

Corticosteroid Treatment of Eosinophilic Meningitis

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The role of corticosteroids in the treatment of eosinophilic meningitis has not been definitely established. Patients given a 2-week course of prednisolone (treatment group), 60 mg/day, were compared with those given placebo (control group) in a randomized, double-blind trial. Fifty-five patients were enrolled in each group. There were significant differences between the treatment and control groups, with regard to the number of patients who still had headache after 14 days (5 vs. 25, respectively; $P = .00004$), the median length of time until complete disappearance of headache (5 vs. 13 days, respectively; $P = .00000$), and the number of patients who had repeat lumbar puncture (7 vs. 22, respectively; $P = .002$). Serious side effects were not detected. These results indicate that a 2-week course of prednisolone was beneficial in relieving headache in patients with eosinophilic meningitis.

Eosinophilic meningitis can be caused by a variety of helminthic infections. In Thailand, *Angiostrongylus cantonensis* and *Gnathostoma spinigerum* are the major causative agents of this disease. Acute severe headache with nonfocal neurological findings, with the exception of occasional involvement of the cranial nerve, are the most common presenting symptoms of angiostrongyliasis [1, 2], whereas the classical and most common manifestations of gnathostomiasis of the CNS are radiculomyelitis, subarachnoid hemorrhage, and intracerebral hematoma [3]. There is no specific treatment for angiostrongyliasis. The disease is self-limited. In the majority of patients, most symptoms disappear within 4 weeks of onset [1, 2]. Symptomatic treatment is indicated for symptoms such as headache, nausea, and vomiting.

To assess conclusively the effects of corticosteroid treatment on the course and outcome of eosinophilic meningitis, we conducted a prospective, placebo-controlled, double-blind study of the use of prednisolone to treat eosinophilic meningitis.

Patients and Methods

Study population. Adult patients (aged ≥ 15 years) who had eosinophilic meningitis and who were admitted to the Department of Medicine, Srinagarind Hospital (Khon Kaen, Thailand), were studied. The diagnosis of eosinophilic meningitis was based on

findings of $\geq 10\%$ eosinophils in the CSF, with negative results of Gram, acid-fast bacillus, and india ink staining, cryptococcal antigen testing, and culture.

Patients were excluded if they had undergone previous lumbar puncture before admission or if they had experienced altered consciousness, pregnancy or lactation, or concomitant conditions such as diabetes mellitus and serious infection.

The severity of headache was classified by use of a visual analogue scale: 0 denoted no pain; 1–3, mild pain; 4–7, moderate pain; and 8–10, severe pain (with 10 denoting the worst pain imaginable). A CSF opening pressure of ≥ 300 mm H₂O after the patient was fully relaxed was defined as high CSF pressure.

Sample size and power. In the control group, 60% of patients were expected to have headache after 14 days of treatment, whereas 30% of patients in the treatment group were expected to have headache. The number of subjects in each group was estimated to be 50, by use of a 2-sided test with an α error of 5% and a β error of 20%.

Randomization and treatment. Subjects were stratified according to the severity of headache and CSF opening pressure and were randomized to receive either prednisolone or placebo. A block-of-4 randomization was used to ensure balance between groups. Patients were given either prednisolone, 60 mg/day, or identical-appearing placebo tablets that were to be taken orally with alum milk in 3 divided doses after meals for 2 weeks. The placebo tablets were provided by Siam Pharmaceutical (Bangkok).

Studies to monitor efficacy and toxicity. Before treatment, the following studies were performed: complete blood count; Venereal Disease Research Laboratory and *Treponema pallidum* hemagglutination assay tests; measurements of blood glucose, electrolytes, serum blood urea nitrogen, and creatinine; and liver function tests. CSF samples were obtained for an india ink preparation, for Gram and Ziehl-Neelsen stains, to be cultured for bacteria, for determination of opening pressure, for total cell counts with differential, for determination of levels of glucose and protein, and for cryptococcal and bacterial antigen tests. In addition, chest radiography was done.

During treatment, 2 tablets of acetaminophen (500 mg each) were given to relieve headache every 4–6 h if the headache persisted or

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The study protocol was reviewed and approved by the institutional review board and the ethics committee of Khon Kaen University. Subjects gave written informed consent.

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Table 1 Comparison of initial clinical features between patients treated with prednisolone for eosinophilic meningitis and control subjects.

Feature	Treatment group (n = 55)	Control group (n = 55)	P
Age, y, mean (range)	33.69 (15–70)	33.54 (16–63)	.94
Sex, male	37	39	.83
Incubation, d ^a	15 (1–90)	21 (1–90)	.47
Signs or symptoms			
Headache			
Duration, d ^a	7 (1–30)	7 (1–30)	.63
Degree			.74
Moderate	6	4	
Severe	49	51	
Vomiting	21	31	.85
Stiff neck	32	27	.44
Fever (T ≥ 38.0°C)	2	6	.27
6th CNP	4	1	.42
7th CNP	1	1	1.0
Hyperesthesia	4	4	1.0

NOTE. Data are no. of subjects, unless indicated otherwise. CNP, cranial nerve palsy; T, temperature.

^a Median (range).

recurred. Repeat lumbar puncture were done for patients with severe headache that was not relieved by acetaminophen.

Evaluation. After a baseline evaluation, patients were evaluated every day until the 2-week study was completed and every 2 weeks until the patients completely recovered. At each visit, a physical examination was done and any adverse events were assessed and recorded. During treatment and until headache completely disappeared, frequency of acetaminophen use and repeat lumbar puncture were also recorded. Compliance was checked by the pill-count method.

The day of complete recovery was defined as the first day that the patient thought the headache had disappeared and had taken no acetaminophen nor undergone lumbar puncture, if the headache did not recur within 1 month. For the patients who had post-lumbar puncture headache, the day of complete recovery was defined as the first day that the patient thought the headache had disappeared while the patient was supine and had taken no acetaminophen.

Study design and statistical analysis. The primary outcome in this study was the number of patients in the 2 groups who still had headache after the 2-week course of treatment. The secondary outcome was the length of time until complete disappearance of headache in each of the 2 groups. Information obtained from the subjects and laboratories were recorded on case-record forms. Data were analyzed by descriptive statistics, Student *t* test, χ^2 test, Fisher exact probability test, and survival analysis when appropriate.

Results

Study population. From October 1997 through March 1999, 129 patients (63 in the treatment group and 66 in the control group) were enrolled in the present study. However, 19 patients (8 in the treatment group and 11 in the control group) were removed from the study because they were lost to follow-up and clinical data were incomplete. Therefore, 55 patients

were studied in each group. The clinical presentations and severity of headache were similar in both groups at randomization (tables 1 and 2). A total of 108 patients had eaten raw pila snails before this illness developed. The other 2 patients had eaten boiled pila snails. Of the 5 patients who had 6th cranial nerve palsy, 3 had bilateral involvement (2 in the treatment group and 1 in the control group) that was associated with high CSF pressure. Both of the 2 patients who had 7th cranial nerve palsy had unilateral involvement. The patients with hyperesthesia presented with localized symptoms at some part of the body, such as the chest wall, face, or limbs.

Outcome. During the treatment period, 1 patient in the control group had bilateral papillitis develop on day 7 of hospitalization. The patient was treated with methylprednisolone and had good recovery, and the headache disappeared on the next day. In both groups, the patients with cranial nerve palsy recovered completely.

The number of patients with complete disappearance of headache in the treatment and control groups, respectively, were 43 (78.2%) versus 16 (29.1%) at 7 days after treatment, 7 (12.7%) versus 14 (25.5%) at 8–14 days after treatment, 0 versus 10 (18.2%) at 15–21 days after treatment, 2 (3.6%) versus 7 (12.7%) at 22–30 days after treatment, 1 (1.8%) versus 5 (9.1%) at 31–45 days after treatment, and 2 (3.6%) versus 3 (5.5%) at 46–60 days after treatment ($P < .0001$).

As shown in table 3, there were significant differences between groups with regard to the number of patients who still had headache after 14 days of treatment ($P = .00004$), the median length of time until complete disappearance of headache ($P = .00000$), the number of patients who had repeat lumbar puncture ($P = .002$), and the frequency of acetaminophen use in patients who had complete disappearance of headache within 14 days of treatment ($P = .038$). As shown in figure 1, there was a significant difference between groups with regard to the length of time to complete disappearance of headache. Also, there were significant differences between groups with regard to the length of time to complete disappearance of headache in patients who had CSF pressure <300 mm H₂O ($P = .0007$) and CSF pressure ≥ 300 mm H₂O ($P = .0113$). No gastroin-

Table 2 Comparison of initial laboratory features between patients treated with prednisolone for eosinophilic meningitis and control subjects.

Feature	Treatment group (n = 55)	Control group (n = 55)	P
Blood eosinophilia (≥ 700 cells/mm ³)	40	46	.24
CSF abnormalities			
High opening pressure (≥ 300 mm H ₂ O)	21	21	1.00
WBC/mm ³	760 (50–5700)	782 (85–2390)	.91
Eosinophilia, %	46 (10–81)	45 (12–84)	.72
Protein content, mg/dL	113 (31–574)	110 (27–470)	.68
Glucose ratio, CSF/blood, %	42 (18–71)	46 (17–100)	.60

NOTE. Data are no. of subjects or median (range).

Table 3 Comparison of clinical variables between patients treated with prednisolone for eosinophilic meningitis and control subjects.

Variable	Treatment group (n = 55)	Control group (n = 55)	P
Headache after 14 days of treatment, no. (%) of patients	5 (9.1)	25 (45.5)	.00004
Time until complete disappearance of headache, median d (range)	5 (1–60)	13 (1–56)	.00000
Repeat lumbar puncture, no. (%) of patients	7 (12.7)	22 (40.0)	.002
Frequency of acetaminophen use in patients who had complete disappearance of headache within 14 d of treatment, median no. of times	10.5	25.0	.038

testinal bleeding or hyperglycemia was seen, and there were no cases of recurrent meningitis in either group.

Discussion

In humans, the ingestion of raw, infected snails is the most common source of *A. cantonensis* infection [4]. When third-stage larvae are ingested, they penetrate the blood vessels in the intestinal tract and are carried to the meninges, where they soon die. A presumptive diagnosis may be made for patients who have symptoms of meningitis with CSF eosinophilia and a history of consumption of raw snails. A number of serological tests have been used to support the diagnosis of angiostrongyliasis. ELISA appears to show the most promise [5, 6].

Although headache is not a fatal condition, it is a distressing symptom that interferes with the personal and professional lives of patients. Corticosteroid therapy is of doubtful value [7]. Punyagupta et al. [1] reported that after 14 days of treatment with

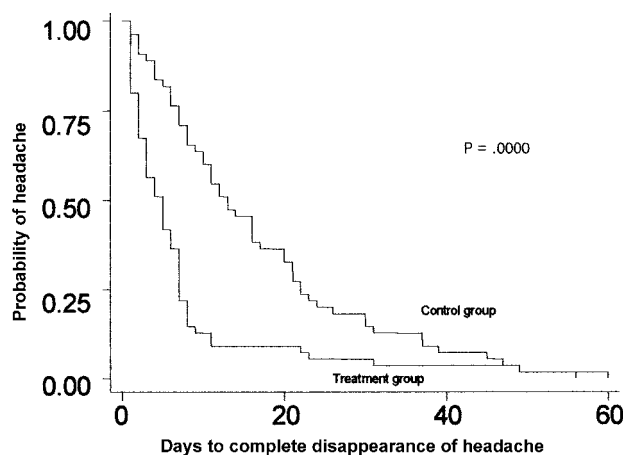
analgesics alone, ~60% of 284 patients who had eosinophilic meningitis probably caused by *A. cantonensis* still had headache. These authors also concluded that prednisolone showed no definite beneficial effect. However, the study did have possible shortcomings. First, it was not a randomized, double-blind, placebo-controlled study. Second, steroids were not continued beyond the initial 5-day study period with the various dosages (30–60 mg/day). Third, within the first 7 days of treatment, 7% of 284 patients in the group given analgesics only and 15% of 96 patients in the group given steroids recovered completely, which was a significant difference between the 2 groups ($P = .04$). Anecdotal reports of steroid use have shown conflicting results [7, 8].

In our patients, although serological testing was not available in our hospital, *A. cantonensis* was most likely the causative agent of eosinophilic meningitis, because all patients had a history of ingestion of snails before this illness and had clinical manifestations that were similar to those in the patients described by Punyagupta et al. [1]. Table 3 and figure 1 of our study show the beneficial effect of prednisolone on the course and outcome of eosinophilic meningitis. In addition, no harmful effect of treatment was demonstrated.

In conclusion, the results of our study lead us to believe that adjunctive prednisolone therapy improves the outcome of eosinophilic meningitis, and we recommend the use of a 2-week course of prednisolone, 60 mg/day, to treat eosinophilic meningitis.

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**Figure 1.** Kaplan-Meier survival estimates of length of time to complete disappearance of headache for patients treated with prednisolone for eosinophilic meningitis and control subjects.