
Cluster headache history, mean (SD), y	12.3 (9.1)	11.3 (8.2)
Previous use, No.		
Sumatriptan injection	30	24
Sumatriptan oral or intranasal	16	10
Other triptans	12	9
Other analgesics	23	16
Low-flow oxygen (<4 L/min)	4	3
No documented previous cluster headache medications	31	19
	(n = 28)	(n = 19)
Patients taking preventive medications	4	2

to follow-up before treatment, and there is no data available as to why they withdrew. When one compares the treated population with the overall recruited population (Table 1), the study group is no different. Moreover, half the withdrawals were because patients with episodic cluster headache came out of their bout. This cannot be avoided because it is part of the biology of the condition. Our data provide some useful basis upon which to design further studies with this biology in mind. Some patients did not fill in the diaries for the full hour of each attack, and some did not fill the diary at all but conveyed information about the primary end point only, and therefore information relating to secondary end points was missing. Further explanations for missing secondary end point information include the discounting of data for periods after the rescue medication was taken because it was uncertain as to whether the effects were due to the trial treatment or the rescue medication. Given that oxygen will be used on an outpatient basis, our study reflects to

some extent the realities of its clinical use. Moreover, although trial populations are self-selecting almost by definition, that is an inescapable complication of the conduct of clinical trials.

Three hundred patients were screened for the trial but only 109 (33%) of cohort were randomized and only 23% completed the trial. Reasons for this included (1) patients were ineligible for the study if they had already taken oxygen or if their attacks were too short or long, (2) patients' not wanting to take a placebo when a clinically well-established treatment was available, and (3) patients with episodic cluster headache coming out of their bout of headaches before being able to complete the study.

As the study progressed the issue of preexposure became increasingly troublesome and would certainly limit such studies in the future. We took the view that to include patients familiar with high-flow oxygen would bias in favor of a positive outcome since patients who had failed would be less willing to take part. A disadvantage is that

Table 2. All End Points^a

	No. of Attacks	No. (%) of Attacks	
		Air	Oxygen
No. of attacks treated	298	148	150
Pain free at 15 min	298	29 (20)	116 (78)
Pain free at 30 min ^{b,c}	187	19 (24)	78 (72)
Reduction in pain scale at min			
15	256	25 (20)	88 (68)
20 ^{b,c}	209	28 (30)	93 (81)
30 ^{b,c}	182	28 (38)	93 (85)
60 ^{b,c}	167	38 (59)	95 (92)
Need for rescue medication from 15 min	249	76 (53)	30 (28)
Overall response to the treatment and overall functional disability ^{b,c}	248	18 (15)	75 (60)
Effect on associated symptoms ^{b,c}	250	40 (31)	81 (66)

^aPatients' data available for each end point varied with compliance in completing the diary.

^bIncluded last observation carried forward.

^cExcludes patients who took rescue medication.

Table 3. Adverse Events

Patient No.	Description of Adverse Event	Related to Treatment	Withdrew From Study	Outcome
1	Cough for 3 wk	No	No	No action taken
2	Died of acute myeloid leukemia before started the treatments	No	Yes	Withdrew before started treatments
3	Felt a bit tired	No	No	No action taken
4	Prolonged "spickier" [sic] pain	Possibly	No	No action taken
5	Admitted to hospital with gallstones and severe gastritis	No	No	Medications changed, resumed trial
6	Pins and needles, nausea, asthma attack	Probably not	No	No action taken
7	Head felt "more tender than if had taken injection"	Possibly	No	No action taken
8	Cylinder empty after 10 min	Yes	No	No action taken
9	Canister only lasted 12 min	Yes	No	No action taken

Table 4. Protocol Violations

Patient No.	Description of Protocol Violation
1	Was still taking verapamil during the trial (episodic cluster headache), but was included as still having attacks at a stable dose
2	Treatments taken out of their time order, but were clearly marked by the patient so easily analyzed in their correct order
3	For treatment round 3, cylinder ran out at 10 min, took rescue medication at 10 min
4	For treatment rounds 1 and 2: cylinders taken in wrong order but clearly marked by patient so were analyzed in their correct order
5	Admitted to hospital with gallstones and severe gastritis (Table 3)

our results do not necessarily apply to patients who have already used oxygen in that we could not predict whether they would continue to respond. On balance this seemed a question best suited to a further multiple attack study, perhaps addressing issues including ideal flow rate.

The study protocol stipulated that patients' attacks should be at least 45 minutes long. This does not entirely correlate with the International Headache Society criteria, which stipulate attacks may be as short as 30 minutes.¹ This duration was specified so that an acute attack treatment at 15 minutes would be short enough to be different from the patient's usual length of attacks. Neverthe-

less, it is possible in some patients that their attack was shorter than usual, regardless of the treatment used, and this may give false information about the efficacy of the treatment. The repeated attack and crossover designs as well as the placebo control are likely to have balanced this issue out. Conversely, a few patients took the treatment when the attack was already under way for some time and not at the commencement of the attack as specified in the protocol, again the placebo control and repeated attacks balance out this problem.

It is possible that if patients with either episodic or chronic cluster headache were analyzed separately, there may be a difference in the responsiveness between these 2 groups. However, only 21% of the study participants had chronic cluster headache,² and in the enrollment of this study, it was found that many patients with chronic cluster headache had tried oxygen treatment before. Therefore we could not analyze patients with chronic cluster headache as a separate group. In clinical practice the acute attack treatment for both types of headache is largely the same and does not discriminate between the 2 groups. We saw no statistical difference in the regression term for cluster type, although this may have been a false-negative.

Kudrow¹⁴ noted significant relief from cluster pain in 75% of 52 randomly selected out-patients treated with 100% oxygen administered through a facial mask at a rate of 7 L/min for 15 minutes. Oxygen at 6 L/min for 15 minutes was compared with air inhalation in a double-blind crossover study of 19 participants.¹⁵ Eleven patients used both gases. Nine out of 16 patients (56%) who used oxygen perceived a complete or substantial relief in 80% or more of their cluster attacks compared with only 1 of 14 patients (7%) who used air. The efficacy of inhaled oxygen has also been widely observed in clinical practice, such that it is recommended as a treatment for acute cluster headache by the European Federation of Neurological Societies treatment guidelines¹⁶ and is recom-

mended by the British National Formulary (<http://www.bnf.org>). However, until this study, there were no adequately powered placebo-controlled trials to confirm this view.

Current data and clinical practice advises the use of sumatriptan subcutaneously or by nasal spray^{8,24} or zolmitriptan intranasally,^{10,11} as an acute attack treatment for cluster headache. However, triptan agents have their drawbacks; namely, they are contraindicated in patients with ischemic heart disease or vascular disease.¹³ Furthermore, its use is limited to twice a day (subcutaneously) or 3 times a day (intranasally). Oxygen is not contraindicated in ischemic heart disease or vascular disease, and because it is given for short inhalations, it can be used more frequently than triptan agents and may therefore prove invaluable for patients with at least 2 to 3 attacks in 24 hours. One issue we have not addressed is a comparison of a triptan and oxygen. Given the data, a head-to-head comparison is both warranted and feasible.

One caveat would be the use of oxygen in patients who smoke, for whom there would be a perceivable incendiary risk with open flames near the cylinders. Many cluster headache patients are known to be smokers (67% in a large study²), and it would be unfortunate to deny this potentially very effective treatment to a large proportion of the cluster headache population. Therefore, smokers were not excluded from the study but were instructed not to have any smoking materials near the cylinders. None of the patients reported a smoking-related adverse event. Therefore, we can conclude that patients take the responsibility to keep the cylinders away from smoking and naked flames and that the benefit of oxygen as an acute attack therapy outweighs the incendiary risk in this population.

CONCLUSION

Treatment of patients with cluster headache at symptom onset using inhaled high-flow oxygen compared with pla-

cebo was more likely to result in being pain-free at 15 minutes. Even though issues such as dosing and further studies of repeated attacks are warranted, the use of placebo in this patient group will be increasingly complex to use. This work paves the way for further studies to optimize the administration of oxygen and its more widespread use as an acute attack treatment in cluster headache, offering an evidence-based alternative to those who cannot take triptan agents.

Author Contributions: Dr Goadsby had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Cohen, Goadsby.

Acquisition of data: Cohen.

Analysis and interpretation of data: Cohen, Burns, Goadsby.

Drafting of the manuscript: Cohen, Burns, Goadsby.

Critical revision of the manuscript for important intellectual content: Goadsby.

Statistical analysis: Cohen, Goadsby.

Obtained funding: Goadsby.

Administrative, technical, or material support: Burns. **Study supervision:** Goadsby.

Financial Disclosures: None reported.

Funding/Support: The trial was jointly sponsored by University College London and BOC Limited (now Linde Gases, Priestley Road, Guildford, Surrey, UK), who supplied the cylinders and the masks.

Role of the Sponsor: BOC (now Linde) gases initially supplied blinded materials and handled logistics of the cylinder delivery, assuming the role of sponsorship from a regulatory viewpoint and providing some administrative costs during the study. Dr Goadsby has provided advisory board advice to Linde and Air Products about cluster headache and its treatment, particularly the use of oxygen.

Previous Presentation: The data were presented in preliminary format at the XIVth International Headache Congress (Stockholm, June 2007).

Additional Information: The eFigure is available at <http://www.jama.com>.

Additional Contributions: We thank the Organisation for Understanding Cluster Headache (OUCH-UK) for assistance with recruitment of participants and M. S. Matharu, MRCP, for assistance with the initiation of the study, for which he received no compensation.

REFERENCES

- Headache Classification Committee of The International Headache Society. The International Classification of Headache Disorders (second edition). *Cephalalgia*. 2004;24(suppl 1):1-160.
- Bahra A, May A, Goadsby PJ. Cluster headache: a prospective clinical study with diagnostic implications. *Neurology*. 2002;58(3):354-361.
- Dexter JD, Weitzman ED. The relationship of nocturnal headaches to sleep stage patterns. *Neurology*. 1970;20(5):513-518.
- Sjaastad O, Bakkeiteig LS. Cluster headache prevalence. Vaga study of headache epidemiology. *Cephalalgia*. 2003;23(7):528-533.
- Goadsby PJ, Cohen AS, Matharu MS. Trigeminal autonomic cephalalgias- diagnosis and treatment. *Curr Neurol Neurosci Rep*. 2007;7(2):117-125.
- Ekbom K; The Sumatriptan Cluster Headache Study Group. Treatment of acute cluster headache with sumatriptan. *N Engl J Med*. 1991;325(5):322-326.
- Ekbom K, Monstad I, Prusinski A, Cole JA, Pilgrim AJ, Noronha D; The Sumatriptan Cluster Headache Study Group. Subcutaneous sumatriptan in the acute treatment of cluster headache: a dose comparison study. *Acta Neurol Scand*. 1993;88(1):63-69.
- van Vliet JA, Bahra A, Martin V, et al. Intranasal sumatriptan in cluster headache- randomized placebo-controlled double-blind study. *Neurology*. 2003;60(4):630-633.
- 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(9):1832-1839.
- Cittadini E, May A, Straube A, Evers S, Bussone G, Goadsby PJ. Effectiveness of intranasal zolmitriptan in acute cluster headache. A randomized, placebo-controlled, double-blind crossover study. *Arch Neurol*. 2006;63(11):1537-1542.
- Rapoport AM, Mathew NT, Silberstein SD, et al. Zolmitriptan nasal spray in the acute treatment of cluster headache: a double-blind study. *Neurology*. 2007;69(9):821-826.
- Paemeleire K, Bahra A, Evers S, Matharu MS, Goadsby PJ. Medication-overuse headache in patients with cluster headache. *Neurology*. 2006;67(1):109-113.
- Dodick D, Lipton RB, Martin V, et al; Triptan Cardiovascular Safety Expert Panel. Consensus statement: cardiovascular safety profile of triptans (5-HT_{1B/1D} Agonists) in the acute treatment of migraine. *Headache*. 2004;44(5):414-425.
- Kudrow L. Response of cluster headache attacks to oxygen inhalation. *Headache*. 1981;21(1):1-4.
- Fogan L. Treatment of cluster headache: a double blind comparison of oxygen vs air inhalation. *Arch Neurol*. 1985;42(4):362-363.
- May A, Leone M, Afra J, et al; EFNS Task Force. EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias. *Eur J Neurol*. 2006;13(10):1066-1077.
- Olesen J, Goadsby PJ, eds. *Cluster Headache and Related Conditions (Frontiers in Headache Research)*. Vol 9. Oxford, England: Oxford University Press; 1999.
- Cohen AS, Matharu MS, Burns B, Goadsby PJ. Randomized double-blind, placebo-controlled trial of high-flow inhaled oxygen in acute cluster headache. *Cephalalgia*. 2007;27:1188.
- Headache Classification Committee of The International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. *Cephalalgia*. 1988;8(suppl 7):1-96.
- Snijders TAB, Bosker RJ. *Multilevel Analysis: An Introduction to Basic and Advanced Multilevel Modelling*. London: Sage Publications; 1999.
- Yang M, Goldstein H, Heath A. Multilevel models for repeated binary outcomes: attitudes and voting over the electoral cycle. *J R Stat Soc Ser A Stat Soc*. 2000;163:49-62.
- Akerman S, Holland PR, Lasalandra MP, Goadsby PJ. Oxygen inhibits neuronal activation in the trigemino-cervical complex after stimulation of trigeminal autonomic reflex, but not during direct dural activation of trigeminal afferents. *Headache*. 2009;49(8):1131-1143.
- Matharu MS, Levy MJ, Meeran K, Goadsby PJ. Subcutaneous octreotide in cluster headache- randomized placebo-controlled double-blind crossover study. *Ann Neurol*. 2004;56(4):488-494.
- Ekbom K, Waldenlind E, Cole JA, Pilgrim AJ, Kirkham A. Sumatriptan in chronic cluster headache: results of continuous treatment for eleven months. *Cephalalgia*. 1992;12(4):254-256.