



Suboccipital steroid injections for transitional treatment of patients with more than two cluster headache attacks per day: a randomised, double-blind, placebo-controlled trial

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Summary

Background Suboccipital steroid injections can be used for preventive treatment of cluster headache but few data are available for the efficacy of this approach in clinical trials. We aimed to assess efficacy and safety of repeated suboccipital injections with cortivazol compared with placebo as add-on therapy in patients having frequent daily attacks.

Methods In our randomised, double-blind, placebo-controlled trial at the Emergency Headache Centre in Paris, France, we enrolled adults aged 18–65 years with more than two cluster headache attacks per day. We randomly allocated patients to receive three suboccipital injections (48–72 h apart) of cortivazol 3.75 mg or placebo, as add-on treatment to oral verapamil in patients with episodic cluster headache and as add-on prophylaxis for those with chronic cluster headache, on the basis of a computer-generated list (blocks of four for each stratum). Injections were done by physicians who were aware of treatment allocation, but patients and the evaluating physician were masked to allocation. The primary outcome was reduction of the number of daily attacks to a mean of two or fewer in the 72 h period 2–4 days after the third injection. We assessed all patients who received at least one dose of study drug in the intention-to-treat analysis. This study is registered with ClinicalTrials.gov, number NCT00804895.

Findings Between November, 2008, and July, 2009, we randomly allocated 43 patients (15 with chronic and 28 with episodic cluster headache) to receive cortivazol or placebo. 20 of 21 patients who received cortivazol had a mean of two or fewer daily attacks after injections compared with 12 of 22 controls (odds ratio 14.5, 95% CI 1.8–116.9; $p=0.012$). Patients who received cortivazol also had fewer attacks (mean 10.6, 95% CI 1.4–19.9) in the first 15 days of study than did controls (30.3, 21.4–39.3; mean difference 19.7, 6.8–32.6; $p=0.004$). We noted no serious adverse events, and 32 (74%) of 43 patients had other adverse events (18 of 21 patients who received cortivazol and 14 of 22 controls; $p=0.162$); the most common adverse events were injection-site neck pain and non-cluster headache.

Interpretation Suboccipital cortivazol injections can relieve cluster headaches rapidly in patients having frequent daily attacks, irrespective of type (chronic or episodic). Safety and tolerability need to be confirmed in larger studies.

Funding None.

Introduction

Cluster headache is probably the most severe primary headache disorder¹ and is characterised by attacks of strong periorbital pain with ipsilateral autonomic signs, recurring at intervals ranging from once every 2 days to eight times a day.² In episodic cluster headache, attacks occur in phases for weeks or months separated by remissions.³ About 10% of patients develop chronic cluster headache and have ongoing attacks.³

Management of cluster headache usually necessitates a combination of acute and prophylactic treatments.^{2,4} The mainstay of acute treatment is subcutaneous sumatriptan⁵ or oxygen inhalation.⁶ Most patients respond to treatment, but sumatriptan is restricted to two injections a day to avoid overmedication, and an oxygen cylinder is difficult to carry around. Prophylactic drugs, mainly verapamil^{7–9} and lithium,² are used to reduce the frequency of attacks and sustain improvement. Transitional or add-on prophylaxis might be useful to suppress attacks rapidly at the beginning of a cluster while waiting for the delayed efficacy of long-term preventative drugs (ie, verapamil and lithium), or for

patients presenting with frequent daily attacks. Although no randomised trials have been undertaken, oral steroids are considered to be efficient^{5,10,11} and are widely used, but they might induce rebound attacks on weaning off¹² and have potential serious side-effects even with short-term use.¹³ Suboccipital steroid injections (SSI) targeting the greater occipital nerve have been proposed as an alternative to oral steroids.^{14–18} Only one randomised, controlled trial of SSI for cluster headache has been published,¹⁹ with highly positive results, but 15 of the 23 patients included had fewer than two attacks a day at baseline. SSI are not included in the European guidelines for the treatment of cluster headache.⁵

We have used SSI with cortivazol²⁰ for more than 10 years in our clinic for the transitional treatment of cluster headache. Cortivazol has a powerful affinity for the glucocorticoid receptor and a long half-life.²¹ We aimed to assess the efficacy and safety of SSI with cortivazol in addition to usual care in patients with frequent daily attacks, stratified by type of cluster headache (episodic or chronic).

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Methods

Study design and patients

We did a 90 day, single-centre, double-blinded, randomised, add-on, placebo-controlled trial. We screened all patients who presented with cluster headache to the Emergency Headache Centre in Paris, France, between November, 2008, and July, 2009. We enrolled adults aged 18–65 years who met the international classification of headache disorders (ICHD-II) diagnostic criteria for episodic (3.1.1) or chronic (3.2.1) cluster headache³ and had a mean of more than two attacks per 24 h in the 3 days preceding the day of inclusion; episodic patients also needed to have been in their present phase of attacks for no more than 1 month, on the basis of reports from patients and medical records if available. We excluded patients if they had another type of headache that could confuse the assessment of attacks, had a contraindication to cortivazol, were taking anticoagulants, had a known bleeding disorder, or were unable to meet study requirements. Patients with episodic cluster headache were also excluded if they had a contraindication to verapamil. All patients provided written informed consent before enrolment and the study was approved by local and national ethics committees.

Randomisation and masking

We randomly assigned eligible patients in a one-to-one ratio to receive three suboccipital injections of cortivazol (Altim [Sanofi-Aventis, France], 3.75 mg in 1.5 mL)²⁰ or saline (PROAMP [Aguettant, France] 1.5 mL). We chose cortivazol on the basis of its half-life (>60 h),²¹ convenience (kit with prefilled syringe), and our experience with its use in more than 1000 patients with cluster headache since 2000. Patients were classified as episodic or chronic at baseline by the assessing doctor (EL). We stratified randomisation with blocks of four (two placebo and two cortivazol) for each type of cluster headache, and allocated patients on the basis of two computer-generated randomisation lists (episodic and chronic) produced by an

investigator at the clinical research unit (EV) and transmitted to the hospital pharmacy department. The pharmacist made boxes containing the material for three injections with placebo or cortivazol. Two sets of boxes, labelled with the randomisation numbers and as episodic or chronic were then delivered to the Emergency Headache Centre and kept in a locked cabinet. At enrolment, every patient was assigned the next box, in sequential order, for their subgroup (episodic or chronic). At every injection visit, the doctors responsible for assessment and injection checked that the box with the correct randomisation number was used. No boxes were lost, stolen, or damaged. No mistakes were made in the attribution according to the checking done after the unmasking. Unmasking was done after the final long-term follow-up telephone call.

Patients were masked to treatment allocation. We used two investigators for every patient: EL recruited and assessed all patients and remained unaware of treatment allocation, and six other doctors did the injections (AD, CR, IT, DV, and two others from the Emergency Headache Centre). These doctors prepared syringes and needles out of the view of the patient, injected from behind the patient, and were not allowed to discuss clinical changes with the patient. Local anaesthetics were not used, preventing paraesthesias that might have broken the masking.

Procedures

Acute treatment with sumatriptan or oxygen was permitted as needed.²² Patients with episodic cluster headache who were not already taking verapamil were started on verapamil 120 mg twice per day for 2 days, followed by three times per day for 2 days. Escalation could be continued every 2 days until 720 mg per day, with electrocardiographic monitoring for adverse effects on cardiac conduction. Escalation was stopped when patients could not tolerate verapamil, at which point the previous dose was used, or when daily attacks were reduced to less than two per day. Episodic patients already receiving verapamil were prescribed the same escalation. Patients with chronic cluster headache continued the prophylaxis that they were taking before inclusion. Additional prophylactic treatments could be added when needed after day 15 of the study. Oral steroids were not permitted.

We recorded demographic and clinical characteristics at baseline, including the number of attacks during the 3 days before the day of first injection (days –1 to –3). Patients had an electrocardiogram, a blood test (including a pregnancy test for women), and a medical examination, and received diary cards on which to record cluster headache attacks, use of concomitant drugs, and side-effects on a daily basis for 90 days.

Figure 1 shows the study timeline. We did three SSI, 48–72 h apart according to the patient's availability. Our clinical experience with SSI suggested that some patients might improve after one dose, but that most patients would need two or three injections (2–4 days apart) to stop attacks. Injections were made ipsilateral to attacks under the

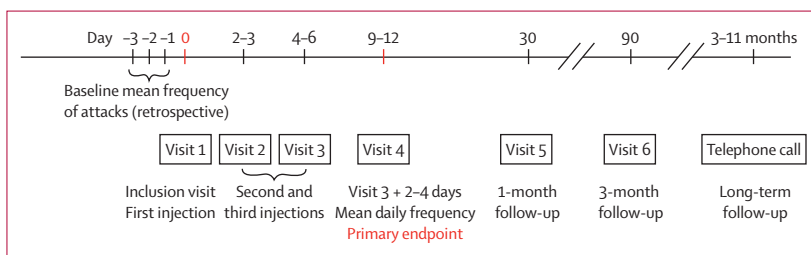


Figure 1: Study timeline

Patients were included at visit 1 (day 0), when the first injection was given. We assessed frequency of attacks per day retrospectively at the inclusion visit. The second injection was scheduled for day 2 or day 3 and the third injection on day 4, day 5, or day 6. Visit 4 was scheduled between day 9 and day 12 (5 to 6 days after the third injection). At visit 4, we assessed the number of attacks during the second to fourth days after the third injection (ie, during 72 h including day 6, day 7, and day 8 for those who had the third injection on day 4; day 7, day 8, and day 9 for those who had the third injection on day 5; and day 8, day 9, and day 10 for those who had the third injection on day 6) in person or by telephone. The patient was asked to return to the clinic on day 30 (visit 5) for assessment of cluster headache attack frequency, return of the diary cards, and provision of a new diary for the rest of the study (days 31–90); they were asked to return again on day 90 (visit 6) and all patients received a telephone call for long-term follow-up before the final analysis.

occipital bone at the medial third between the inion and mastoid process. The needle was inserted until it started to touch the bone; the injection was made in three directions, upwards, 45° left, and 45° right. Cortivazol was injected with a 25 mm needle contained in the commercial kit; in the absence of 25 mm needles in our hospital, saline was injected with the closest available needle type (16 mm). Patients could refuse the injection at any visit and the reason for refusal was recorded. We reported vital signs, adverse events, and concomitant treatments at every visit. All patients were contacted by telephone after 3 months or more, just before the final analysis of the data, for an assessment of their overall satisfaction with SSI.

The primary endpoint was reduction in the mean number of attacks per day to two or fewer during the second, third, and fourth days after the third injection. This endpoint was assessed from the patient's diary cards at the fourth visit (scheduled for 9–12 days after enrolment). The timing of assessment could vary by a few days between patients, dependent on delay between the first and third injections. If the third injection was omitted, the calculation was based on the second, third, and fourth days after the day on which the third injection would have taken place.

Secondary endpoints were total number of attacks between day 1 and day 15, percentage of patients with a 50% reduction in frequency of attacks at day 15, remission rate at day 30, delay to remission (defined as at least 7 days pain free), percentage of patients with two or fewer attacks per day at day 30, and tolerability and safety.

Tertiary endpoints were the number of sumatriptan doses between day 1 and day 15, dose of verapamil needed in patients with episodic cluster headache, need for additional prophylaxis between day 15 and day 30, and long-term subjective satisfaction on a 4-point scale (4 indicating greater satisfaction). Finally, we did a post-hoc analysis to assess sustained pain-free status from the fourth day after SSI to day 30 to allow comparison with the previous trial of SSI for cluster headache reported by Ambrosini and colleagues.¹⁹

Statistical analysis

We calculated that a sample size of 22 patients per treatment group was needed to detect a 45% difference between groups for the primary outcome, with a power of 80% and a 5% bilateral significance threshold. The previous trial¹⁹ showed a 61% difference between groups with a sample size of 23 patients (sustained pain-free status from day 4 to day 30 was reached by eight of 13 patients injected with betamethasone compared with none of ten controls).¹⁹ We expected an equivalent treatment effect and a higher placebo effect in our study. We assessed all patients who received at least one injection (intention-to-treat population).

We used the Cochran-Mantel-Haenszel test to assess the primary endpoint, stratified by type of cluster headache, and the Breslow-Day test for homogeneity of odds ratios to

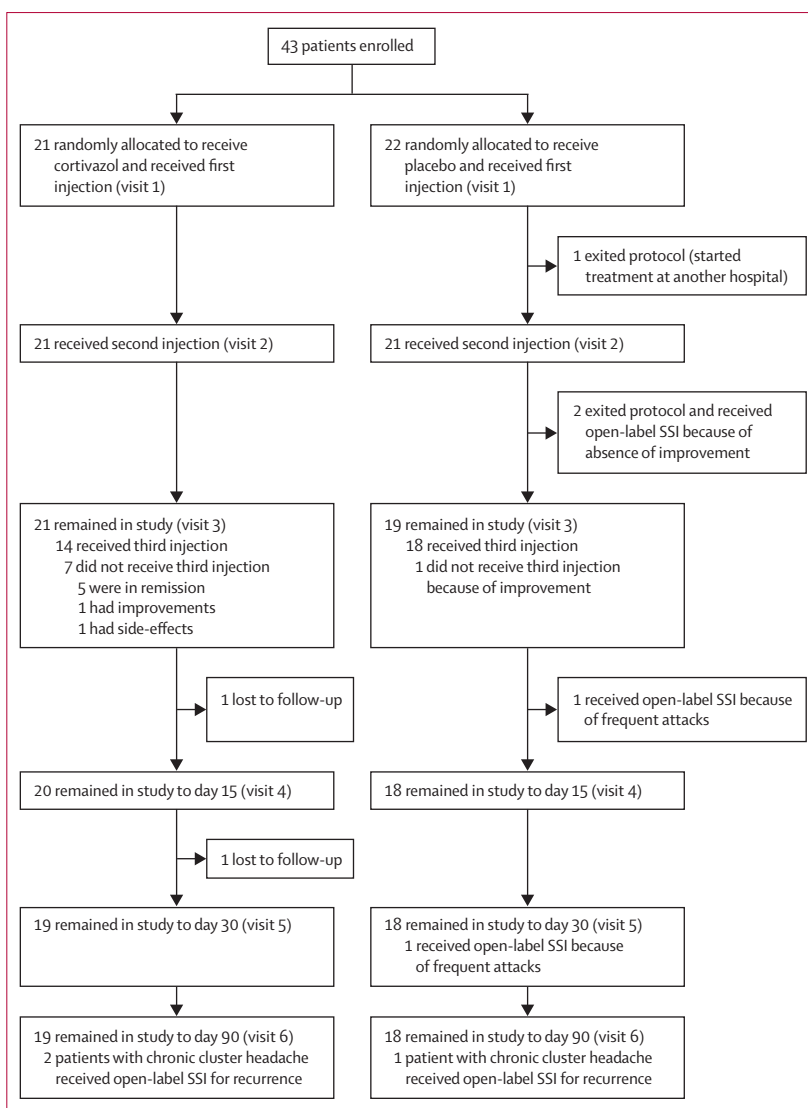


Figure 2: Study profile
SSI=suboccipital steroid injections.

	Cortivazol group (n=21)		Placebo group (n=22)	
	Chronic cluster headache (n=7)	Episodic cluster headache (n=14)	Chronic cluster headache (n=8)	Episodic cluster headache (n=14)
Sex (male)	6 (85%)	13 (93%)	8 (100%)	11 (79%)
Age (years)	41.3 (13.3)	40.0 (7.8)	42.8 (11.9)	41.9 (10.4)
Number of attacks per day at baseline*	4.0 (1.4)	3.6 (1.3)	3.6 (1.4)	4.7 (1.9)
Patients previously treated with SSI for cluster headache	5 (71%)	2 (14%)	2 (25%)	4 (29%)
Days in present phase	..	29.3 (16.4)	..	28.5 (16.4)
Days with more than two attacks per day†	121.4 (167.4)	..	24.2 (15.9)	..

Data are n (%) or mean (SD). SSI=suboccipital steroid injection. *Mean number of attacks per day over the 3 days before inclusion. †Days with more than two attacks per day before enrolment (for chronic patients).

Table 1: Baseline demographic and clinical characteristics of patients

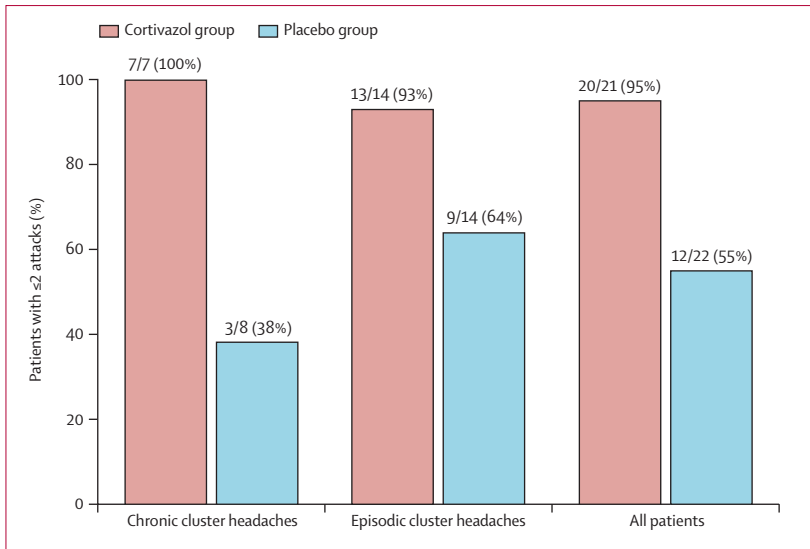


Figure 3: Primary endpoint
 Percentages of patients with a mean of two or fewer attacks per day in the second, third, and fourth days after the third injection. Unadjusted results are shown for the episodic and chronic subgroups. Statistical analysis was done as planned only for the overall sample, because the Breslow-Day test did not reject the homogeneity of odds ratios of the two subgroups.

	Cortivazol group (n=21)	Placebo group (n=22)	Comparison*	p value
Secondary endpoints				
Mean (95% CI) attacks per person, total days 1–15†	10.6 (1.4–19.9)	30.3 (21.4–39.3)	19.7 (6.8–32.6)	0.004‡
Patients with 50% reduction of attacks at day 15	18 (86%)	13 (59%)	OR 4.06 (0.92–17.89)	0.064§
Patients in remission at day 30	16 (76%)	13 (59%)	OR 2.14 (0.58–7.92)	0.252§
Median (95% CI) number of days to remission	9 (5–13)	16 (0–36)	7	0.036¶
Patients with ≤2 attacks per day at day 30	17 (81%)	17 (77%)	OR 1.23 (0.28–5.41)	0.783§
Adverse events	18 (86%)	14 (64%)	OR 4.39 (0.80–24.07)	0.162
Neck pain	13 (62%)	10 (45%)	..	0.364
Non-cluster headache	7 (33%)	4 (18%)	..	0.310
Tertiary endpoints				
Mean (SD) sumatriptan doses per person, total days 1–15**	7.2 (6.4)	21.8 (20.7)	..	0.006
Maximum verapamil dose (episodic patients)††				
Mean (SD) number of 120 mg verapamil pills per day	3.5 (1.0)	4.7 (1.5)	..	0.043‡‡
Mean maximum dose (mg)	420 (SD 120)	564 (SD 180)	..	
Additional prophylaxis (before day 30)	1 (5%)	6 (27%)	..	0.095
Mean (SD) satisfaction score (4-point scale)§§	3.6 (0.6)	2.9 (1.1)	..	0.028‡‡

Data are for 21 patients in the cortivazol group and for 22 in the placebo group unless otherwise stated. *Difference (95% CI) or odds ratios (95% CI). †21 patients in each group. ‡Two-way ANOVA (group and strata); interaction was not significant. §Cochran-Mantel-Haenszel test. ¶Generalised Wilcoxon test. ||Fisher's exact test. **19 patients in the cortivazol group and 18 in the placebo group. ††11 patients in the cortivazol group and 11 in the placebo group. ‡‡Student's *t* test. §§Higher scores are better; assessed for 18 patients in the cortivazol group and 19 in the placebo group.

Table 2: Secondary and tertiary endpoints

establish whether the effects of treatment differed between the episodic and chronic subgroups. Missing data were counted as a treatment failure.

We tested differences in overall number of attacks from day 1 to day 15 between treatment groups with the Student's *t* test and a last-observation-carried-forward method for missing data. Remission was assessed from day 1 until a patient had an event, until the patient was censored, or until data cutoff (day 30). We used the Cochran-Mantel-Haenszel test to examine differences between treatment groups for the proportions of patients in remission at day 30 or with two or fewer attacks per day at day 30, stratified by type of cluster headache. Missing data were regarded as treatment failures for these two endpoints.

We report time to 7 day remission with Kaplan-Meier estimates. We used the generalised Wilcoxon test to explore the significance of the difference between the two treatments. We compared the changes in daily attack frequency in the groups with repeated measure ANOVA.

We analysed tertiary endpoints with Fisher's exact and unpaired Student's tests.

The Clinical Research Unit designed the statistical analysis and the Statistical Consulting Service of the University of Montreal did the final analysis with SPSS version 15.

This study is registered with ClinicalTrials.gov, number NCT00804895.

Role of the funding source

There was no funding source for this study. All authors had full access to all of the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

Figure 2 shows the trial profile. We enrolled 28 patients with episodic cluster headache and 15 with chronic cluster headache (table 1). All 43 patients received at least one dose of study drug and were included in the intention-to-treat analysis.

The treatment groups were well matched (table 1). The mean number of daily attacks at baseline was 3.7 (SD 1.3) for patients in the cortivazol group and 4.3 (1.8) for controls. There was no difference between the groups in duration of the phase of episodic cluster headache. We included six patients with episodic cluster headache despite duration of the present phase of longer than 1 month (mean 63 days, range 40–101), because of the persistence or the recent increase of frequent daily attacks; three of these patients received placebo and three received cortivazol.

Fewer patients in the cortivazol group than controls had a mean of more than two attacks per day during the second, third, and fourth days after the third injection (primary endpoint; figure 3). We noted this reduction of daily attacks in 20 (95%) of 21 patients receiving cortivazol compared with 12 (55%) of 22 controls (odds ratio 14.5, 95% CI 1.8–116.9; *p*=0.012). The net therapeutic gain of

40% corresponded to a number needed to treat of 2.5. Effect of treatments did not differ by type of cluster headache ($p=0.29$).

For secondary endpoints, patients who received cortivazol had fewer attacks between day 1 and day 15 (table 2). Change in frequency of attacks was higher in the cortivazol group than in the placebo group ($p=0.037$; figure 4). At day 15, the proportion of patients with a 50% reduction in attack frequency did not differ between patients in the cortivazol group and controls (table 2). Remission rates at day 30 were much the same between groups (table 2). Cortivazol induced 7 day remission at a median of 7 days earlier than did placebo (table 2; figure 5). At day 30, the proportion of patients having two or fewer attacks a day was much the same between groups (table 2).

We noted adverse events in 18 (86%) of 21 patients who received cortivazol and 14 (64%) of 22 controls ($p=0.162$); the most common adverse events were neck pain at the site of injection and headache other than cluster headache (table 2). None of the adverse events was serious and none resulted in discontinuation from the study.

Compared with placebo, the use of cortivazol reduced the need for sumatriptan injections between day 1 and day 15, reduced the need for verapamil in patients with episodic cluster headache, and was associated with higher satisfaction scores at the end of the study (total follow-up 3–11 months; table 2). However, rates of additional prophylactic drug use before day 30 did not differ between groups (table 2).

In our post-hoc analysis, seven (33%) of 21 patients given cortivazol remained pain free from 4 days after the first injection to day 30 compared with two (9%) of 22 controls, and 11 (52%) of 21 patients given cortivazol remained pain free from the fourth day after the last SSI to day 30 compared with four of 22 (18%) controls. In the cortivazol group, 15 (71%) of 21 patients entered remission before day 15 and, in the absence of a rebound, were pain free at day 30.

Discussion

We show that repeated SSI with cortivazol is effective compared with placebo for transitional treatment of cluster headache in patients who have frequent daily attacks. Although patients injected with cortivazol had fewer attacks per day during the first 15 days of the study, by day 30 both groups had similar results. A potential explanation for this outcome is that concomitant treatment with verapamil became efficacious and patients with episodic cluster headache in both groups entered remission. Furthermore, our exploratory analyses suggested that cortivazol injections are better than placebo in terms of reducing the need for sumatriptan and verapamil. There were no serious adverse events related to the trial injections and the number of patients with side-effects (eg, ipsilateral neck pain and non-specific headache) did not differ between groups. No patient exited the study because of side-effects. Alopecia and

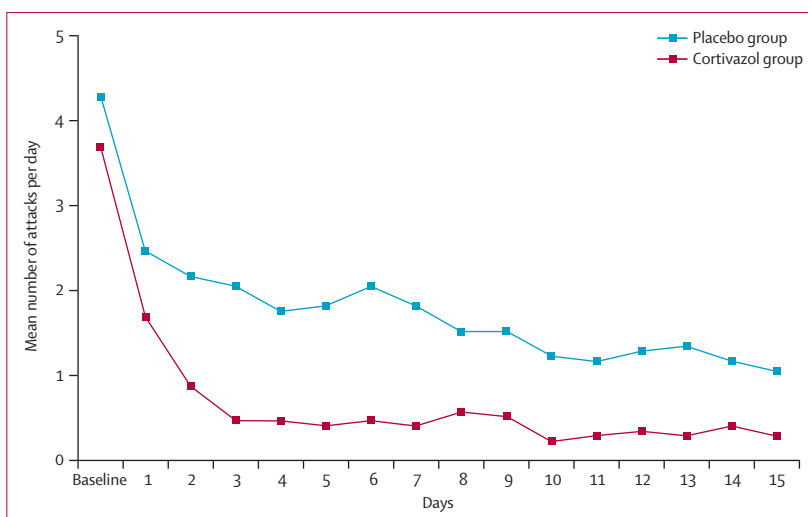


Figure 4: Mean number of attacks during days 1–15

Number of attacks at baseline was a mean of the 3 days before the day of inclusion, assessed retrospectively at day 0. ANOVA with repeated measures suggested that frequency of attacks differed between groups ($p_{\text{interaction}}=0.037$).

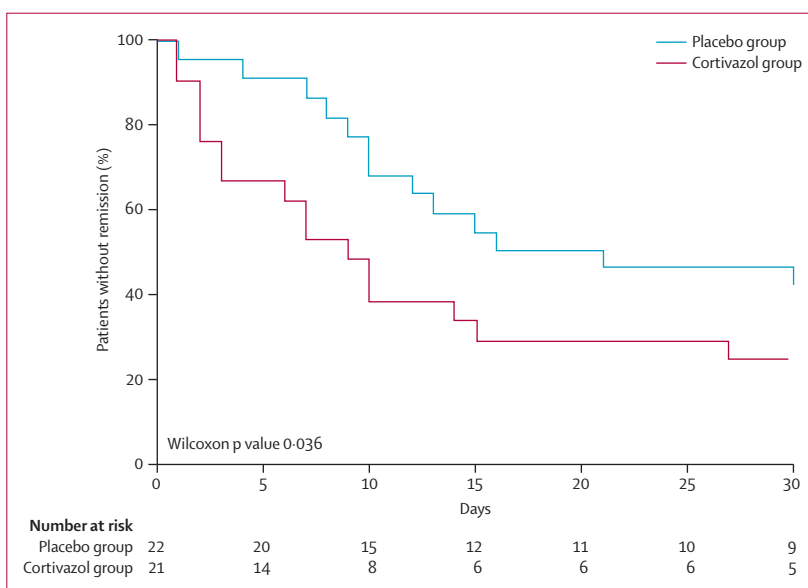


Figure 5: Kaplan-Meier curves of remission before day 30

Remission was defined as at least 7 consecutive days without an attack.

cutaneous atrophy have been described as rare complications of SSI²³ but were not noted in this study.

The efficacy of SSI for the prophylactic treatment of cluster headache has previously been suggested by open-label studies with various drugs and protocols^{14–18} and assessed by one randomised placebo-controlled trial (panel).¹⁹ In the trial by Ambrosini and colleagues,¹⁹ 23 patients (16 with episodic cluster headache and seven with chronic cluster headache) received one injection of lidocaine 2% mixed with either betamethasone or saline (allocated at random). By contrast, we included patients who had a higher frequency of attacks at baseline (mean of 4.0 [SD 1.6] vs 1.6 [0.85] in Ambrosini and colleagues'

Panel: Research in context**Systematic review**

We searched PubMed for articles published in English and French between January, 1947, and May, 2011 with the MeSH terms "cluster headache" AND "occipital nerve", "occipital nerve block", "occipital nerve infiltration", "occipital nerve injection", "GONB", OR "steroids"; we also searched for "algie vasculaire de la face". We identified five case series suggesting that greater occipital nerve injections with steroids, sometimes combined with an anaesthetic, reduce the frequency of cluster headache attacks.¹⁴⁻¹⁸ We identified only one randomised, placebo-controlled trial of 23 patients who received a one-off suboccipital injection of lidocaine 2%, which was randomly allocated to be mixed with either betamethasone or saline.¹⁹ In that study,¹⁹ eight (61%) of the 13 patients in the lidocaine plus betamethasone group were pain free from day 4 to day 30 compared with none of 10 patients in the lidocaine plus placebo group.

Interpretation

Our study is the second, and the largest, randomised placebo-controlled trial to assess suboccipital steroid injections (SSI) in cluster headache. Our study and that by Ambrosini and colleagues¹⁹ suggest that SSI can improve a cluster headache rapidly, irrespective of the type of cluster headache. However, differences between the design of the trials mean that the most efficient dose, number of injections, and type of steroid remain to be established.

trial¹⁹), did three injections versus one injection, and did not use anaesthetics. The primary endpoint in Ambrosini and colleagues' trial was the proportion of patients who remained pain free from day 4 after the injection to day 30, which was reached by eight (61%) of 13 patients in the betamethasone group but none of the 10 controls.¹⁹ In a post-hoc analysis, we noted that 11 (52%) of our patients receiving cortivazol were pain free from the fourth day after the last SSI to day 30 compared with four (18%) in the placebo group. Both studies support the use of SSI for the transitional prophylaxis of cluster headache. Moreover, we show that repeated SSI are efficient in patients with frequent daily attacks, and that anaesthetics are not necessary to obtain this efficacy.

The mechanisms through which SSI rapidly decrease the frequency of cluster headache attacks are not known. A systemic effect has been suggested,^{15,19} and cannot be ruled out in the absence of double-blind trials comparing suboccipital with intramuscular or intravenous injections of the same doses of steroids. Three injections of 3.75 mg cortivazol are equivalent to 187.5 mg prednisone;²⁰ high doses of oral steroids are usually necessary to reduce attacks, with prednisone 60–100 mg given daily for at least 5 days, then decreased by 10 mg every day to a total dose of 450–950 mg.² Attacks often resume when oral steroids are tapered down, whereas such a rebound was not reported with SSI in our study or others.^{14-18,19} SSI probably therefore have a local effect through the greater occipital nerve. Experimental evidence suggests that C2 afferents converge in nucleus trigeminalis caudalis on second order nociceptors with afferents from the first division of the trigeminal nerve.²⁴⁻²⁶ Stimulation of the greater occipital nerve might be useful for preventive treatment in intractable chronic cluster headache.^{27,28} The long delay

(~2 months) between implantation of the stimulator and significant clinical improvement suggests that the stimulation acts via slow central neuromodulatory changes.^{27,28} Conversely, the efficacy of SSI is notable within a few days. Methylprednisolone blocks neurotransmission in normal C fibres and decreases heat hyperalgesia and mechanohyperalgesia in a nerve injury model.^{29,30} These findings might explain how SSI in the vicinity of the greater occipital nerve could induce a rapid change in central nociceptive processing, possibly through an action on the trigeminocervical relay.¹⁸

The placebo response was high (55%) in our study, reinforcing the need for a placebo group in cluster headache studies.³¹ Part of the placebo response could be attributable to the natural course of episodic cluster headache (ie, spontaneous resolution) or to the use of verapamil, which is expected to decrease attacks after 1 week,⁹ or simply to regression to the mean. The placebo effect has been described in other cluster headache studies and is suspected to be in the same range as in migraine trials.³¹ This effect is affected by the mode of delivery, and injections might be more likely to cause a placebo effect for pain diseases.^{32,33}

Our study has some limitations. It was done at only one centre and we could have included more patients, but we were reluctant to inject placebo into a high number of severely affected patients. We assessed the number of attacks for only a short time (3 days) before randomisation, but recording exact numbers for a longer time might have been hampered by recall bias, and an equivalent variability of attacks was expected in both treatment groups. Spontaneous remission rates could account for the improvement of patients with episodic cluster headache who enrolled late in a cluster cycle. Three of the six patients who enrolled while in a phase of episodic cluster headache for more than 1 month received placebo; therefore, we do not think that including these patients significantly biased our results. The study was an add-on trial and verapamil was available to both groups because we regarded denial of an effective treatment as unethical. The need for verapamil was lower in the cortivazol group, suggesting that SSI could be used as a verapamil-sparing drug.

Efficacy of SSI as monotherapy and the optimum number of injections remain unknown. In our study, six of 21 patients in the cortivazol group refused the third injection because they were in remission or significantly improved after two injections. Only one patient in the placebo group improved enough to stop after two injections. The trial by Ambrosini and colleagues¹⁹ used one injection in patients with a lower mean daily baseline frequency of attacks.¹⁹ Therefore, the number of SSI might need to depend on individual responses until future studies have established the optimal number of injections and the optimal dose of steroid.

Overall, repeated SSI with cortivazol can rapidly decrease the frequency of attacks in patients with episodic and chronic cluster headaches. SSI seemed to be safe

and well tolerated within this trial. They have few contraindications, and can be added to any acute or other long-term preventive treatment for cluster headache.²⁰ SSI are an accessible technique that should be considered in the early management of phases or exacerbations of cluster headaches. Nonetheless, a confirmatory multi-centre trial and large prospective cohort studies are needed to fully assess safety.

Contributors

EL contributed to study design, recruitment of patients, data acquisition, analysis, and interpretation of the results, and produced the first draft and participated in the revision of the report. DV contributed to study conception and design, screening and injecting of patients, data interpretation, and revision of the report. IT contributed to screening and injecting of patients, data acquisition, data interpretation, and revision of the report. EV participated in trial design, statistical analysis, and data interpretation. MC participated in data collection and cleaning, statistical analysis, and data interpretation. CR contributed to screening and injecting of patients and data acquisition, data interpretation, and revision of the report. AD contributed to study conception and design, screening and injecting of patients, oversight and interpretation of data, and writing and reviewing of the report.

Conflicts of interest

EL has received fellowship grants from the University of Montreal and Institut Servier, payment for board membership from Allergan, Merck, and Pfizer, payment for expert testimony from Merck, payment for lectures from Johnson and Johnson, Merck, and Pfizer, payment for preparation of educational presentation by Johnson and Johnson and Merck; and travel, accommodation, or meeting expenses from Merck. EL's institution (Hôpital Notre-Dame, Montreal, QC, Canada) has received grants from Pfizer and Teva Neuroscience. DV has received payment for board membership from Allergan, Merck, and Bristol-Myers Squibb, payment for lectures from Air Liquide, Almirall, AstraZeneca, Merck and Pfizer; and travel, accommodation, or meeting expenses from Allergan and Merck. Grants have been paid to DV's institution (Emergency Headache Centre, Lariboisière Hospital, Paris, France) from Linde Healthcare. EV has received consulting fees from Pfizer, Amgen-Abbott, and Sanofi-Aventis and has served on data and safety monitoring boards for Sanofi-Aventis and Lilly. CR has received lecture fees from Pfizer and received travel, accommodation, or meeting expenses from Almirall, Merck, and Menarini. AD has received payment for board membership from Novartis, lecture fees from Almirall, AstraZeneca, GlaxoSmithKline, Merck, and Pfizer, and travel, accommodation, or meeting expenses from Almirall and Pfizer. IT and MC declare that they have no conflicts of interest.

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