Original Article

Cephalalgia
An International Journal of Headache

International Headache Society

Cephalalgia
2022, Vol. 43(1) 1–10

DOI: 10.1177/03331024221128273
journals.sagepub.com/home/cep

SAGE

Continuous positive airway pressure in cluster headache: A randomized, placebo-controlled, triple-blind, crossover study

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Abstract

Background: Oxygen inhalation aborts cluster headache attacks, and case reports show the effect of continuous positive airway pressure. The aim of this study was to investigate the prophylactic effect of continuous positive airway pressure in chronic cluster headache.

Methods: This was a randomized placebo-controlled triple-blind crossover study using active and sham continuous positive airway pressure treatment for chronic cluster headache. Patients entered a one month's baseline period before randomly being assigned to two months' active continuous positive airway pressure treatment followed by a four weeks' washout period and two months' sham continuous positive airway pressure or vice versa. Primary outcome measure was number of cluster headache attacks/week.

Results: Of the 30 included participants (12 males, median age 49.5 years, min-max 20–66 years), 25 completed both treatment/sham cycles (two discontinued, three lost to follow-up). The median number of cluster headache attacks per week was reduced from 8.25 (0.75–89.75) attacks to 6.25 (0–56.00) attacks for active continuous positive airway pressure and to 7.50 (0.50–43.75) attacks for sham continuous positive airway pressure, but there was no difference in active versus sham ($p = 0.904$). One patient had a serious adverse event during active treatment, none occurred during sham treatment.

Conclusions: Continuous positive airway pressure treatment did not reduce the number of cluster headache attacks compared to sham treatment in chronic cluster headache patients.

Trial registration Clinicaltrials.gov: NCT03397563

Keywords

Chronic cluster headache, continuous positive airway pressure, CPAP, preventive treatment, sham

Date received: 22 May 2022; revised: 12 August 2022; accepted: 5 September 2022

Introduction

Chronic cluster headache (CCH) is a severe primary headache disorder (1) and limited therapeutic options exist (2,3). In a significant proportion of cluster

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headache (CH) patients, preventive drug therapy is not sufficient (2) and several surgical techniques have been tried (4–7). However, all surgical techniques have insufficient documentation on efficacy, many techniques have serious side-effects, and most are expensive (3,4). There is a need for new low-cost, non-invasive therapeutic options with a favorable side-effect profile.

Studies have found a high prevalence of obstructive sleep apnea and sleep-related headache in patients suffering from CH (8–10), and in CCH some recent studies have found obstructive sleep apnea prevalence of around 30% (11,12) compared to about 20% in the general population (13). Obstructive sleep apnea is also a headache trigger (14). Continuous positive airway pressure (CPAP) devices use air pressure delivered by a tube and facial mask to keep the airways open, and are used by patients with sleep disordered breathing. It is the standard treatment for obstructive sleep apnea (15) where air pressure is usually automatically adjusted between 4 and 20 cm H2O and adherence is defined as four hours of nightly use (16,17). Studies have shown that sham CPAP can be used as placebo in blinded, controlled intervention since it has been documented that it is difficult for patients to detect the difference between CPAP treatment and sham (18,19). Previous single cases of CH treated with CPAP have reported reduced attack frequency and longer periods of remission (20–22). In a case-control study where five CH patients used CPAP for one week, one reported improvement of headache (12). However, in another study, two patients with CCH and four with probable CH, all with obstructive sleep apnea, received CPAP treatment for six months, without any improvement (23). A review has suggested that CPAP could have a preventive potential and further investigation is needed (24).

The gold standard for sleep evaluation is polysomnography (25–29), but few studies using this have been performed in CH patients (11,23). The aim of the present study was to investigate whether CPAP could be helpful in CCH patients. Also, we wished to investigate the sleep pattern with polysomnography and see whether the presence of obstructive sleep apnea could predict treatment effect.

Methods and materials

Study design

This was a single-center randomized, triple-blind (patients, personnel and statistician) crossover study using active and sham CPAP treatment for CCH. We followed the recommendations of the his IHS guidelines for controlled trials of drugs in CH. These allow for crossover design (30).

Patients were recruited from the outpatient clinic at the Department of Neurology and Clinical Neurophysiology through advertisements in social media (n = 13), or they were referred from neurologists throughout the country (n = 17).

Inclusion and exclusion criteria

All patients aged 18–75 who fulfilled the diagnostic criteria for CCH according to International Classification of Headache Disorders 3 (ICHD-3 3.1.2) were eligible (1). Exclusion criteria were: disorders with contraindications for CPAP use, pregnancy, change in preventive headache or sleep medications less than one month prior to inclusion, severe depression or other psychiatric disorder, abuse of alcohol or illicit drugs, and other severe chronic pain conditions. Patients could use acute treatment of choice such as sumatriptan, oxygen or other throughout the study.

Flow of participants through the study

After the inclusion visit, all patients entered a one month baseline period followed by a treatment period of two months, then a four week washout period, and eventually a second treatment period of two months. For each patient, the study lasted six months. After the baseline period, all participants underwent a one night polysomnography registration. The next day a pulmonologist (LA) set the CPAP device as either real or sham CPAP for the first treatment period according to a randomisation list (see below). A respiratory nurse instructed the patient on how to use the CPAP device and selected a fitting ventilation mask. The need for adjustments of the CPAP equipment was evaluated the following week. After the washout period the treatment was changed to the treatment not used in the first period. CPAP use was registered locally and monitored through an online patient management system (Airview®). Throughout the study, patients were called by a headache nurse (GBG) every two weeks to record tolerability, adverse events and adherence to the protocol including CPAP use. The participants kept a paper headache diary for all six months, and a sleep diary in the baseline period and the last week in each treatment period. Thermal and pressure pain threshold measurements were conducted before randomization and directly after each treatment period (not described in this paper).

Polysomnography

Sleep quality was scored according to American Academy of Sleep Medicine (AASM) scoring manual 2.4 (2017) guidelines, and hypopneas according to both A and B criteria and to the "Chicago criteria" (31–33).

To score hypopnea, the strictest scoring criteria for respiration during sleep require an accompanying 4% desaturation (Criteria 1B), and the moderate criteria an accompanying 3% desaturation or an EEG-arousal is necessary (Criteria 1A). For the most liberal scoring criteria, hypopnea does not require arousal or desaturation if flow is reduced by $\geq$50%. If flow is reduced by 30–50%, accompanying 3% desaturation or EEG arousal was necessary. For all the different scoring criteria, participants with apnea-hypopnea index (AHI) $\geq$5 were categorized as having obstructive sleep apnea.

Randomisation and blinding

The sham treatment was designed according to previous published studies (18,19). The sham adapted components were made at the hospital's medical technical department and tested at the thoracic department. For CPAP naïve patients it should not be possible to detect if active or sham CPAP was given. There were no visible components revealing the adjustments, and the noise created by the machines was similar. Active treatment provided standard automatically adjusted air pressure ranging from 4 to 20 cm H2O. Sham treatment yielded a pressure of <3 cm H2O.

The Clinical Research Unit (CRU) at the Hospital generated a randomization list with blocks of six. This assigned each patient to one of two treatment sequences, 1: active CPAP – sham CPAP, or 2: sham CPAP – active CPAP. The pulmonologist was the only one who explicitly knew which treatment the patient received using a predetermined randomization list. He was not involved in the evaluation of the patients, but was consulted for the handling of adverse events. The ongoing treatment type (active CPAP or sham CPAP) was not recorded in the patients' medical record.

The experienced respiratory nurse would be able to detect small differences in sham vs active if looking inside the attached tubes when assembling the device, but was carefully instructed not to reveal the type of treatment, directly or indirectly, to the patient or to any other study personnel. All data were recorded without knowing the treatment sequence by a research assistant not otherwise involved in the study, under supervision of the independent neurophysiologist (ME) who never met the participants. After completion of the study, results and adverse event data were categorized under the headings treatment A and treatment B after receiving the list of sequences from the pulmonologist.

Outcome measures

All study outcomes were predefined by the study protocol. The primary outcome was the number of CH attacks per week during the four last weeks of active CPAP and sham CPAP treatment. Secondary outcomes were weekly number of cluster attacks during night-time (between 23.00 and 07.00), hours with CH and days with CH, during the four last weeks in each treatment period. In addition, secondary outcomes were CH attacks requiring use of sumatriptan or oxygen, sumatriptan doses, oxygen use events, acute headache pain medication intakes (all categories), attack duration, as well as headache intensity and presence of autonomic symptoms during CH attacks.

Adverse event registration

All adverse events were collected by the neurologic department. The thoracic department contacted the participant directly without revealing type of treatment when the discomfort was possibly related to the treatment equipment.

Definition of dropouts and intention-to-treat patients

A patient was counted a dropout if he or she discontinued the study before the second treatment, not providing viable data. Non-compliers included in the intention-to-treat (ITT) analysis were the patients who used the CPAP less than four hours per night, or kept a headache diary less than 90% of the days.

Data handling and statistics

We used IBM® **SPSS**® Statistics (version 27.0.1.0) to analyze the data.

The main hypothesis was that outcomes would not be different in the two treatment periods (CPAP and sham CPAP). We performed intention-to-treat comparisons between the active and placebo treatment periods using the paired nonparametric Wilcoxon signed rank test as group sizes were small and the outcome measures not normally distributed. The statistical significance was set to $p < 0.05$ for rejecting the main hypothesis. We also tested whether any of the periods were different from baseline.

A potential carry-over effect was evaluated by comparing the attack frequency in the sham period when it came first to when it came last.

Missing headache diary data were replaced by the daily mean in the same four weeks' period. When the patient recorded "many attacks all day", the number of daily attacks was imputed from the maximum number of attacks per day within the four weeks' period in question. All attacks registered by the patient as CH attacks were registered as such, even if each attack did not fulfill the criteria (e.g. too short or too long). As there were no earlier studies to build upon, no power calculation was performed prior to study start.

We assumed that it would be possible to recruit 30 patients with this condition during a two year period to get 20 evaluable patients, anticipating a dropout rate of 30%.

Ethics and study registration

The study was approved by the Regional Ethical Committee 2017/1491 and registered at ClinicalTrials.gov NCT03397563 (34) and conducted according to Good Clinical Practice (GCP) (35). We obtained written informed consent from all patients.

Results

In total 30 patients were included in the study between 16 January 2018 and 12 February 2019. Of the 30 participants, 25 completed the study with some study protocol violations.

A CONSORT flowchart regarding inclusions and exclusions/dropouts for the study is provided in Figure 1. The final visit was 21 August 2019. Background data of participants at inclusion are shown in Table 1. Thirteen patients used preventive drugs: one used four different (and had cervical

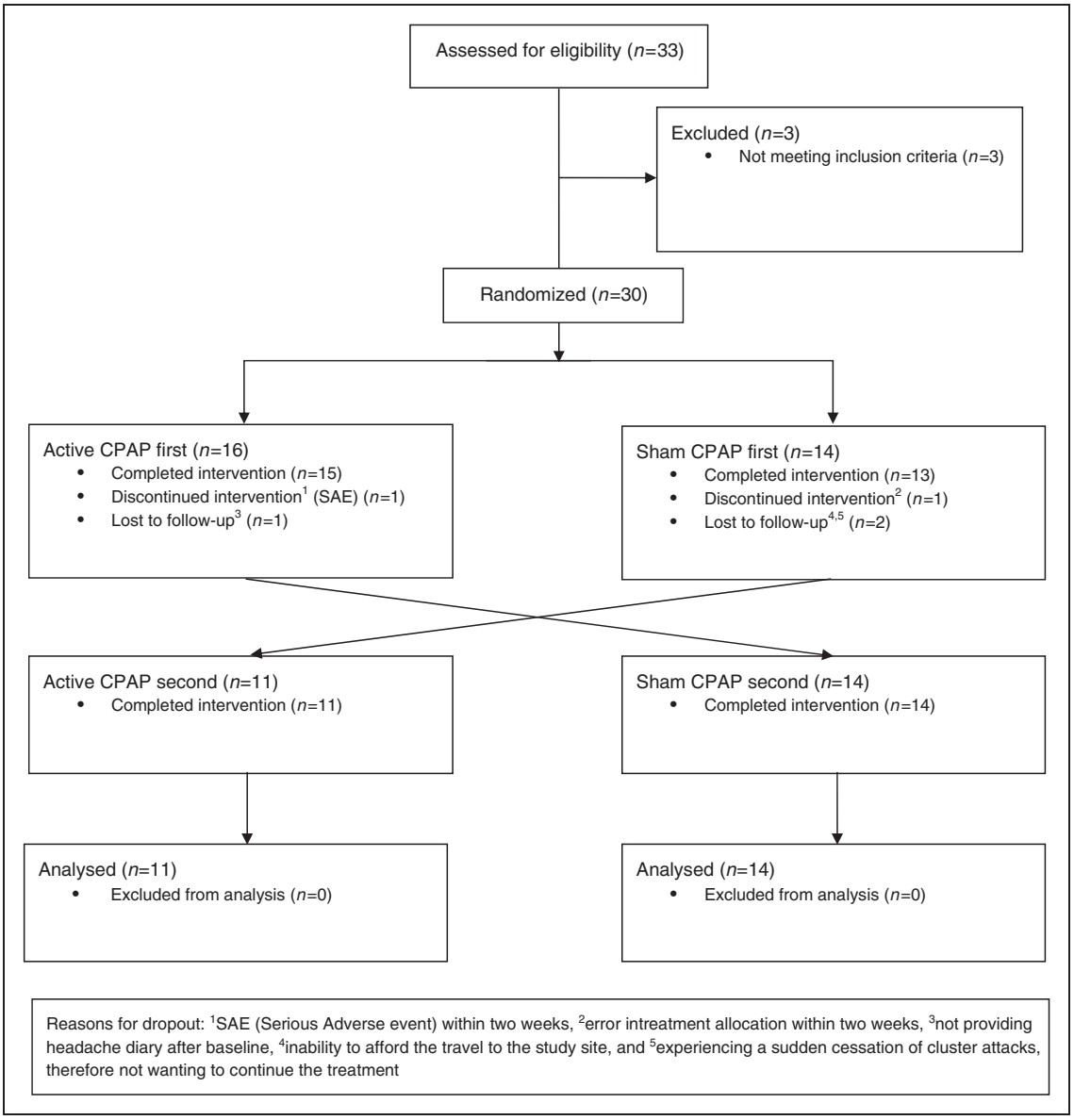

Figure 1. CONSORT flowchart of inclusions and exclusions/dropouts.

Table 1. Background data of participants at inclusion.[1]

Age, year (mean SD)	48 (10.21)
Gender (male/female)	12/18
Years since cluster headache diagnosis (mean SD)	10.60 (9.09)
Duration of cluster headache, years since symptom debut (mean SD)	16.43 (9.77)
Duration of chronic cluster headache, years (mean SD)	10.67 (9.03)
Mean attack frequency, per week (mean SD)	20.90 (21.35)
Days with cluster headache, per month (mean SD)	23.17 (7.42)
Body Mass Index (mean SD)	27.59 (4.97)
Preventive treatment (n)[2]	13 (43%)
Use of sumatriptan injections (n)	17 (57%)
Use of oxygen (n)	4 (13%)
Use of other triptans (n)	4 (13%)
Other acute medications (all categories)[3]	6 (20%)
No acute medication (n)	3 (10%)
MOH (n)	2 (7%)
Ethnicity	
Norwegians	27 (90%)
Non-Norwegians	3 (10%)

[1]At the inclusion visit (n = 30).
[2]Preventive treatment: Verapamil (n = 9), Topiramate (n = 6), Valproate (n = 1), Melatonin (n = 4), Candesartan (n = 2), cervical epidural spinal cord stimulator (n = 1) and SPG microstimulator (Pulsante device) (n = 1).
[3]Other acute medications used as first choice: oxycodone (n = 1), tolfenamic acid (n = 1), diclofenac (n = 1), combination of codeine and paracetamol (n = 1), paracetamol (n = 1), and tramadol (n = 1). Three patients did not use acute medication.
Reasons for treatment choice were concomitant medical history, lack of effect in combination with side-effects.

epidural spinal cord stimulator), one used three, four used two (of whom one had a SPG micro stimulator [Pulsante device®]), and seven used one preventive drug. The patients' medication was stable throughout the study.

Primary outcome

We observed a marked reduction from the baseline median of 8.25 attacks per week to 6.25 attacks for active CPAP and to 7.50 attacks for sham CPAP, but no difference in active versus sham periods ($p = 0.904$, Table 2). Thirteen patients (52%) had reduced numbers of CH attacks during both treatments and one patient (4%) had an increased number during both treatments. Of the patients experiencing a reduction of CH attacks during only one treatment, five (20%) had a reduction during active CPAP and six (24%) during sham CPAP.

Secondary outcomes

There was no difference in the secondary outcomes between active and sham CPAP (Table 2).

No obvious carry-over effect was found as the number of attacks with sham in treatment period one was not markedly higher than when sham came in period two. Rather, the tendency was the opposite. (10.66 attacks/week (n = 11) vs 13.26 attacks/week (n = 14), $p = 0.228$).

Obstructive sleep apnea

With the strictest scoring criteria for obstructive sleep apnea nine of 25 (36%) participants (not counting dropouts) had AHI $\geq$ 5, 17 (68%) with the moderate criteria, and 24 (96%) with the liberal criteria. Patients fulfilling the indication for obstructive sleep apnoea CPAP use, and who expressed a wish to continue the CPAP treatment after finishing the study (n = 6), were referred to their local hospital to continue their treatment. The sleep diary during baseline showed an average sleep per night (between 19.00 and 10.00) of 5.73 hours (n = 30) with an average awake period of 1.60 hours (n = 30). In addition, 40% (n = 30) reported sleep during the day more than once a week, and 13% was up before five every morning.

Post-hoc analyses

A post hoc analysis of the patients (n = 9) with obstructive sleep apnea according to the strictest scoring criteria showed no differences in attack rate between active CPAP and sham CPAP ($p = 0.813$). Also, there were no differences between active CPAP and sham CPAP in the six patients who continued using CPAP after the study ($p = 0.600$), but there was a significant reduction in baseline vs active, but not in baseline vs sham (Table 2). One of these patients was a frequent user of oxygen during cluster attacks. To investigate CPAP compliance, a subgroup analysis was done,

Table 2. Outcomes during both treatment periods (n = 25).

Variable[1]		Baseline	Active CPAP	Sham CPAP	Active versus Sham, (P value)[2]	Baseline versus Active (P value)	Baseline versus Sham (P value)
Primary outcome:							
Mean number of cluster headache attacks per week (SD)		15.69 (19.61)	12.45 (14.19)	12.27 (11.66)	0.904	0.023	0.036
Median (min–max)		8.25 (0.75–89.75)	6.25 (0–56.00)	7.5 (0.50–43.75)			
OSA[3] (n = 9)	Mean (SD)	18.42 (27.68)	10.50 (11.08)	10.72 (9.41)	0.813	0.066	0.066
	Median (min–max)	7.00 (2.25–89.75)	6.25 (0.25–36.00)	5.25 (2.00–28.75)			
Continued CPAP use (n = 6)	Mean (SD)	26.29 (32.25)	13,75 (12.62)	15.67 (9.42)	0.600	0.046	0.345
	Median (min–max)	11.50 (7.00–89.75)	7.38 (4.50–36.00)	14.75 (4.50–28.75)			
Self-reported CPAP use >4 hours both periods (n = 12)	Mean (SD)	22.98 (25.96)	16.17 (17.03)	15.25 (12.99)	0.893	0.054	0.013
	Median (min–max)	14.50 (0.75–89.75)	11.25 (0–56.00)	15.38 (0.50–43.75)			
Secondary outcome:							
Mean nightly cluster attack frequency per week (SD)		5.50 (5.57)	3.78 (5.28)	4.08 (5.36)	0.710	0.009	0.010
Median (min–max)		3.75 (0–22.00)	1.50 (0–23.00)	1.75 (0–23.00)			
OSA (n = 9)	Mean (SD)	5.81 (5.82)	2.17 (2.03)	2.66 (3.43)	0.514	0.021	0.018
	Median (min–max)	3.00 (0.75–17.75)	1.50 (0–6.75)	1.00 (0–10.25)			
Mean hours with cluster headache per week (SD)		14.30 (20.55)	13.86 (17.30)	13.36 (16.27)	0.563	0.898	0.677
Median (min–max)		5.19 (0.29–75.66)	5.02 (0–54.23)	7.13 (0.17–62.75)			
OSA (n = 9)	Mean (SD)	17.44 (25.70)	13.45(16.05)	12.79 (15.21)	0.374	0.575	0.678
	Median (min–max)	4.21 (0.59–75.66)	3.35 (0.13–43.96)	7.69 (1.08–43.88)			
Mean days with cluster headache per week (SD)		5.10 (2.17)	4.43 (2.63)	4.60 (2.50)	0.431	0.015	0.037
Median (min–max)		6.00 (1.00–7.00)	5.25 (0–7.00)	5.5 (0.50–7.00)			
OSA (n = 9)	Mean (SD)	5.28 (1.92)	4.11 (2.57)	4.31 (2.08)	0.553	0.046	0.018
	Median (min–max)	6.00 (2.00–7.00)	4.25 (0.25–7.00)	4.25 (1.50–7.00)			
Mean cluster headache intensity[4] (SD)		2.75 (0.72)	2.64 (0.73)	2.64 (0.77)	0.961	0.346	0.241
Mean cluster attack duration in minutes[5] (SD)		55.47 (46.22)	70.83 (52.76)	85.79 (90.31)	0.909	0.005	0.007
Attack characteristics:							
– with autonomic symptoms		69%	75%	74%	0.760	0.135	0.243
– treated with sumatriptan or oxygen		48%	43%	44%	0.344	0.334	0.381
– treated with sumatriptan intake		36%	35%	36%	0.814	0.477	0.379
– treated with oxygen		22%	16%	16%	0.507	0.433	0.470
– treated with acute headache pain medication (all categories)		19%	17%	21%	0.701	0.221	0.877

[1]The table displays values for primary and secondary outcomes. Attack characteristics are displayed as percentage of attacks.
[2]Wilcoxon paired rank test.
[3]OSA (obstructive sleep apnea) strictest criteria.
[4]Cluster headache intensity ranges from 1–4 (mild, moderate, strong, excruciating).
[5]If we remove one outlier (a patient reporting cluster attack lasting much longer than four hours), the average duration of cluster headache in the sham period goes down to 72.40.

suggesting that compliance and duration of CPAP use did not seem to be important factors ($p > 0.8$) for any of the subgroups (Table 2).

Compliance with protocol

Twelve patients reported CPAP use of more than four hours per night in both treatment periods (Table 3). Seven of these 12 could not be confirmed in the device report (Airview®, see above), thus sham was not always registered correctly by the device. Patient-reported causes for not using the device for at least four hours per night were upper-airway infections, allergies, unintentional removal of the CPAP mask during sleep and CH attacks causing very short periods of sleep during the night. The CPAP use decreased from the first to the second treatment period. Additional protocol deviations included minor changes in medications and erroneous or missing parts out of the headache diaries.

Adverse effects

Known side-effects of CPAP use, such as bloating, burping and gas were only reported in active CPAP treatment (Table 4). Nasal congestion, skin irritation, facial tenderness, pressure sores and acne were also more often reported during active CPAP. Upper-airway infections were common during both treatments. The number of patients that removed the CPAP during sleep was similar in the first treatment period, but more prevalent when the second treatment was sham CPAP. Only three reported breathing difficulties in the first treatment period, but when sham CPAP was the second treatment 71% complained of breathing difficulties and/or not getting enough air.

Table 3. Patient reported CPAP use.[1]

Hours of CPAP use per night	First treatment	Second treatment	Active CPAP	Sham CPAP
All (n = 25)				
Mean (SD)	4.90 (1.70)	3.78 (2.11)	4.58 (1.98)	4.10 (1.98)
Median (min–max)	5.00 (2–8)	4.00 (0–8)	5.00 (0–8)	4.00 (1–8)
OSA strict criteria (n = 9)				
Mean (SD)	4.17 (1.80)	3.50 (2.06)	3.67 (2,17)	4.00 (1.73)
Median (min–max)	4.00 (2–8)	4.00 (0–7)	4.00 (0–7.50)	4.00 (2–7)
Continued CPAP use (n = 6)				
Mean (SD)	5.33 (1.75)	4.67 (1.75)	5.17 (1.60)	4.83 (1.94)
Median (min–max)	5.50 (3–8)	4.00 (3–8)	4.50 (4–8)	4.50 (3–8)

[1]The table displays the patient reported CPAP use. Data from sham CPAP were not always registered accurately in the device. Of the 21 patients reporting use of CPAP four hours or more per night in the first treatment period, only 11 could be verified through data from Airview and memory cards from the CPAP device.

Table 4. Side effects/complaints possibly related to the CPAP-treatment (n = 30).

	Active treatment			Sham treatment		
Treatment period:	First	Second	Total	First	Second	Total
Bloating, burping and gas	4	1	5 (17%)	0	0	0 (0%)
Nasal congestion[1]	3	3	6 (20%)	0	3	3 (10%)
Dry mucosa[2] (mouth, nose, throat)	3	4	7 (23%)	4	2	6 (20%)
Ocular irritation[3]	3	0	3 (10%)	1	1	2 (7%)
Skin irritation, tenderness, sores and acne[4]	5	2	7 (23%)	1	2	3 (10%)
Difficulty breathing	1	4	5 (17%)	2	10	12 (40%)
Difficulty sleeping	1	0	1 (3%)	2	3	5 (17%)
Unintentional removal of the CPAP mask during sleep[5]	5	2	7 (23%)	6	5	11 (37%)
Upper airways infections	7	5	12 (40%)	5	3	8 (27%)
Headache	2	0	2 (7%)	1	2	3 (10%)
SAE discontinued[6] (most likely unrelated)	1					
SAE continued (most likely unrelated)		1				

Additional symptoms reported by a single patient during both treatments were dry cough, dizziness, nosebleed and nausea.
[1234]Symptoms were temporary and improved by remote adjustments of the CPAP by the respiratory nurse.
[5]Reported spontaneously by the patients when asked if they experienced any side effects and/or other health issues.
[6]Serious adverse event.

There were four serious adverse events registered in the study, none of which were deemed related to the CPAP treatment. One patient was excluded from further participation (discontinued intervention) because of cardiac problems four days into the first treatment period resulting in hospitalization. One patient was hospitalized because of high fever and influenza symptoms in the washout period but continued the study. One patient was hospitalized for a short period in baseline and again during active treatment owing to worsening of the CHs.

Adverse events most probably unrelated to the treatment were equally prevalent in the two treatment periods.

Discussion

This randomized blinded placebo-controlled crossover study did not show an effect of standard CPAP treatment on number of attacks in CCH. The same was true for a subgroup fulfilling criteria for obstructive sleep apnea at inclusion. Both active CPAP treatment and sham CPAP treatment resulted in a marked reduction in the number of cluster attacks compared to baseline. The difference from baseline may reflect the natural course of the disorder, regression toward the mean, a placebo effect related to the personal investment of study participation, or that both sham and CPAP actually had an equal effect. On a group level, the CPAP treatment was not well tolerated as 27 of 30 patients (90%) reported at least one adverse event. There were no treatment-related serious adverse events in the study. In previous studies researchers have identified subpopulations of CH patients diagnosed with obstructive sleep apnea and described some effect of CPAP treatment (11,12,23). As in our study, they were not able to identify which parameters could predict a significant impact on CH frequency from CPAP treatment. Probably many of our patients were not able to use the treatment properly, as their sleep was so disturbed. Also, a disordered lifestyle made it difficult for many of them to provide a reliable headache diary data. Most people need some time to adapt to the CPAP device when it is turned on at the beginning of a sleep period (16,17). The patients reported that facial tenderness in combination with repeated adaptation periods during night owing to sleep disruption by attacks made it hard to use the equipment. We observed that treatment adherence and motivation seemed to go down during the study as the CPAP use decreased markedly in the second treatment period. The lack of significant CPAP effect compared to sham CPAP on CH could be because obstructive sleep apnea in most patients is not a very important headache triggering factor or that CPAP is not the optimal treatment for this group. In this study there were more women than men (male-to-female ratio 2:3), in contrast to the male-to-female ratio in previously published cohorts of CCH which is 2-3: 1. In a recent study of diagnosed CH in Norway (36) the male to female ratio was 1.47. A Danish study supports this gender tendency (2:1) (37), and possibly more women than men are willing to participate in trials. According to the IHS guidelines (30) patients should have been without other preventive treatments. However, we believed it would be unethical and very difficult to recruit severely affected chronic patients if they had to stop medication with a partial effect.

Strengths and limitations

There are several strengths of this study. It is the largest study on CPAP in CH to date and to our knowledge one of the largest studies ever performed on this patient group. In addition, all patients underwent polysomnography. We used a rigorous sham controlled design. The crossover design increased statistical power and eliminated background differences within the group that could influence treatment efficacy. Blinding reduced bias in reporting and data handling. Further, 83% of the patients completed the study. The secondary analyses show that lack of measured effect was not caused by a carry-over effect. The washout period we applied also made this unlikely. A main weakness of the study was the missing data of headache attacks and the exact duration of CPAP use. No power calculation was performed due to lack of reliable previous studies to build upon. The study also showed that fragmented sleep in these patients made continuous CPAP use difficult, or almost impossible. CPAP was not well tolerated which reduced compliance with the protocol. Furthermore, the patients did not use the CPAP when they had seasonal allergies and upper respiratory tract infections which occurred frequently. Including the whole study population, not excluding minor protocol violators, and imputing missing data, increased the representativeness of the study for real life situations. Possible improvements for future studies include the use of electronic headache diaries and testing other obstructive sleep apnea treatments that might be easier for these patients to comply with.

Conclusion

In this first clinical intervention trial using sham CPAP and active CPAP in chronic cluster headache patients we found no significant effect on cluster headache on a group level.

Article highlights

- CPAP treatment did not reduce the number of cluster headache attacks compared to sham treatment in chronic cluster headache patients.
- CPAP treatment in this population was not well tolerated. Device improvements could possibly increase tolerability in future studies.

Acknowledgements

We are grateful for the contributions from all participants, and from our collaborators (nurse Nina Bredesen at Department of Thoracic Medicine, nurse Camilla Brattbakk at Department of Neuroscience, St. Olav University Hospital and staff engineer Marit Stjern at Department of Neuromedicine and Movement Science (INB), NTNU).

Author contributions

ET, ME, LA, LJS and GBG participated in the conception and design of the study, and in the acquisition, analysis and interpretation of data. GBG wrote the first draft of the manuscript.
MHB and KIM participated in the acquisition and interpretation of the data.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: GBG has received consultant fees from Novartis, Teva, Allergan and Lundbeck. LA reports no conflict of interest. LJS has received lecture fees or research funding from Allergan, Teva, Lundbeck, Novartis and Lilly. ME has received lecture fees from ResMed and Philips. KIM reports no conflict of interests. MHB reports institutional fees from contract work from market authorization holders of valproate, consultancy fees from Novartis Norway, advisory board honoraria from Jazz Pharmaceuticals, Angelini Pharma and Eisai, and speaking honoraria from Teva and from Lilly outside the submitted work. ET has received consultant fees from Allergan, Amgen, Novartis, Eli Lilly, Teva, Roche, Lundbeck, is a board member and shareholder in Palion Medical AS, and shareholder in Nordic Brain Tech AS.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The study was be performed as part of the regular activities of personnel at the Norwegian Advisory Unit on Headaches and funding from the Liaison Committee for Education, Research and Innovation in Central Norway (Samarbeidsorganet).

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