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ORIGINAL

Riboflavin prophylaxis in pediatric and adolescent migraine

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Abstract Migraine is a common disorder in childhood and adolescence. Studies on adults show the effectiveness and tolerability of riboflavin in migraine prevention, while data on children are scarce. This retrospective study reports on our experience of using riboflavin for migraine prophylaxis in 41 pediatric and adolescent patients, who received 200 or 400 mg/day single oral dose of riboflavin for 3, 4 or 6 months. Attack frequency and intensity decreased ($P < 0.01$) during treatment, and these results were confirmed during the follow-up. A large number of patients (77.1%) reported that abortive drugs were effective for controlling ictal events. During the follow-up, 68.4% of cases had a 50% or greater reduction in frequency of attacks and 21.0% in intensity. Two patients had vomiting and increased appetite, respectively, most likely for causes unrelated to the use of riboflavin. In conclusion, riboflavin seems to be a well-tolerated, effective, and low-cost prophylactic treatment in children and adolescents suffering from migraine.

Keywords Riboflavin · Migraine · Headache · Treatment · Childhood · Adolescence

Introduction

Migraine is a common neurological disorder in childhood and adolescence; it has a prevalence of 3% in infancy/early childhood, increasing up to 23% in adolescence [1]. If intensity and frequency of migraine become excessive, they may cause a relevant impairment of quality of life. In such cases, a prophylactic treatment is necessary to avoid excessive drug intake, and improve the quality of life [2].

Many drugs used as migraine prophylaxis in adults have not been adequately tested on children, for whom symptomatic drugs are usually preferred.

Riboflavin is the precursor of flavin mononucleotide and flavin adenine dinucleotide which are involved in mitochondrial electron transport chain. Administering of riboflavin in migraine treatment is based on the hypothesis of a deficient mitochondrial energy reserve as a causal factor in migraine [3, 4], and on the findings of its effectiveness at high doses (100–200 mg/day) in the treatment of patients suffering from classic mitochondriopathies [5–8]. Literature reports four studies (two open trials, and two randomized and controlled) about riboflavin high doses (400 mg/day) that suggest its efficacy and tolerability for preventing migraine in adults [9–12]. A recent randomized, controlled trial reports that riboflavin is not so effective in children [13].

At present, there are no further studies about riboflavin prophylaxis in pediatric migraine [14].

We have undertaken this retrospective study to evaluate the effectiveness and tolerability of riboflavin in children and adolescents with resistant migraine.

Patients and methods

We have examined retrospectively 41 outpatients (16 males, 25 females) who were treated in the Child Neurology and Psychiatry Unit of the Department of Neurological Sciences of the University of Bologna from February 2002 to December 2007. Mean age was 13 years, 7 months

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(range 8 years, 11 months–18 years, 10 months). Mean follow-up from the first to the last observation was 1 year, 6 months. Patients received the following diagnoses, according to the criteria of the International Headache Society [15]: migraine without aura (24), migraine with aura (8), migraine without aura and frequent episodic tension-type headache (7), basilar-type migraine (1), benign paroxysmal vertigo of childhood and frequent episodic tension-type headache (1). Inclusion criteria were: resistant migraine with failure of previous prophylactic therapy (flunarizine, magnesium, and pizotifen); at least three moderate–severe or two severe attacks per month; and no prophylactic treatment for 3 months before the study. Exclusion criteria were: organic or psychiatric diseases. Intensity of attacks was functionally evaluated on a 3-point scale: "1" for mild headache that allowed for carrying out an activity as usual, "2" for moderate headache that slackened an activity without stopping it, and "3" for severe headache that stopped an activity, and needed repose or sleep.

Our patients were treated with a dose of either 200 or 400 mg/day chosen at random, in galenic preparation, at breakfast [5, 9–11]. Each patient kept a journal to record: number and intensity of attacks, concomitant symptoms, and symptomatic medication with its degree of efficacy. Informed consent was obtained from all patients' parents. Riboflavin was administered for 3, 4, or 6 months.

We have thus subdivided our study in the following 3-month periods: a baseline period without prophylactic medications (Phase 1), riboflavin treatment (Phase 2), and follow-up after the suspension of riboflavin (Phase 3). We have also considered two more phases in patients who assumed riboflavin for 4 or 6 months, and evaluated the last 3 months of therapy: Phase 2a (2nd, 3rd, and 4th month) and Phase 2b (4th, 5th, and 6th month), respectively (Fig. 1). We compared attack frequency, intensity, and symptomatic therapy efficacy in Phases 2, 2a, 2b, and 3 with Phase 1. Primary end-point of the study was the reduction of mean attack frequency; secondary end-points were the reduction of mean headache intensity and the increase of symptomatic therapy responsiveness. Responders were patients with a frequency and/or intensity reduction of at least 50%, while semi-responders showed a 25–50% reduction. We have also considered: riboflavin effect on aura symptoms; correlation between riboflavin efficacy and sex, age (under or over 12 years), different migraine types, and age of headache onset (under or over 10 years).

We have utilized Wilcoxon sign rank and Fisher exact test for statistical analysis.

Results

Twenty-one patients (51.2%) took 200 mg/day of riboflavin, 20 patients (48.8%) 400 mg/day. Forty patients (97.6%) took riboflavin regularly for 3 months at least, concluding Phase 2; one dropped out due to vomiting. Fourteen patients (35.0%) continued therapy for 4 months, 11 (27.5%) for 6 months. Thirty-eight patients (95.0%) completed Phase 3; for two patients we do not have a 3-month follow-up because they dropped out of the study (Fig. 1).

With regard to the primary end-point, our data show a significant reduction of mean attack frequency in Phase 2 compared with baseline (21.7 ± 13.7 vs. 13.2 ± 11.8; $P < 0.01$); this was confirmed during the follow-up in Phase 3 (21.9 ± 14 vs. 8 ± 9; $P < 0.01$). Mean frequency decreased even more in Phase 2a (23.4 ± 12.2 vs. 8.9 ± 9.4; $P < 0.01$), while the decrease was not

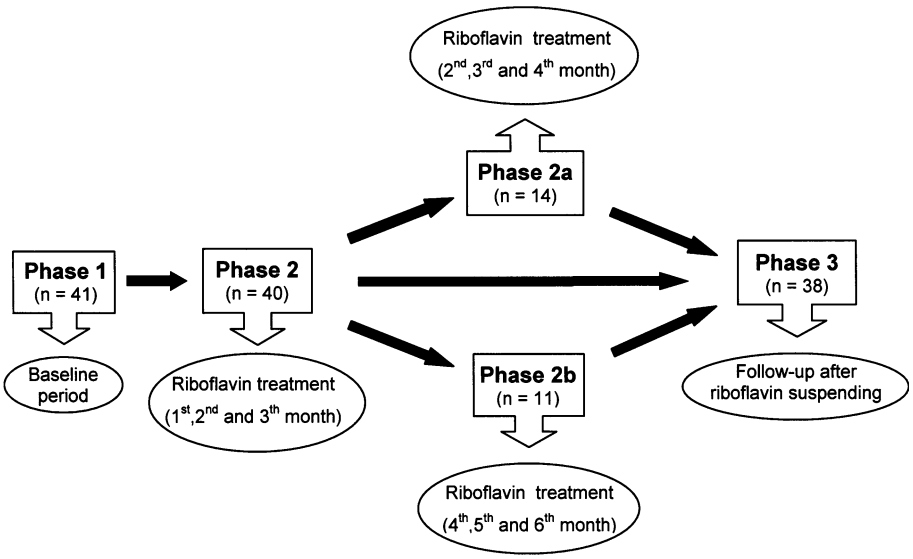

Fig. 1 Study flow-chart

significant in Phase 2b (19.3 ± 13.4 vs. 11.4 ± 9.6; $P > 0.05$) (Fig. 2).

Mean headache intensity decreased from 2 (±0.5; Phase 1) to 1.6 (±0.8; $P < 0.01$) in Phase 2, and continued to decrease in Phase 3 (2 ± 0.5 vs. 1.4 ± 0.9; $P < 0.01$); whereas there was no significant reduction in headache intensity both in Phase 2a (1.8 ± 0.4 vs. 1.3 ± 0.9; $P > 0.05$) and in Phase 2b (2.1 ± 0.4 vs. 1.9 ± 0.8; $P > 0.05$) (Fig. 3).

Five patients (12.5%) did not use symptomatic drugs during Phases 2 and 3, due to the complete remission of headache or the mildness and infrequent occurrence of migraine attacks; while 27 out of 35 patients (77.1%) reported that symptomatic drugs (e.g., ibuprofen, paracetamol, nimesulide, ketoprofen, acetylsalicylic acid, metamizole sodium, noramidopyrine, zolmitriptan, sumatriptan, and piroxicam) were more effective during riboflavin treatment.

Seventeen patients (42.5%) showed at least a 50% reduction in attack frequency (responders) in Phase 2, while 7 (17.5%) showed a 25–50% reduction (semi-responders) in the same phase. The rate of frequency responders increased to 83.3% in Phase 2a, decreased to 45.4% in Phase 2b, and was 68.4% in Phase 3. Semi-responders rate was 0% in Phase 2a, 18.2% in 2b and 18.4% in Phase 3. With regard to attack intensity, the responder rate was 21.0% in Phase 3 (Phase 2: 10.0%; 2a: 21.4%; 2b: 9.1%), while the semi-responder rate in the same phase was 26.3% (Phase 2: 25.0%; 2a: 28.6%; 2b: 18.2%). Statistical analysis showed no significant differences between frequency/intensity responders and non-responders for a 200 or 400 mg/day dose, different migraine types, and age of headache onset. As regards, the correlation between riboflavin efficacy and sex or age, we have found a significant prevalence of males in the intensity-responder group ($P < 0.05$), and of patients under 12 years in the frequency-responder group ($P < 0.05$).

Among the eight patients suffering from migraine with aura, riboflavin had the following effects in all phases: two patients (25.0%) no longer had attacks with aura; two patients (25.0%) no longer had attacks with aura, or aura symptoms became shorter and less intense; in one patient (12.5%) aura intensity and duration decreased considerably.

During the treatment, one patient dropped out because of vomiting probably caused by the unpleasant flavor of the compound; another patient had increased appetite, but without weight gain. Finally, some patients reported a temporary yellow-orange coloration of urine.

Discussion

While the literature reports positive data concerning migraine treatment with riboflavin in adult patients [9–12], a recent trial has found no significant effects in childhood [13]. We estimated whether the use of this vitamin can provide benefits also for children and adolescents, and to possibly determine the right dose and duration of the therapy.

Our data suggest that riboflavin prophylactic treatment significantly reduces migraine frequency and intensity ($P < 0.01$) during the trial (3-month treatment, Phase 2) and also in the follow-up (Phase 3). These results are in line

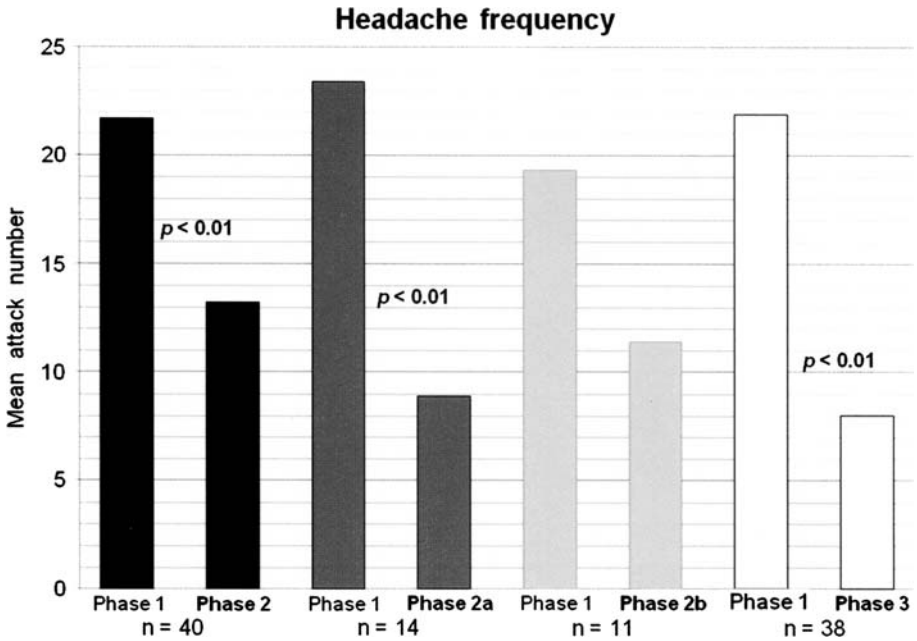

Fig. 2 Mean headache frequency: comparison between Phase 1 and, respectively, Phase 2 ($P < 0.01$), Phase 2a ($P < 0.01$), Phase 2b ($P > 0.05$), Phase 3 ($P < 0.01$)

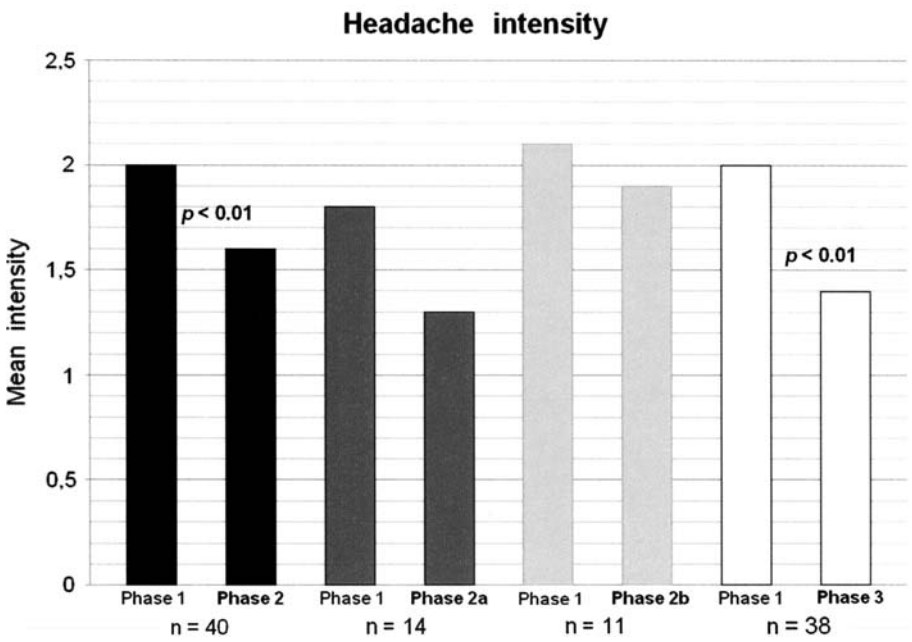

Fig. 3 Mean headache intensity: comparison between Phase 1 and, respectively, Phase 2 ($P < 0.01$), Phase 2a ($P > 0.05$), Phase 2b ($P > 0.05$), Phase 3 ($P < 0.01$)

with previous adult studies only with regard to headache frequency, but not to headache intensity [9–11]. In a recent pediatric trial, riboflavin (200 mg daily) was not more effective than placebo for responders in the number of migraine attacks, mean severity per day, days with nausea or vomiting, or number of attacks treated with symptomatic treatment [13]. Our recommendation to parents and patients about an immediate symptomatic pharmacological intervention during riboflavin treatment could have influenced positively the results about headache intensity; in fact in 77.1% of patients there was an increase of symptomatic therapy responsiveness. The prevalent effect of riboflavin was the reduction of migraine frequency (68.4% responders, 18.4% semi-responders, particularly among younger patients, under 12 years: 91.7% responders). We did not find such significant data for intensity considering all patients; however, our results show an important effect of riboflavin on intensity in males. The gender difference is difficult to explain particularly for prophylactic treatment. Nevertheless, for acute treatment some literature data suggest a higher response rate in boys [16].

We chose a riboflavin dose of 200 or 400 mg/day considering other trials [9–11], the absence of reports on riboflavin toxicity, and finally, the hypothesis that prolonged retention of the vitamin in the intestine can increase the total amount absorbed [17], although riboflavin intestinal absorption is a saturable process [18]. We also tested a 200 mg/day dose, on the basis of dosage utilized in mitochondriopathies [5–8]. Our results confirmed that 200 mg/day of riboflavin may be adequate.

As regards treatment duration, in the Australian trial patients were given riboflavin for 3 months [13], whereas, in our opinion, 4 months seem to be necessary to achieve the best results; in fact, frequency reduction increased up to the 4th month of therapy (Phase 2a), when there was the most elevated rate of responders. The apparent decrease of riboflavin effectiveness in Phase 2b for headache frequency and in Phases 2a and 2b for intensity may be related to the smaller number of patients who reached these phases.

It is also important to underscore that riboflavin was effective in eliminating or reducing the intensity and duration of aura symptoms in five out of eight patients. No data on this topic were reported [9–13].

Our results suggest that riboflavin may be effective for any type of migraine, with any onset age, in childhood and adolescence.

Riboflavin was well tolerated by our patients with an excellent compliance rate: only two patients reported vomiting or increased appetite, probably due to causes not related to the treatment.

We are aware that our results may be open to questioning and discussion because of the placebo response, which has been systematically evaluated in open adult trials for migraine prophylaxis [19], and could be considerably higher in a pediatric study [13]. However, we believe that it would have been unethical to propose a placebo to younger patients with severe and resistant migraine who had come to a specialized university centre for headache treatment and for whom previous therapies had failed. In the pediatric Australian trial [13], the sample was mainly community-based as most of the children were recruited via school newsletters. We suggest that due to this sampling, it is possible that the symptomatology addressed in that trial was less severe than the one we

observed in our patients, and that as a consequence, the placebo administration was simpler and the results about riboflavin were less encouraging than ours.

Our study has several positive aspects. Sample size is larger than in other studies [9, 11, 20, 21]. Riboflavin is devoid of adverse effects, so it is easy to recommend its use as a therapeutic option to parents of younger patients, who often have reservations about pharmacological therapy. Moreover, its cost is lower than that of most drugs used for migraine prevention.

In conclusion, we suggest that riboflavin might be a safe, well-tolerated, and effective alternative prophylactic treatment for children and adolescents with migraine, while recognizing that randomized controlled studies with a larger number of patients and other standard efficacy parameters could be useful to confirm our results.

Conflict of interest None.

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Research Submissions

Oral Magnesium Oxide Prophylaxis of Frequent Migrainous Headache in Children: A Randomized, Double-Blind, Placebo-Controlled Trial

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Objective.—To assess whether, in children, oral magnesium oxide reduces migrainous headache frequency, severity, and associated features compared to placebo.

Background.—There is no single, safe, widely well-tolerated, and effective prophylactic treatment for all children and adolescents with frequent migrainous headache.

Design.—Randomized, double-blind, placebo-controlled, parallel-group trial.

Methods.—This study was conducted between June 1997 and January 2000 using 7 selected Northern California Kaiser Permanente sites. We recruited children of ages 3 to 17 years who reported a 4-week history of at least weekly, moderate-to-severe headache with a throbbing or pulsatile quality, associated anorexia/nausea, vomiting, photophobia, sonophobia, or relief with sleep, but no fever or evidence of infection. Subjects were randomly assigned to receive either magnesium oxide (9 mg/kg per day by mouth divided 3 times a day with food) (n = 58) or matching placebo (n = 60) for 16 weeks. The number of headache days (days with at least one headache) during each of eight 2-week intervals was chosen to be the primary outcome variable.

Results.—Of those enrolled, 86 (73%) completed the study (42 received magnesium oxide and 44 placebo); 74 of 192 eligible subjects declined to participate. Baseline information on demographic factors, health status, and headache history was similar comparing the 2 groups. By intention-to-treat analysis, we found a statistically significant decrease over time in headache frequency in the magnesium oxide group ($P = .0037$) but not in the placebo group ($P = .086$), although the slopes of these 2 lines were not statistically significantly different from each other ($P = .88$). The group treated with magnesium oxide had significantly lower headache severity ($P = .0029$) relative to the placebo group.

Conclusions.—This study does not unequivocally determine whether oral magnesium oxide is or is not superior to placebo in preventing frequent migrainous headache in children, but treatment with the active agent did lead to a significant reduction in headache days. Larger trials involving this safe, appealing complementary therapy are needed.

Key words: headache, magnesium, migraine, pediatric, randomized, trial

Abbreviations: HA headache, Mg magnesium, MgO magnesium oxide, Ca calcium, GEEs generalized estimating equations

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Migraine headaches (HAs) affect at least 3% to 13% of children, 6% to 8% of men, and 18% of women,[1-5] and are likely the most debilitating and underdiagnosed neurologic problem affecting otherwise healthy children in the United States.[6-9] Clinicians caring for children and adolescents with migraine have been hampered by the absence of a truly safe, widely well-tolerated, and universally effective prophylactic treatment for patients with frequent HAs or poor tolerance of abortive therapies.

Intriguingly, low systemic magnesium (Mg) levels have been demonstrated in the serum, blood cells, saliva, cerebrospinal fluid, and brain of migraineurs compared to nonmigraineur controls,[10-24] which has led investigators to wonder whether migraine could be a Mg-deficiency disease, at least in part. Randomized trials of various Mg salts available in Europe for oral migraine prophylaxis in adults have produced conflicting results. Two such trials noted a benefit,[25,26] while another did not.[27] It is unclear whether this discrepancy reflects differing doses and bioavailability of the Mg salts used, methodological issues such as the primary outcome measures examined, or underlying pathophysiological heterogeneity of migraine in different populations. Intravenous administration of Mg sulfate effectively aborted migraine in patients enrolled in open-label series.[28] No published trial has been performed in the pediatric age group, although case series have been presented.[29]

In this study, we report our results of a randomized, double-blind, placebo-controlled, parallel-group trial to assess whether oral Mg oxide (MgO) is superior to placebo in reducing migrainous HA frequency, severity, and associated features among otherwise healthy children.

METHODS

Patient Recruitment.—Patients were enrolled on a rolling basis from June 10, 1997 through September 14, 1999 and were recruited from 7 catchment areas of Northern California Kaiser Permanente, a nonprofit, staff model, health maintenance organization. Potentially eligible participants were identified by virtue of a "headache" or "migraine" diagnosis on Kaiser Permanente's computerized outpatient database. In addition, physician referrals and patient self-referrals were encouraged through the use of study advertisement signs posted in outpatient common waiting areas and individual examination rooms. Patients and their families were not reimbursed.

Migraine Definition.—For the purposes of this study, patients between 3 and 17 years of age who weighed less than 197 pounds (to simplify calculation of number of capsules to be distributed) were defined as having migrainous HA and being potentially eligible for study participation if they had a history of at least weekly, moderate-to-severe HA during the previous 4 weeks. The HAs must have been associated with anorexia/nausea, vomiting, photophobia, sonophobia, a pulsatile or throbbing quality, or relief with sleep, but not with fever or evidence of infection. We *conservatively* counted a maximum of one HA per day for those with intermittent HA throughout a single day, and set no required HA duration, given the difficulty inherent in assessing such factors in school-aged children. In addition, we did not require unilaterality of HAs given the bilaterality of a significant proportion of pediatric migraine.

Patients with renal insufficiency, diabetes mellitus, psychosis, or who were pregnant were excluded. Patients were also excluded if they took any migraine prophylactic drug therapies (such as cyproheptadine, beta-blockers, tricyclic antidepressants, calcium (Ca)-channel blockers, valproic acid), Mg, or feverfew within 4 weeks of potential study entrance, or if they regularly used any drug known to be associated with HAs (such as central nervous system stimulants, sympathomimetic agents for asthma, steroids, birth control pills) at the time of study evaluation. Patients with unremitting "24-hour-per-day" continuous HAs were excluded in an attempt to eliminate patients with a higher likelihood of somatoform disorder or factitious HA, which may be less frequently observed in those whose HAs abate. Those unable to swallow capsules whole were also excluded.

Study Design.—Approved by the Kaiser Permanente Institutional Review Board, this was a 16-week, randomized, double-blind, placebo-controlled, parallel-group trial with a single treatment arm and a placebo arm. The first 14 participants were instructed to follow a migraine elimination diet for the duration of the study (no caffeine, chocolate, cured delicates-

sen meats, or cheese) in order to give all participants some form of "treatment." These 14 also had a 4-week run-in period during which time we gave them placebo and monitored their compliance. The run-in period was subsequently eliminated for the last 104 patients to increase the duration of potential Mg exposure from 12 weeks to 16 weeks, to simplify capsule distribution, and to increase recruitment and retention. At the same time, the dietary requirement was eliminated to hasten patient enrollment, as many potentially eligible early subjects were dissuaded from participating by having tried some version of a migraine elimination diet without benefit.

Subjects filled out a 49-item baseline HA questionnaire collecting information on demographic factors, health status, HA history, associated symptomatology, medication, and school time lost. The questionnaires were completed by parents or guardians caring for younger children, and by older participants themselves. Each day participants were asked to note on a 16-week HA calendar whether or not a HA had occurred. For each HA day, information was sought on HA severity and duration, and whether anorexia, photophobia, or sonophobia were noted. Regardless of age, study subjects were asked to indicate the maximal HA severity for each HA day using the 6-point Wong-Baker Face Pain Rating Scale.[30]

Potentially eligible subjects visited either the study coordinator or the site coordinator to review the study protocol, be weighed, confirm continued interest in participation, and provide serum and urine samples. Informed consent was obtained from the parent or legal guardian and informed assent was obtained from the child. Blood was drawn at baseline to check serum total Mg and total Ca, ionized Mg and ionized Ca, electrolytes, blood urea nitrogen, creatinine, albumin, antinuclear antibody, hemoglobin, hematocrit, urinalysis, and, for postmenarchal girls, a urine pregnancy test. All sera and urine specimens were analyzed at the Kaiser Permanente regional laboratory in Berkeley, California, with the exception of serum ionized Mg and serum ionized Ca, which were performed at the University of Louisville, Kentucky using the AVL 988-4 analyzer (AVL, Graz, Austria).[31] Sera for ionized Mg and ionized Ca determination were obtained by immediately centrifuging the blood, harvesting the serum in cryotubes, and freezing in cryotubes at −20°C at the local site laboratory prior to transport to Berkeley, California for storage.

After renal insufficiency was ruled out in every patient, patients were individually randomized to either MgO (9 mg elemental Mg/kg per day, by mouth, divided 3 times a day with food; MgO in capsules containing 84.5 mg of elemental Mg supplied by The Blaine Company, Burlington, Ky) or identically appearing placebo (microcrystalline cellulose and stearic acid, supplied by Schwarz Pharmaceutical Manufacturing, Inc, Seymour, Ind). Patients took between 1 and 3 capsules per dose. The total daily Mg dose was chosen based on a positive trial in adults (assuming a weight of 70 kg) taking 600 mg of elemental Mg.[26] Randomization occurred within age (<10 years, ≥10 years) and sex strata, as these demographic factors have been shown to be highly correlated with pediatric HA prevalence.[32,33]

Regardless of whether they completed the study, all subjects were asked to indicate the arm of the study to which they thought they had been randomized, why, how well they felt the capsules had worked, and side effects. Dropouts were asked to state their reason(s) for not completing the study.

Blinding and Compliance.—Subjects, the study and site coordinators, and all investigators were not aware of the study drug assignment until after the study statistician had analyzed all study data. Compliance was assessed through the use of capsule counts, which were performed at week 4 and again at study's end. The allocation schedule was generated using Proc Plan in the Statistical Analysis System's (SAS) software, version 6.11. Randomization plans were created separately for each age/sex strata within each study facility. Once the patient was deemed eligible and had signed an informed consent, the project manager made a request to an appointed study staff person who had no patient contact. The information presented was the child's study identification number, age, weight, and medical facility. With this information, the staff person checked the randomization table for the next available spot within that particular stratum, entered the child's study information into the table, and then put together a packet of the appropriate capsules in unlabeled bottles. These were

given to the project manager who then dispensed the bottles to the study subjects. The randomization book was only available to the staff person.

The placebo and MgO capsules were identical in shape, color, and taste. The code book for randomization was kept locked in a file cabinet throughout the study. Access was available only to the staff person doing the randomization. The assignment was broken by the statistician when all patients had completed the study. The outcomes were self-reported. The data analyst was aware of the randomization when analyzing the data.

Statistical Analyses.—Our target sample size was 60 subjects in each group. This would have allowed us to detect a between-group difference in the change in HA frequency over time of 20%, using a 2-sample *t* test at the 5% significance level, a power of 80%, and assuming a standard deviation of 40%. Subjects in the 2 study arms (placebo and MgO) were compared based on their baseline characteristics. These characteristics included age, sex, race, number and type of comorbidities, family history of migraine, age at onset of HAs, number of HAs in previous month and previous 6 months, number of doctor visits in the previous 3 months, number of school days missed during the past 3 months, and laboratory tests. Categorical variables were compared using chi-square tests, and continuous variables were compared with *t* tests or Wilcoxon rank sum tests. All tests were 2-sided using a type I error rate of 5%.

Dropout rates in the 2 groups were then determined and compared using a chi-square test. We also compared those who dropped out to those who completed the study based on the baseline variables listed above as well as the randomized treatment group.

Outcome Measures.—For each subject, the number of HA days (days with at least one HA) during each of the eight 2-week intervals of the study was determined. These summary numbers were the primary outcome measurements. For those 14 subjects who had 4 weeks of placebo before being randomized to receive treatment or placebo for 12 weeks, only the 12 weeks of treatment were used. On intention-to-treat analysis, regression models were used to compare HA frequencies over time between the treatment and control groups, adjusting for the stratifying variables of age and sex. The models accounted for within-subject correlation while comparing the 2 groups using generalized estimating equations (GEEs), allowing the distributions of the outcome variables to have normal or Poisson distributions when appropriate. This model included a term for the interaction between treatment and time. Additionally, since the test for interaction had low power, we analyzed the 2 groups separately, and tested for a linear trend across time.

Secondary measures that could be summarized every 2 weeks for each subject were proportion of HAs with each symptom and average severity score on the Wong-Baker Face Pain Rating Scale. These outcomes were also analyzed using GEE models, this time with binary or Gaussian distributions, as appropriate.

RESULTS

Subject Enrollment.—Four hundred sixty-six patients were screened (see trial profile, Figure 1). Study referral sources included outpatient database (n = 175), self-referral (n = 128), physician advice to patients (n=101), direct physician calls (n = 48), and other/unknown (n = 14). One hundred ninety-two patients (41%) were eligible for study participation and, of these, 118 patients enrolled. Of those enrolled, 86 (73%) completed the study (42 received MgO and 44 placebo) and 32 (27%) dropped out (16 randomized to MgO and 16 to placebo). One hundred of those enrolled (85%) were between 9 and 16 years of age, inclusive.

Baseline Differences.—Subjects randomized to MgO and placebo were compared, regardless of whether they completed the study, for each of the 49 baseline questionnaire variables. Statistically significant differences were found only for self-defined asthma (more in the placebo arm, $P = .012$), history of anorexia (more in the MgO arm, $P = .023$), and serum ionized Ca (higher in the MgO arm, $P = .036$) (Table). There was no significant difference between serum total or serum ionized Mg levels comparing the 2 study arms. No other significant differences between the 2 groups were noted regarding baseline demographic variables, HA features, or associated symptoms.

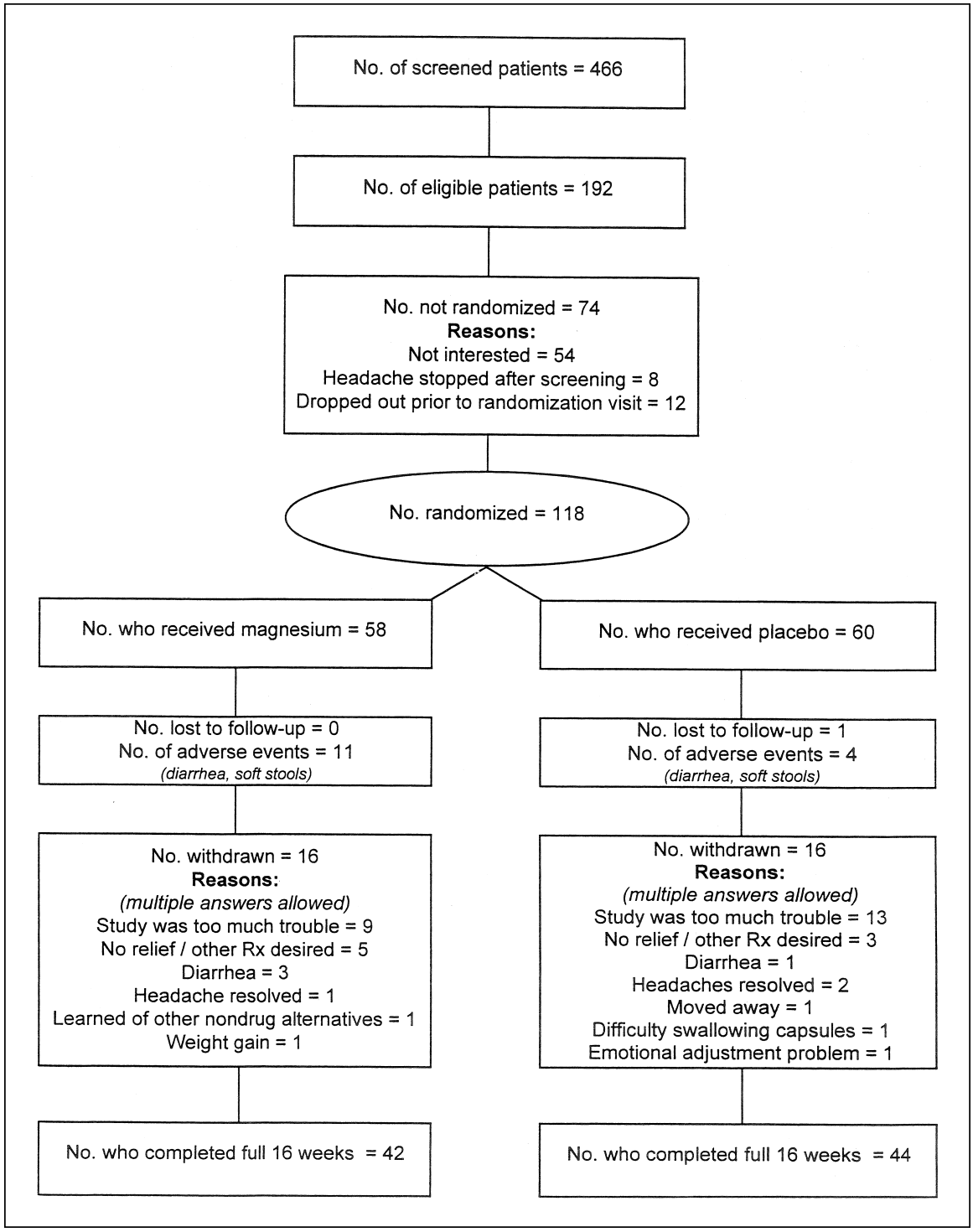

Fig. 1.—Trial profile.

Primary Outcomes.—The proportion of days with a HA was computed for each of the 2 study arms in 2-week increments (Figure 2). A sustained decrease in HA frequency in the MgO arm was noted throughout the study, while an apparent placebo response waned after about 6 weeks in the placebo

Baseline Comparisons of Children With Migraine Randomized to Magnesium Oxide or Placebo*

Variable	Total Children (N = 118)	Magnesium Oxide Group (n = 58)	Placebo Group (n = 60)	*P* Value
Completed study	86 (66.2)	42 (72.4)	44 (73.3)	
Completed part of study	23 (17.7)	13 (22.4)	10 (16.7)	
Sex				.39
Male	37 (31.4)	16 (27.6)	21 (35.0)	
Race/ethnicity				.40
White	70 (59.3)	30 (51.7)	40 (66.7)	
Hispanic	20 (17.0)	12 (19.0)	8 (13.3)	
Other	8 (6.8)	5 (8.6)	3 (5.0)	
Multiethnic	20 (17.0)	11 (19.0)	9 (15.0)	
Allergies	41 (34.8)	16 (27.6)	25 (41.7)	.11
Asthma	18 (15.4)	4 (6.9)	14 (23.7)	.012
Chronic daily headache	22 (18.8)	9 (15.5)	13 (22.0)	.37
Depression	10 (8.5)	4 (6.9)	6 (10.0)	.74
Time to headache intensity				
Can not tell	26 (22.0)	14 (24.1)	12 (20.0)	
Gradually	58 (49.2)	30 (51.7)	28 (46.7)	
Suddenly	28 (23.7)	9 (15.5)	19 (31.7)	
Gradually and suddenly	6 (5.1)	5 (8.6)	1 (1.7)	
Symptoms associated with headache				
Anorexia	69 (58.5)	40 (69.0)	29 (48.3)	.023
Nausea	78 (66.1)	41 (70.7)	37 (61.7)	.30
Vomiting	49 (41.5)	24 (41.4)	25 (41.7)	.98
Sonophobia	103 (87.3)	51 (87.9)	52 (87.7)	.84
Photophobia	96 (81.4)	47 (81.0)	49 (81.7)	.93
Age, mean (SD), y	12.0 (3.0)	12.2 (2.7)	11.8 (3.3)	.43
Visits to MD for headache in past year, mean (SD), No.	2.2 (2.0)	2.2 (2.2)	2.2 (1.8)	.98
Age at first headache, mean (SD), y	8.5 (3.7)	8.3 (3.4)	8.6 (4.0)	.70
Headaches in last month, mean (SD) [median], No.	10.5 (6.7) [8]	9.3 (4.7) [8]	11.5 (8.1) [8]	.53
Ionized calcium, mean (SD), mmol/L	1.00 (0.16)	1.03 (0.16)	0.97 (0.15)	.036
Ionized magnesium, mean (SD), mmol/L	0.49 (0.05)	0.50 (0.05)	0.49 (0.05)	.26

* Values are number (percentage) unless otherwise indicated.

arm. The proportion of HAs individually associated with photophobia, sonophobia, and anorexia, and the average severity per HA were calculated in similar fashion (not shown).

Poisson regression models with repeated measures (GEE models) were fit to the number of HAs per 2-week block. Model predictors were age group (≤10 years, >10 years), sex, treatment or placebo group, baseline (self-reported) HA frequency, and the 3 imbalanced baseline variables (asthma, anorexia, and serum ionized Ca level). The model was first fit with a time-by-treatment interaction, but this was dropped when it was found not to be significant ($P = .88$). In this model, there was no treatment effect associated with MgO use and no effect tied to age, asthma, or serum ionized Ca. Boys were only two thirds as likely as girls to have a HA during each day of the study ($P = .0081$). For each log (base 10) increase in number of baseline HAs (from 1 to 10, for example), the odds of additional HAs during the study was increased by 33% ($P = .074$). If HAs with anorexia were reported at baseline, the odds of a HA day were 41% higher than for those subjects without anorexia-associated HAs at baseline ($P = .015$).

Similar Poisson regression models were then fit focusing on each group separately, with time included as a continuous variable in order to test for linearity over time. For the MgO group, the HA frequency signifi-

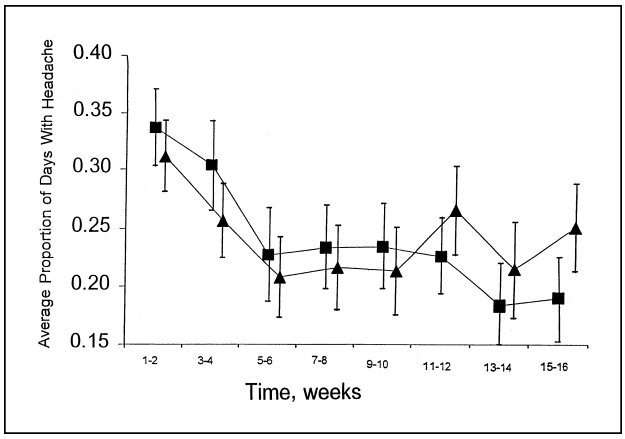

Fig. 2.—Average proportion of days with headache as function of time comparing children randomized to oral magnesium oxide or placebo. Squares represent randomization to magnesium and triangles to placebo. *P* values tested for a linear trend across time in each of the 2 study arms: magnesium, *P* = .0037; placebo, *P* = .086.

cantly decreased with time ($P = .0037$), but evidence for such a time trend in the placebo group was not significant ($P = .086$).

Secondary Outcomes.—Symptoms on the daily HA forms were then examined among all subjects. Generalized estimating equation Poisson models using 2-week increments were fit for photophobia, sonophobia, and anorexia. For the subject-defined Wong-Baker pain severity scale, a GEE model with normal errors was used, also using 2-week increments. For severity, there was not a significant interaction between time and treatment group, but there was a significant treatment effect ($P = .0029$), with the MgO group having significantly lower severity than the placebo group after adjusting for baseline serum ionized Mg. There was no significant trend in severity over time in either group (MgO group, $P = .85$; placebo group, $P = .80$).

For photophobia, sonophobia, and anorexia, the interaction between treatment and time was not significant ($P = .70$, $P = .20$, $P = .66$, respectively). In the MgO group, there were no significant trends over time (photophobia, $P = .52$; sonophobia, $P = .79$; anorexia, $P = .76$). However, significant positive (*adverse*) trends were found in the placebo group (photophobia, $P = .0078$; sonophobia, $P = .042$; anorexia, $P = .0011$).

Adverse Effects.—When patients completed or dropped out of the study, they were asked what preparation they thought they had received. Of those who received MgO (n = 58), 26 responded that they did not know what they had been taking, 10 chose placebo, 12 chose MgO, and 9 thought they had received both. One patient did not respond. Of those who received placebo (n = 60), 29 did not know what they had received, 12 chose placebo, 14 chose MgO, and 5 thought they had received both.

Eleven (19%) of 58 patients randomized to MgO reported having diarrhea or soft stools, while 4 (7%) of 60 in the placebo group experienced this. This difference was statistically significant ($P = .04$). However, of those 11 in the MgO group who reported this side effect, only 4 guessed correctly that they received MgO, 2 thought they received placebo, and 5 either did not know or thought they had received both MgO and placebo. There were no other significant side effects reported.

COMMENTS

We found a statistically significant downward trend in HA frequency over time in the MgO group but not in the placebo group. We were not able, however, to show that the slopes of the 2 lines were significantly different from each other. As can be seen in Figure 2, this is mostly due to the large variability between subjects. Therefore, this study does not unequivocally determine whether oral MgO is or is not superior to placebo in preventing frequent migrainous HA in children. The finding of a significant slope in the MgO group would be consistent with earlier European studies indicating that other oral Mg salts prevent adult migraine,[25,26] and would complement more recent research on the use of intravenous Mg sulfate in aborting acute migraine.[28] Given the high prevalence of migraine, particular significance of more definitive results would stem from a potentially large population benefit attributable to Mg. As we have previously shown that the age- and sex-specific prevalence of episodic HA in the Northern California Kaiser Permanente population mirrors that of general populations, we suggest that definitive findings within the Kaiser population may be generalizable to the population at large.[32]

Use of MgO at the therapeutic dose used was free of serious side effects compared to placebo amongst our healthy population of children. Indeed, the serious or at least bothersome side effects caused by many currently available migraine preventive therapies, such as sedation, fatigue, weight gain, bronchospasm, and arrhythmia, often lead parents and pediatric patients to forego pharmacological migraine prevention therapy altogether. As a ubiquitous mineral supplement normally present in the human body, Mg may be more appealing to much of the population as a safe, well-tolerated alternative worth trying. Also, Mg is relatively inexpensive and readily available in many foods and in tablet or capsule form in supermarkets and health food stores across the western world.

We purposefully chose a simple migraine case definition to expedite patient enrollment. Our protocol was submitted to the Kaiser Permanente Institutional Review Board prior to publication of a proposed pediatric migraine definition more sensitive, but possibly less specific, than the International Headache Society criteria for adult migraine as applied to children.[34] Because there is no pathophysiological reason to believe that Mg might work for any HA types but migraine (see below) and cluster HAs, the latter of which was not observed in our study sample, we suggest that use of a more specific case definition may have eliminated some patients with nonmigraine HA from our study. This, in turn, might have led to stronger results, should Mg indeed be shown by others to be effective in preventing pediatric migraine. However, use of a more specific migraine definition would likely have required even longer than the 27 months over which we diligently recruited patients.

The anticipated challenges of recruiting primarily adolescent subjects into such a long trial stemmed from requiring 4 study visits, daily HA diary and calendar entries while on MgO or placebo, 3 times a day dosing with as many as 9 capsules per day, the need to undergo phlebotomy at baseline, and the ability to swallow capsules whole. Migrainous HA may also represent a heterogeneous condition in which only a subset of patients respond to oral Mg therapy. We did not require that the daily HA diary be completed prior to randomization (only that there be a history of at least weekly, moderate-to-severe HA during the 4 weeks prior to study entry) and so could not identify those who had chronic daily HA, although unremitting, continuous HAs did result in exclusion. In addition, there was no financial incentive to complete the trial. We did not monitor blood levels of Mg during the course of or at the end of this trial, as such levels correlate poorly with total body Mg status and having such a requirement would have dissuaded even more children from enrolling in the trial.[35] The long equilibrium half-life of Mg (42 days) suggests that any therapeutic effect would require at least several weeks to appear.[36,37] Finally, the traditionally high placebo response rate seen in pediatric HA studies mandated that a very strong treatment effect had to exist in order to detect such an effect in this trial, while any beneficial effect attributable to Mg may, in fact, be mild.

How Mg may work in decreasing migraine frequency and associated symptomatology, including anorexia, photophobia, and sonophobia is unclear because the root causes of migraine pain are unknown. Magnesium deficiency could play a pathophysiological role in migraine expression in any of several different ways. First, familial hemiplegic migraine could be a Ca channelopathy and one could hypothesize that, acting as a physiological antagonist of Ca, Mg might exert a beneficial effect in more prevalent forms of migraine.[38,39] Second, in the primary neuronal hypothesis, migraine pain is thought to result from sterile neurogenic inflammation induced by stimulation of trigeminovascular afferent fibers.[40-42] This process may be linked to cortical spreading depression of Leão triggered by stimulation of *N*-methyl-D-aspartate (NMDA) receptors. Magnesium blocks this process in vitro.[43,44] Third, Mg may also exert an antimigraine effect by inhibiting platelet hyperaggregability and, fourth, by relaxing vascular tone.[45-50]

We recommend longer, larger trials using higher but still tolerable doses of well-absorbed Mg salts in carefully chosen study populations to definitively establish the place of Mg therapy in migraine prophylaxis.

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