Safety and efficacy of prednisone versus placebo in short-term prevention of episodic cluster headache: a multicentre, double-blind, randomised controlled trial

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Summary

Background Prednisone is commonly used for initial short-term therapy of episodic cluster headaches before preventive medication such as verapamil becomes effective, but this strategy has not been tested in large randomised trials. We aimed to access the safety and efficacy of this treatment approach.

Methods This study was a multicentre, randomised, double-blind, placebo-controlled trial done in ten specialised headache centres in Germany. Patients with episodic cluster headaches who were aged between 18 and 65 years and within a current pain episode for not more than 30 days, received 100 mg oral prednisone for 5 days followed by tapering of 20 mg every 3 days, or matching placebo (17 days total exposure). All patients received oral verapamil for long-term prevention, starting with 40 mg three times daily and increasing to 120 mg three times daily by day 19; patients then continued with verapamil 120 mg throughout the study. Randomisation was computer-generated at a 1:1 ratio by use of an interactive web-response system, with stratification according to age, sex, and participating site. Participants, investigators, and those assessing outcomes were unaware of treatment allocation. The primary endpoint was the mean number of attacks within the first week of treatment with prednisone compared with placebo. An attack was defined as a unilateral headache with moderate-to-severe intensity of at least five on a numerical rating scale. All efficacy and safety analyses were done in the modified intention-to-treat (mITT) population, which consisted of all patients who had been randomly assigned to a trial group and received at least one dose of prednisone or placebo. The study was stopped early due to slow recruitment and expired funding. The study was registered with EudraCT (2011–006204–13) and with the German Clinical Trials Register (DRKS00004716).

Findings Between April 5, 2013, and Jan 11, 2018, 118 patients were enrolled in the study. Two patients dropped out immediately and 116 patients were randomly assigned (57 patients to prednisone and 59 patients to placebo); 109 patients were included in the mITT analysis (53 patients assigned to prednisone and 56 patients assigned to placebo). Participants in the prednisone group had a mean of 7·1 (SD 6·5) attacks within the first week compared with 9·5 (6·0) attacks in the placebo group (difference –2·4 attacks, 95% CI –4·8 to –0·03; p=0·002). Two serious adverse events occurred, both in the placebo group (inguinal hernia and severe deterioration of cluster headache). A total of 270 adverse events were observed: in the prednisone group, 37 (71%) of 52 patients reported 135 adverse events (most common were headache, palpitations, dizziness, and nausea) and in the placebo group, 39 (71%) of 55 patients had 135 adverse events (most common were nausea, dizziness, and headache).

Interpretation Oral prednisone was an effective short-term preventive therapy in our population of patients with episodic cluster headache. Our findings support the use of prednisone as a first-line treatment in parallel to the up-titration of verapamil, although the efficacy of prednisone alongside other long-term prevention requires additional investigation.

Funding German Federal Ministry for Education and Research.

Introduction

Cluster headache is a primary headache disorder characterised by intense unilateral attacks of facial and head pain, lasting between 15 and 180 min and accompanied by trigeminal autonomic symptoms. Attacks occur from once every other day to up to eight times per day, with each episode lasting between 1 week and several months. Headache episodes in people with episodic cluster headache (also known as bouts) are followed by symptom-free intervals that have a duration of 3 months to several years and usually follow a circadian as well as a circannual rhythm.[1]

Treatment for episodic cluster headaches consists of attack-stopping treatment (eg, high-flow oxygen, triptans, or intranasal lidocaine) in addition to preventive medication (eg, verapamil or lithium) to reduce the number of attacks and potentially terminate the current bout.[2–4]

Lancet Neurol 2020

Published Online November 24, 2020 https://doi.org/10.1016/S1474-4422(20)30363-X

See Online/Comment https://doi.org/10.1016/S1474-4422(20)30402-6

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Research in context

Evidence before this study

We searched PubMed using the search terms "cluster headache" AND "treatment". This search resulted in 2154 results between database inception and June 5, 2020 in English. We then narrowed the search terms to "episodic cluster headache" AND "treatment", which resulted in 141 results for further evaluation. Original articles were preferred but comprehensive reviews, guideline recommendations, and papers on the history of cluster headache treatment were also included.

The current standard of care and guideline-recommended first-line treatment for cluster headache prophylaxis is verapamil; lithium is recommended, but well powered randomised trials of this drug are missing so far. Corticosteroids in different dosages are also recommended, but always referred to as not having proven effective in randomised controlled trials yet. Recommended dosages range between 100 mg orally and 500 mg intravenously over changing time intervals. Occipital nerve blocks using corticosteroids were investigated in two controlled trials and are often recommended as initial treatment until verapamil becomes effective, but repeated injections are needed, so that the acceptance by physicians and patients is limited.

Added value of this study

This multicentre, randomised, controlled, clinical trial evaluated the safety and efficacy of 100 mg prednisone applied orally over 5 days then tapered by 20 mg every 3 days. This regimen resulted in a total corticosteroid exposure of 17 days, which is presumably enough time for verapamil to begin working sufficiently as long-term prevention. We were able to show a robust effect of prednisone on the reduction of cluster headache attacks with recorded adverse events similar to placebo. We provide a treatment regimen that could help patients through their first weeks of a new cluster headache episode.

Implications of all the available evidence

Few advances have been made in the treatment of cluster headache in the recent years and high-quality clinical trials were scarce. Treatment recommendations have been based mainly on expert opinion and specialists' treatment habits. The trial with galcanezumab, a calcitonin gene-related peptide monoclonal antibody, and our trial are among the few randomised controlled studies in patients with episodic cluster headache. Our findings suggest that patients with episodic cluster headache without any concurrent health issues could receive prednisone treatment for each new cluster headache episode along with the initiation of preventive treatment for the longer term. Future research should investigate which long-term preventive medications prednisone could be combined with for maximum benefit.

Verapamil has shown efficacy in one randomised placebo-controlled study.[5] Due to verapamil's delayed onset of action of usually 10–14 days and slow titration to assure tolerability, international guidelines recommend initiating short-term preventive treatment with corticosteroids to suppress or at least attenuate cluster headache attacks until long-term prevention becomes effective.[6,7] Lithium also has a delayed onset and requires slow titration to prevent side-effects. Lithium did not show efficacy in one randomised clinical trial in patients with episodic cluster headache.[8] Corticosteroid treatment in cluster headaches is widely used in clinical practice, but the absence of a standardised dosage regimen, continued discussion about its uncertain clinical benefits, and potential side-effects result in limited use by pain specialists, general neurologists, and affected patients. The concern about side-effects is not generally based on realistic probability, but often confuses transient and infrequent short-term effects (eg, glaucoma, increased blood pressure, fluid retention, mood swings, etc) and common long-term side-effects (eg, suppressed adrenal gland hormone production or osteoporosis).[9] Several carefully described studies and case series assessing the efficacy of corticosteroids for cluster headache have been done over the past 40 years, but do not completely satisfy modern standards in terms of randomisation procedures, blinding of participants, and data analysis.[8–14] The aim of the prednisone in cluster headache (PredCH) trial was to assess the efficacy and safety of 100 mg oral prednisone daily for the short-term preventive treatment of episodic cluster headaches.

Methods

Study design and participants

The multicentre, randomised, double-blind, placebo-controlled trial was done at ten sites in Germany. All study sites were specialised pain and headache centres. The full study design was published previously.[15] The study was approved by the ethics committees at all participating study sites. The study conformed to the Declaration of Helsinki, the German legal regulations of the medicinal products act, and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines.

All patients provided written informed consent before enrolment in the study. Eligible patients were aged 18–65 years and had a history of episodic cluster headaches according to the International Classification of Headache Disorders.[16] The age limit was 65 years to minimise adverse events due to potential comorbid conditions, such as cardiac arrhythmias or metabolic comorbidities, that could be affected by verapamil or prednisone. Patients had to be of legal competence, with sufficient knowledge of written and spoken German, and capable of attending

regular follow-up visits. Patients were required to have had at least one previous cluster headache episode, with a mean duration of previous untreated episodes of at least 30 days, a duration of the current episode of less than 30 days, and an expected remaining duration of the current episode of more than 30 days. The duration of the current episode was established by the patients' self-reported history and marked the beginning of cluster headache attacks in the current pain episode until study inclusion. The expected duration was estimated based on previous patient experience. We included only patients with a duration of previous cluster episodes of more than 30 days to minimise the influence of early natural spontaneous remission of cluster episodes. The previous cluster episode should have ended at least 30 days before inclusion in the study. Most patients were already known to their recruiting study site and were identified to be screened for study inclusion when they presented with a new pain episode without preventive medication prescription. They were deemed ineligible for screening when medical records or prescreening contact via telephone or email found that patients were no longer in their current bout, were in their bout for too long, or had already started on preventive medication.

The following were exclusion criteria: history of severe allergic diathesis; intolerance or contraindications against verapamil, prednisone, pantoprazole, or potassium; diabetes; cardiac arrhythmia; arterial hypotension or hypertension; gastrointestinal ulceration; severe osteoporosis; glaucoma; tuberculosis; current infection; poliomyelitis; lymphadenitis; chronic cluster headache according to the International Classification of Headache Disorders;[16] or use of prednisone or verapamil less than 30 days before study inclusion. Participation in a different clinical trial less than 30 days before inclusion, previous inclusion into PredCH, parallel participation in a different clinical trial, ongoing substance or alcohol abuse or dependence, psychiatric disease with risk of suicide, severe chronic or terminal illness, or HIV infection were also exclusion criteria. The criteria also excluded the following participants: those who had chronic disease that caused impairment of absorption, metabolism, or secretion of study medication; patients with chronic hepatic disease or neuromuscular disease; women who were nursing or pregnant; fertile women with insufficient contraception; and participants who did not give consent.

Patients could use their preferred choice of acute attack treatment, but were limited to oral, intranasal, or subcutaneous triptans, high-flow oxygen, intranasal lidocaine, ergotamine, and oral analgesics. The detailed study protocol including the complete inclusion and exclusion criteria, as well as permitted and restricted concomitant medication, was published previously.[15]

Randomisation and masking

All enrolled and eligible patients were randomly assigned 1:1 to receive either oral prednisone or placebo for 17 days. Randomisation was done by means of a central computer-generated random sequence with an audit trail and an interactive web-response system (TenALEA) with stratification according to age (<30 years *vs* ≥30 years), sex, and participating site. Study staff at each study site enrolled patients and used the computer system to randomly assign the patients; the staff took care of the patients throughout the trial. The trial medications (prednisone and placebo) had an identical appearance for tablets and packaging and were produced and labelled according to good manufacturing practice at the University Pharmacy Heidelberg, Heidelberg, Germany. The random code of the trial medication was implemented in the web-response randomisation system. Unmasking via emergency envelopes was not done in this trial. Overall, only two people were unmasked: the manufacturer at the University Hospital Pharmacy, Heidelberg and one person at the trust centre of the Center for Clinical Trials Essen. These people were not involved in the treatment, procedures, conduct, or analysis of this trial.

Procedures

Included patients had to be in an active cluster headache episode without any current prophylactic medication. Screening (visit –1) and randomisation (visit 0, baseline) could occur on the same day, but not more than 3 days apart (visit days –1 and 0). The mean number of cluster headache attacks at baseline was recorded from patients' memory of the past 3 days for each day separately before randomisation. Day 7 was 7 days after randomisation and day 28 was 28 days from randomisation. Prednisone was started the morning of the day after randomisation at 100 mg per day for 5 days, and was then tapered by 20 mg every 3 days.[15] All patients received an increasing dose of oral verapamil, starting at day 1 after randomisation with 40 mg three times per day. The dose was increased every 3 days by 40 mg according to a predefined dosing scheme to a maximum of 360 mg per day.[15] The total study duration was 28 days. Patients were encouraged to continue treatment with verapamil or switch to lithium once finished. All participating patients received 20 mg pantoprazole to prevent gastric side-effects of prednisone.

Patients were asked to record the following information in their pen and paper-based diaries during each day in the double-blind period: number of cluster headache attacks including duration and pain intensity on a numerical rating scale (NRS; 0=no pain to 10=worst imaginable pain), location of pain, autonomous symptoms (lacrimation, nasal congestion, conjunctival injection, tearing, ptosis, miosis, or face sweating on the side of pain), and use of acute medication (drug, dosage, and effectiveness) as well as oxygen. Attacks were defined as unilateral headache with moderate-to-severe intensity of at least 5 on the NRS.

For the **diaries** see www.predch.de/diary.pdf

At the screening visit and the visit on day 28, a standardised overall health interview, as well as physical and neurological examinations, were done. ECG and vital signs were obtained before verapamil administration.

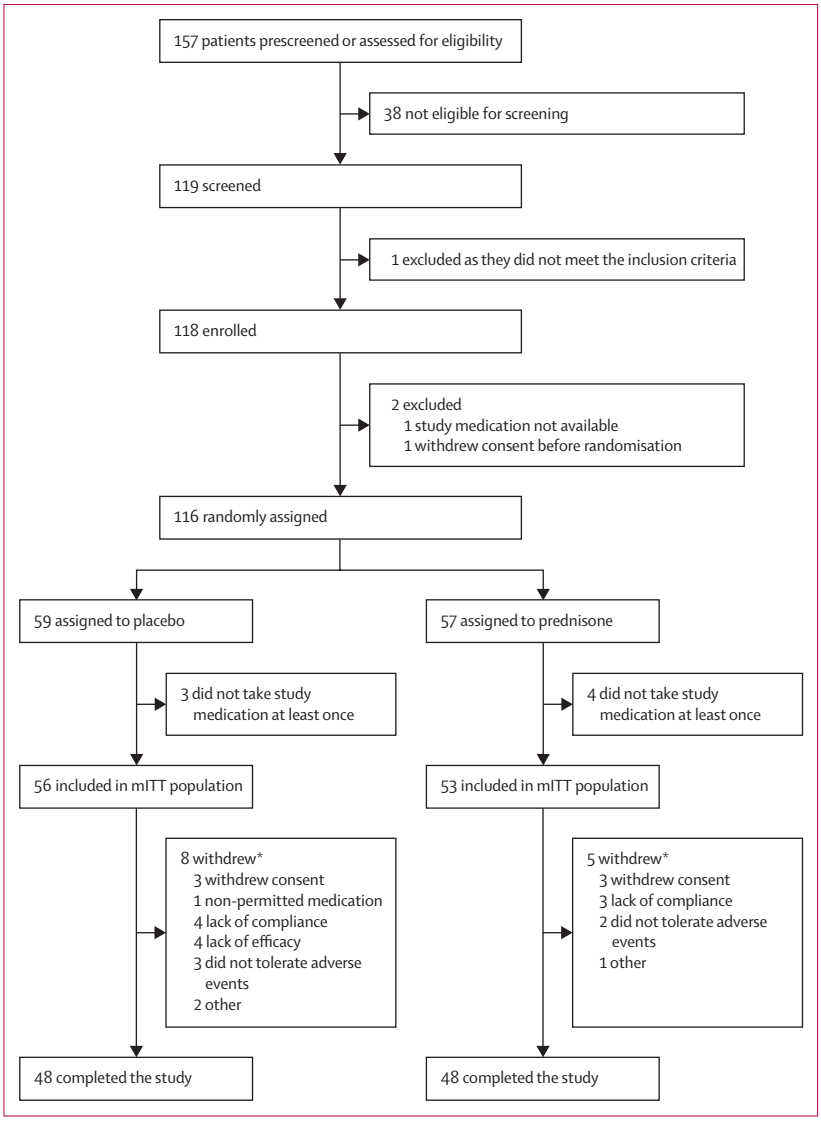

Figure 1: **Trial profile**
The mITT population consisted of 109 patients (53 prednisone and 56 placebo). The mITT population included only patients that took at least one dose of study medication. Patients were ineligible for screening when medical records or prescreening contact via telephone or email found that patients were no longer in their current bout, were in their bout for more than 30 days, or had already started on preventive medication. mITT=modified intention-to-treat. *Patients could have more than one reason for withdrawal.

Urine and blood samples were collected to screen for hyperglycaemia, diabetes, electrolyte disturbances, and systemic infection before prednisone treatment and again after study completion. Individual treatment tolerability was assessed using the clinical global impressions (CGI) scale.[17]

Outcomes

The primary endpoint was the mean number of cluster headache attacks within the first week of treatment with prednisone compared with placebo. We had the following secondary endpoints: number of cluster attacks from day 1 to day 28 of study participation; the number of days with cluster headache attacks from day 1 to day 7 and from day 1 to day 28; episode cessation (yes or no), defined as no further attacks in the 3 days before follow-up on day 7 and day 28; acute medication intake until day 7 and until day 28; responder rate, defined as a ≥50% reduction in the number of daily attacks, was measured until day 7 and then until day 28 as compared with mean number of attacks during the last 3 days before inclusion; presence or absence of trigeminal autonomic symptoms (yes or no) after 7 days and 28 days (lacrimation, nasal congestion, rhinorrhoea, conjunctival injection, ptosis, miosis, or facial sweating on side of pain); impact on quality of life, assessed at screening and day 28 using the 12-Item Short Form Survey (SF-12),[18] Headache Impact Test 6 (HIT-6),[19] and General Depression Scale (Allgemeine Depressionsskala, ADS);[20] and pain intensity (mean) of cluster attacks in the first 7 days and the first 28 days after initial treatment as measured by the NRS.

Safety and tolerability assessment included the recording of spontaneous adverse events and serious adverse events. Adverse events, infections, and dropouts due to the effects of adverse events were monitored and evaluated by the independent data safety monitoring board, which consisted of a neurologist, cardiologist, and biometrician. CGI was assessed on day 7 and day 28.[17]

Statistical analysis

The sample size calculation was based on the parametric evaluation of a two-group comparison using a Student's *t* test, although a more complex model was used as the primary test. Calculations were performed using nQuery software (version 6.0). On the basis of data from the literature, we estimated the average frequency of headache attacks as 8·25 (SD 4·2) attacks per week for the first week and assumed equal standard deviation in both groups. Requiring α=0·05 (two-sided) while aiming at a comparison-wise power of 1–β=0·9, a sample size of 122 patients was necessary for the intention-to-treat analysis to detect a mean difference of 2·5 in average mean frequencies of headache attacks during the first week between treatment by oral prednisone versus placebo. To address a potential dropout rate of 15% overall, another 22 patients had to be randomly assigned. Thus, we aimed to include 144 patients with episodic cluster headache.

All efficacy and safety analyses were done in the modified intention-to-treat (mITT) population, which consisted of all patients who had been randomly assigned to a trial group and received at least one dose of either prednisone or placebo (full analysis set). The mITT analysis excluded patients who were deemed ineligible after randomisation, or patients who did not start treatment.[21] Per-protocol analyses were also done for safety.

Data are summarised as arithmetic mean and standard deviation for continuous variables and as absolute and relative frequencies for categorical variables. The primary endpoint was analysed by a generalised linear mixed model with sex, age, and treatment included as fixed

effects and site as a random effect. To assess the robustness of the primary endpoint analysis, a sensitivity analysis without consideration of covariables was done by Mann-Whitney-Wilcoxon test. Secondary endpoints were analysed by Mann-Whitney-Wilcoxon tests for continuous endpoints and with an (exact) Monte Carlo estimation of the χ^2 test for categorical endpoints. As there was no adjustment for multiple testing of the secondary endpoints, all secondary and the results of safety analyses should be regarded as exploratory.

To assess the robustness of the primary endpoint results, sensitivity analyses for the per-protocol population and best and worst assessments were done. In the best-case calculation, the missing values of the primary endpoint were regarded as no cluster headache attack (best observation carried forward). In the worst-case calculation, the missing values of the primary endpoint were considered as days with cluster headache attack (worst observation carried forward). Reasons for exclusion in the per-protocol populations were missed visit at day 7 and day 28, no headache diary, no cluster headache, and no medication intake. The analyses were described in the study protocol as published elsewhere.[15]

The study was registered with EudraCT (2011–006204–13) and with the German Clinical Trials Register (DRKS00004716).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and vouch for the accuracy and completeness of the data, as well as for the reporting of adverse events. The first author had final responsibility for the decision to submit for publication.

Results

The first patient was enrolled on April 5, 2013. Enrolment was halted on Dec 15, 2017, after 5 years, without the planned sample size having been reached, because of recruitment difficulties and expired funding. No interim analysis was done before halting the study. The last patient finished the study on Jan 11, 2018 (figure 1). Of 157 patients who were documented as prescreened, 119 were screened and 118 were randomly assigned, but two discontinued before allocation to any study group. Of the remaining 116 patients, 59 (51%) were assigned to the placebo group and 57 (49%) were assigned to the prednisone group, of whom 56 (48%) in the placebo group and 53 (46%) in the prednisone group were eligible for the mITT analysis (full analysis set). The trial groups were balanced with respect to demographic and clinical characteristics (table 1).

The mean number of attacks within the first week of treatment (day 1–7) was 7·1 (SD 6·5) in the prednisone group compared with 9·5 (SD 6·0; difference –2·4, 95% CI –4·8 to –0·03 p=0·002) in the placebo group (table 2, figure 2). Therefore, the mean number of cluster headache attacks during the first week of treatment was 25% less in the prednisone group than in the placebo group. The assessment showed similar results in favour of prednisone treatment compared with placebo of mean attacks of 7·1 (SD 6·5) versus 9·8 (6·2) for best observation carried forward (difference –2·7, 95% CI –5·1 to –0·3, p<0·0001), and mean attacks of 7·4 (SD 6·4) versus 10·6 (7·6) for worst observation carried forward (–3·2, –5·9 to –0·5, p<0·0001; appendix pp 7–10).

See Online for appendix

Secondary endpoints are summarised in table 2. The number of cluster headache attacks after 28 days in the prednisone group was still reduced compared with placebo: 15·6 (SD 15·5) versus 20·2 (15·0) attacks (difference –4·7, 95% CI –11·0 to –1·7, p=0·0356). After 7 days, the number of days with cluster attacks was 3·9 (SD 2·4) versus 5·1 (1·8) days (–1·2, 95% CI –2·0 to –0·3 p=0·0141). At day 28, the number of days with cluster headache attacks was 8·8 (SD 7·1) for the prednisone group versus 11·9 (7·1) for the placebo group (–3·2, 95% CI –6·9 to 0·5; p=0·0559). Cluster headache attacks were classed as having ceased after the first 7 days in 17 (35%) of 49 patients with prednisone compared with four (7%) of 54 patients with placebo (table 2). After 28 days, the number of patients who became pain free further increased, but there were no group differences (table 2). The need for acute medication was higher in the placebo group compared with the prednisone group at both time points (table 2; appendix p 1). At least 50% reduction in attack frequency at day 7 was reported by 25 (49%) of 51 patients with prednisone treatment compared with eight (15%) of 55 patients with placebo (table 2). The proportion of participants with at least 50% reduction in attack frequency increased to 36 (71%) of 51 patients

	Prednisone (n=53)	Placebo (n=56)
Age, years	42·4 (11·4)	40·3 (10·5)
Male sex	44 (83%)	47 (84%)
Female sex	9 (17%)	9 (16%)
German nationality	52 (98%)	54 (96%)
Height, cm	180·0 (9·8)	179·3 (8·1)
Bodyweight, kg	82·2 (13·0)	81·3 (15·7)
BMI, kg/m²	25·3 (3·4)	25·2 (3·8)
Disease duration, years	7·3 (3·7)	8·4 (3·9)
Cluster headache attacks in the baseline period*	7·1 (4·0)	6·2 (4·6)
Pain intensity in the baseline period, NRS*	6·6 (1·8)	6·7 (1·7)
Previous cluster headache treatment	52 (98%)	54 (97%)
Verapamil	20 (38%)	21 (38%)
Triptans	42 (79%)	37 (66%)
Corticosteroids	11 (21%)	20 (36%)
Analgesics	8 (15%)	16 (29%)

Data are mean (SD) or n (%). BMI=body-mass index. *Baseline period was day –3 to day 0. NRS=numerical rating scale (0=no pain to 10=worst imaginable pain).

Table 1: **Characteristics and demographics at baseline**

	Prednisone (n=53)	Placebo (n=56)	Difference (prednisone–placebo)	p value
Primary endpoint				
Cluster headache attacks in the first treatment week, baseline to day 7	7·1 (6·5)	9·5 (6·0)	−2·4 (−4·8 to −0·0)	0·002* and 0·0146†
Secondary endpoints				
Cluster headache attacks, baseline to day 28	15·6 (15·6)	20·2 (15·0)	−4·7 (−11·0 to −1·7)	0·0356†
Days with cluster headache attacks				
Baseline to day 7	3·9 (2·4)	5·1 (1·8)	−1·2 (−2·0 to −0·3)	0·0141†
Baseline to day 28	8·8 (7·1)	11·9 (7·1)	−3·2 (−6·9 to 0·5)	0·0559†
Complete cessation of cluster headache attacks‡				
Day 7	17/49 (35%)	4/54 (7%)	27 (12 to 42)	0·0006§
Day 28	25/41 (61%)	29/43 (67%)	−6 (−27 to 15)	0·6510§
Doses of acute medication				
Baseline to day 7	6·0 (6·8)	9·2 (6·6)	−3·2 (−6·0 to −0·3)	0·0012†
Baseline to day 28	12·2 (13·4)	17·1 (13·4)	−4·9 (−11·9 to −2·1)	0·0373†
Patients with at least 50% reduction of cluster headache attacks compared with baseline (day −3 to 0)				
Day 7	25/51 (49%)	8/55 (15%)	34 (18 to 51)	0·0001§
Day 28	36/51 (71%)	25/55 (45%)	25 (7 to 44)	0·0110§
Trigeminal autonomic symptoms (total)				
Day 7	45/53 (85%)	52/56 (93%)	−8 (−20 to 4)	0·2312§
Day 28	48/52 (92%)	53/55 (96%)	−4 (−13 to 5)	0·4266§
SF-12				
Screening	40·9 (9·9)	40·8 (9·5)	0·2 (−3·6 to 3·9)	0·6952†
Day 28	45·3 (9·2)	44·5 (7·1)	0·8 (−2·6 to 4·2)	0·2093†
HIT-6				
Screening	60·8 (6·1)	62·7 (6·4)	−1·96 (−4·4 to 0·4)	0·1297†
Day 28	55·2 (7·9)	59·6 (8·5)	−4·5 (−7·8 to −1·2)	0·0086†
ADS				
Screening	18·4 (11·0)	19·9 (11·3)	−1·5 (−5·9 to 2·9)	0·5678†
Day 28	14·4 (11·3)	14·3 (10·3)	0·1 (−4·4 to 4·6)	0·6474†
Pain intensity				
Day 7	5·1 (2·2)	6·1 (1·8)	−1·0 (−1·8 to −0·2)	0·0146†
Day 28	4·9 (2·0)	5·8 (1·9)	−0·9 (−1·6 to −0·1)	0·0183†

Data are mean (SD), n (%), difference (95% CI), or p value. SF-12=12-Item Short Form Survey. HIT-6=Headache Impact Test 6. ADS=General Depression Scale (Allgemeine Depressionsskala). *Primary analysis model; the primary endpoint was analysed by a generalised linear mixed model with covariables included; a sensitivity analysis without consideration of covariables was done by a Mann-Whitney-Wilcoxon test. †Mann-Whitney-Wilcoxon test. ‡Cessation applies if no more cluster headache attacks have occurred within the 3 days before the respective visit. §Exact Monte Carlo estimation of the χ^2 test.

Table 2: **Results for efficacy endpoints**

in the prednisone group compared with 25 (45%) of 55 patients in the placebo group at visit day 28 (table 2). No difference in the presence or characteristic of trigeminal autonomic symptoms was detected, except that nasal congestion and rhinorrhoea were more often present in the placebo group (appendix p 6). There was no evidence for differences between the groups in quality of life (SF-12; table 2, appendix p 3), impact of headache (HIT-6; table 2, appendix p 2), or depression (ADS; table 2, appendix p 2). Mean pain intensity on a NRS at visit day 7 in patients receiving prednisone was 5·1 (SD 2·2) versus 6·1 (1·8) points in the placebo group (–1·0, 95% CI –1·8 to –0·2, p=0·0146). At visit day 28, pain intensity decreased to 4·9 (SD 2·00) points in the prednisone group and 5·8 (1·9) points in the placebo group (–0·9, 95% CI –1·6 to –0·1, p=0·0183).

Two serious adverse events occurred during the trial, both of which were in the placebo group (inguinal hernia and severe deterioration of cluster headache). There was no evidence for a difference in frequency or severity of adverse events between groups (table 3). A total of 270 adverse events in 76 (71%) of 107 patients were recorded throughout the study, distributed as 37 (71%) of 52 patients with 135 adverse events in the prednisone group and 39 (71%) of 55 patients with 135 adverse events in the placebo group. On average, patients across both groups reported 2·5 (SD 3·5) adverse events during the study (table 3). Five patients discontinued the study due to adverse events: two in the prednisone group and three in the placebo group. Diarrhoea, hyperhidrosis, headache, palpitations, restlessness, and malaise were more common in the prednisone group, whereas vomiting, fatigue, dizziness, and nausea were more common in the placebo group.

Systolic blood pressure was similar in both groups at baseline with a mean difference of –1 mm Hg in the prednisone group compared with the placebo group (95% CI –7·1 to 5·0, p=0·8996). Systolic blood pressure was elevated in the prednisone group at visit day 7 with a mean difference of 6·9 mm Hg compared with placebo (1·2 to 12·5, p=0·0172) and almost normalised again at visit day 28 at 5·4 mm Hg (–1·2 to 12·0, p=0·0674). No clinically relevant differences between groups were observed in urine analysis, neurological examination, heart rate, or ECG. Differences in laboratory findings are summarised in table 3.

The CGI scale showed marked differences between groups (appendix p 4). No patient in the placebo group, but eight (15%) of 52 patients in the prednisone group were rated "normal, not ill at all", and four (7%) of 55 patients in the placebo group were rated severely ill at day 7, but none in the prednisone group. A very good therapeutic effect in the CGI scale was rated for 21 (40%) of 52 patients with prednisone versus four (7%) of 55 patients with placebo at day 7.

Discussion

Short-term prevention of episodic cluster headaches with 100 mg oral prednisone resulted in a greater reduction of cluster headache attack frequency in the first week of treatment compared with placebo. Over one third of patients reported complete cessation of cluster headache attacks after 1 week with prednisone. A reduction of at least 50% of cluster headache attacks was reported by nearly half of the patients with prednisone after 1 week, whereas less than 15% of patients with placebo reported this effect.

Patients who were treated with prednisone also had a marked reduction in the number of days with cluster

headache attacks, supporting the original treatment intention to use corticosteroids to suppress the cluster headache attacks until longer-term preventive medication reached its efficacy. The treatment effect of prednisone persisted to week 4, but the difference from placebo gradually attenuated over time in parallel to the verapamil dose reaching its therapeutic effect. Therefore, attack frequency reduction slowly converged between groups. This result might reflect the spontaneous improvement or remission typical for the natural course of the disease or might hint at the capacity of prednisone to end the bout in some patients, but most likely reflects the preventive treatment effect of verapamil in both patient groups. Spontaneous remission is a recognised problem in cluster headache clinical trials.[22,23] We aimed to reduce this effect by including only patients who were still within the first 30 days of their current pain episode, but patients with short episodes can still show spontaneous remission to a certain extent. The design of this trial conformed to the International Headache Society's guidelines for clinical trials in cluster headache to address the natural history of the disease.[24] Requirement of acute attack treatment (triptans and oxygen) declined over time and was more pronounced in the prednisone group in parallel to the reduction of overall attacks. The high percentage of cluster headache attack treatment with analgesics in nearly 30% of patients in the placebo group at baseline could raise some concern about the education of prescribing physicians and patients about available and efficient treatment options in cluster headache. Use of analgesics was reduced to a minimum over the course of the study but seemed to remain a viable choice for a minority of patients, particularly in the placebo group (appendix p 1).

Limitations of this study must be addressed. The trial was stopped prematurely due to recruitment difficulties and the end of the funding period, which was extended twice. Recruitment turned out to be difficult due to competing trials on neuromodulation and other pharmacological interventions for cluster headache. Moreover, patients with good experience with corticosteroids in previous cluster episodes were hesitant to participate in this trial as they were concerned about being randomly assigned to the placebo group. Previous experience with corticosteroids might have partly unblinded some patients. Estimating the extent of this bias or the effect on success of the blinding procedure is hard, but the possibility of some unblinding must be kept in mind when interpreting our study results. Patients with a negative experience with verapamil were equally hesitant. An underpowered study, such as this one, is prone to type II statistical errors in proving the study hypothesis.[25] The study recruited almost exclusively people of white ethnic origin so that the results might not be generalisable to patients of different ethnic heritage. Spontaneous remission as well as rebound attacks following prednisone reduction might also interfere with study results.

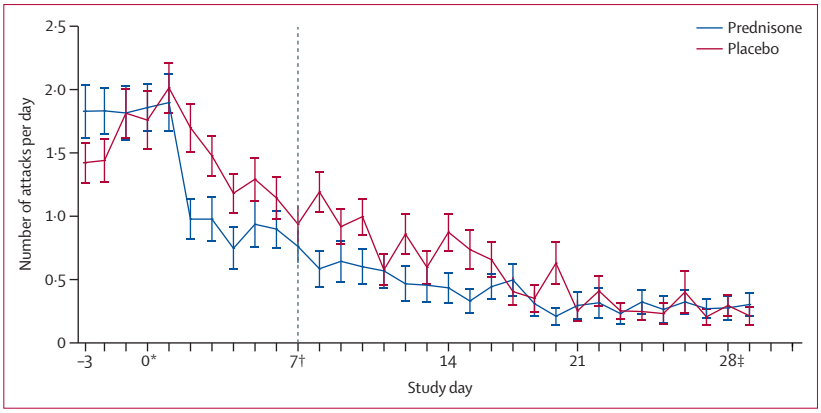

Figure 2: **Mean number of cluster headache attacks per day with prednisone treatment compared with placebo**
Error bars show SD. *V0=randomisation. †V1=visit at day 7 (primary endpoint). ‡V2=visit at day 28.

	Prednisone (n=53)	Placebo (n=56)
Deaths	0	0
Serious adverse events*	0	2
Discontinuation due to adverse events	2 (4%)	3 (5%)
Adverse events per patient	2·5 (3·7)	2·4 (3·3)
Common adverse events†		
Diarrhoea	5	2
Vomiting	1	6
Fatigue	3	6
Hyperhidrosis	5	2
Headache	13	7
Palpitations	7	3
Dizziness	7	13
Nausea	7	13
Restlessness	4	1
Malaise	3	2
Abnormal laboratory findings‡	1 (2%)	2 (4%)

Data are n, n (%), or mean (SD). *Serious adverse events were inguinal herniation and severe deterioration of disease. †Adverse events were considered common when at least five patients reported the event. ‡Abnormal blood laboratory results at day 28 (visit 2; blood) were: alanine aminotransferase (prednisone), C-reactive protein (placebo), and erythrocyte sedimentation rate (placebo).

Table 3: **Safety and tolerability analyses**

Several studies have addressed the efficacy of prednisone in episodic cluster headache but were not able to provide clear evidence to support this therapy, nor offer a clear and authorative treatment regimen.[10–14,26–28] The limitations of available scientific evidence have led to uncertainty among patients and health-care professionals about the risk-benefit ratio of corticosteroid treatment in episodic cluster headache. Comparison of oral corticosteroid treatment with greater occipital nerve injection is warranted to determine the future best medical practice, as occipital nerve injection is a more invasive approach than oral prednisone, but it does provide less systemic corticoid exposure.[22,29] Some milder affected patients might even be

sufficiently treated with verapamil, together with acute attack medication without corticosteroids.

Our data were collected in a multicentre, randomised, and controlled trial, with public funding. We suggest a treatment regimen that might be effective in many episodic cluster headache patients through their first weeks of pain. Only cluster headache attacks with moderate or severe pain intensity (with rating of at least five on the NRS) were counted as attacks, to avoid dilution from milder pain or sensory discomfort sometimes associated with the aftermath of an attack. As most patients discontinue their long-term preventive medication, such as verapamil, months into their pain-free interval and enjoy several months or even years without cluster headache attacks, they become eligible to prednisone treatment again once the new painful episode starts. Prednisone treatment over a short time span was safe and well tolerated.

For the **study protocol, statistical analysis plan, and informed consent** see www.predch.de

In conclusion, oral application of prednisone, at 100 mg for 5 days then tapering by 20 mg every 3 days, is an effective and fast-acting, short-term preventive treatment for episodic cluster headache that can be used to attenuate the early cluster episode until long-term prevention has reached its full efficacy. Patients without concurrent health issues could be considered for prednisone treatment alongside the initiation of verapamil for long-term prevention. The best combination of prednisone with long-term preventive medication should be investigated in future studies.

Contributors

MO, DH, H-CD, ASc, and ZK conceptualised the experimental design. MO, DH, NS, and SN organised the study. TPJ, HK, TF, J-PJ, TK, AB, CG, ASt, DH, SN, and PS acquired the data. DH, H-CD, CO, NS, and MO analysed the data. CO and ASc did the statistical analysis. MO and DH wrote the first draft of the manuscript and interpreted the findings. CK critically revised the manuscript. All authors gave input to the manuscript.

Declaration of interests

MO reports personal fees from Sanofi, Biogen, Novartis, Teva Pharmaceuticals, and Eli Lilly; and grants from Allergan and Heel Pharmaceuticals, outside of this work. SN reports personal fees from Teva Pharmaceuticals, Eli Lilly, Hormosan Pharma, Novartis, and Allergan, outside of this work. CO reports grants from Medice, outside the submitted work. PS has received honoraria from Allergan, Eli Lilly, Hormosan, and Novartis; and research support from Novartis outside of this work. CG reports personal fees from Allergan, Teva Pharmaceuticals, Eli Lilly, Novartis, Boehringer Ingelheim, Desitin Pharmaceuticals, Cerbotex, Reckitt Benckiser, Sanofi Aventis, Gruenenthal, and Electrocore, outside of this work. TK reports personal fees from Allergan, Grünenthal, Teva Pharmaceuticals, and Eli Lilly and Hormosan, outside of this work. ASt reports personal fees from Allergan, Eli Lilly, Novartis, Teva Pharmaceuticals, Sanofi, and Bayer; and grants from the German scientific council and University of Munich, outside the submitted work. TPJ reports grants and personal fees from Novartis; personal fees from Teva Pharmaceuticals, Sanofi, Eli Lilly, and Allergan; and grants from Gemeinsamer Bundesausschuss–Innovationsfonds and Europäischer Fond für regionale Entwicklung, outside this work. H-CD reports grants and personal fees for participation in clinical trials, contribution to advisory boards, or oral presentations from Alder, Allergan, Amgen, Electrocore, Ipsen, Eli Lilly, Medtronic, Novartis, Pfizer, Teva Pharmaceuticals, and Weber & Weber outside of this work; financial support for research projects from Electrocore; and research support from the German Research Council (DFG), the German Ministry of Education and Research (BMBF), and the EU; he serves on the editorial boards of Cephalalgia and *The Lancet Neurology*. HCD chairs the Clinical Guidelines Committee of the German Society of Neurology; and is member of the Clinical Trials Committee of the International Headache Society. ZK reports grants and personal fees from Novartis; and personal fees from Allergan, Teva Pharmaceuticals, Eli Lilly, Daiichi, and Merck, outside this work. DH reports personal fees from Allergan, Eli Lilly, and Hormosan; and grants and personal fees from Teva Pharmaceuticals and Novartis, outside this work. All other authors declare no competing interests.

Data sharing

The PredCH trial data, including deidentified participant data, will be made available on request, from the time of publication of the study, to research parties after approval of a formal written proposal. To gain access, data requestors need to contact the corresponding author. The study protocol, statistical analysis plan, and informed consent are publicly available.

Acknowledgments

The German Federal Ministry of Education and Research (BMBF) funded this study (BMBF 01KG1205). There was no commercial writing support. We thank Prof Heiner Wienecke and Dr Herbert Hirche for their invaluable service at the data monitoring safety board and continuous support for the study. Tremendous thanks go to Jan Burmeister, Susanne van Triel, and Michaela Berent for their relentless organisational and logistic effort for the study.

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